ANTTI AIRIO

# Polymyositis and Dermatomyositis in Finland

## A longitudinal, population-based study

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the Jarmo Visakorpi Auditorium,
of the Arvo Building, Lääkärinkatu 1, Tampere,
on November 20th, 2009, at 12 o'clock.

UNIVERSITY OF TAMPERE

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**LIST OF CONTENTS**

## 1. ABSTRACT

The national hospital discharge registry from the period 1969-1985 was used as a source of case selection to find patients with polymyositis (PM) and dermatomyositis (DM) in order to assess outcomes and associated malignancies and mycobacterial infections in these disorders. The files of the Finnish Cancer Register were used for determining cancer incidence in the patients. The patients were followed up until death or till the end of August 1995, whichever occurred first, using the national mortality files of Statistics Finland. During the follow-up, the total amount of myositis cases increased from 311 to 316 including, finally, 176 patients with PM and 72 patients with DM. In order to have sufficient power to test the association between myositis and specific cancer types, a pooled analysis of published national data from Sweden, Denmark and Finland was performed. The data of the original studies from the other Nordic countries were also based on official national registries.

In the Finnish study, there were 4 haematological cancers versus the 1.1 expected [standardized incidence ratio (SIR) 3.8, 95% confidence interval (CI) 1.0-9.8] in the PM group, otherwise all the excess risk was attributable to DM. The excess risk was observed only in patients 50 years old or older at the time of their DM diagnosis. The risk was increased for cancers of the gastrointestinal tract (SIR 9.0, 3.6-19), for lung cancer (SIR 10, 2.1-29), ovarian cancer (SIR 32, 8.7-82), and for non-melanoma skin cancer (SIR 29, 3.6-106).

In the Scandinavian study, there was a three-fold increase in the risk of malignant disease after the diagnosis of DM for all cancer types. The SIRs for men and women with DM were 3.3 (95% CI 2.5-4.4.) and 2.8 (2.2-3.6), respectively. Since the SIRs were almost the same for sex-neutral cancers, the results for men and women were combined. The highest risks after diagnosis of DM were for ovarian, lung, pancreatic, stomach, and colorectal cancers, and for lymphomas. However, the relative risk of many other malignant diseases was also raised. The SIR for the entire follow-up for PM was 1.4 (95% CI 1.0-1.8) for men and 1.2 (0.9-1.6) for women. The greatest increased risks were for non-Hodgkin lymphoma and lung and bladder cancers. In contrast with DM, there was no increased risk for ovarian, colorectal, stomach, or pancreatic cancers.

In the Finnish series, the five-year survival rate for PM was 75% (95 % CI: 68 to 81%) and that for DM 63 % (50 to 73 %), and the ten-year survival rates were 55 % (47to 62 %) and 53 % (41 to 64 %), respectively. The median time of survival for PM was 11.0 (95 % CI: 9.5 to 13.3) years and that for DM 12.3 (5.5 to 20.7) years. The patients with DM had a 1.47- fold (95 % CI: 0.99 to 2.12) age- and sex-adjusted mortality rate compared to those with PM (p=0.08). The standardized mortality ratio (SMR) for the combined group of PM and DM was 2.92 (95 % CI: 2.48 to 3.44).

Apart from age in both diagnosis groups, delay in diagnosis and initial dose of corticosteroid in the PM group, no other individual factor reached significance as prognostic of death. However, cancer had a hazard ratio of 2.16 (95% CI: 0.95 to 4.50) in the DM group and a hazard ratio of 1.99 (95% CI: 1.01 to 3.94) in the PM group.

The most common main causes of death for both PM and DM patients were circulatory diseases (37 and 31%, respectively) and the musculoskeletal disease itself (29 and 31%, respectively). The patients with DM had excess mortality from cancer compared to the patients with PM, cancer being the main cause of death in 33% and 9% of the patients, respectively.

In the Finnish series, twenty-six (10%) of the 248 patients with myositis had a history of tuberculosis (TB), nineteen of them had PM and seven had DM. Eighteen out of the 26 patients had TB in their disease history and eight additional subjects had chest radiological signs suggestive of earlier TB. However, there were no cases with recent TB before the diagnosis of myositis.

After the diagnosis of myositis, 13/176 (7.4%) patients with PM were documented to have a mycobacterial infection, but only one of them was among the group with a history of tuberculosis, in this case as long as 57 years earlier. 2/72 (2.8%) patients with DM had a TB infection (without an earlier history of TB). This means that altogether 40 (16%) of all the 248 patients with PM/DM had suffered from mycobacterial infections. The cumulative probability of mycobacterial infections

among the patients with PM was 4.8% (95% CI 2.4 to 9.4%) in 5 years and 9.3% (95% CI 5.4 to 15.6%) in 10 years.

In conclusion, the results of this study on the epidemiology of PM and DM in the Finnish population confirm earlier findings from other ethnic populations. The risk of cancer is significantly increased during the first year and declines steadily over the years subsequent to the initial diagnosis of myositis. DM, rather than PM, is more commonly associated with malignancy. Cancers of the gastrointestinal tract, lung cancer, ovarian cancer and non-melanoma skin cancer are the most often noted ones in patients with DM. According to the findings of the present study, patients with PM are at an increased risk of TB and other mycobacterial infections also in non-endemic countries for TB. This also raises the question of the role of a mycobacterial infection as an aetiological factor of myositis.

## 2. TIIVISTELMÄ (ABSTRACT IN FINNISH)

Poly- ja dermatomyosiitti Suomessa – väitöskirjaan on koottu sairaaloiden poistoilmoitusrekisteristä Suomessa vuosina 1969–1985 poly- (PM) ja dermatomyosiittiin (DM) sairastuneet ja tutkittu näiden tautien kuolleisuus, kuolinsyyt, syöpäriski ja ennusteeseen liittyvät riskitekijät. Syöpärekisteriä ja Tilastokeskuksen väestörekisteriä käytettiin syöpätapausten esiintyvyyden ja kuolinsyiden selvittämisen apuna. PM:n ja DM:n seuranta tapahtui edellä mainittujen rekisterien osalta elokuun 1995 loppuun ja pohjoismaisen yhteistutkimuksen osalta v 1997 loppuun. Myosiittien kokonaismäärä kotimaisissa osatutkimuksissa vaihteli 311:stä 316:een sisältäen maksimissaan 176 PM- ja 72 DM-potilasta.

Suomessa myosiittiin liittyvä syöpäriski näytti kohdistuvan pääasiassa DM:iin hematologisia pahanlaatuisia sairauksia lukuun ottamatta. Lisääntynyt syöpäriski todettiin vain yli 50-vuotiailla DM-potilailla ja erityisesti maha-suolikanavan [vakioitu ilmaantuvuussuhde; standardized incidence ratio (SIR) 9.0, 3.6–19], keuhkojen (SIR 10, 2.1–29), munasarjojen (SIR 32, 8.7–82) ja ei-melanooman ihosyövän (SIR 29, 3.6–106) sairastumisriski todettiin kohonneeksi.

Jotta myosiitteihin liittyvää syöpäriskiä voitiin arvioida kattavammin, yhdistettiin Ruotsissa, Tanskassa ja Suomessa kootut syövän esiintyvyyttä koskevat aineistot.

Nämä aineistot perustuivat kansallisiin rekisteritietoihin ja yleisesti hyväksyttyyn Bohanin ja Peterin (1975) julkaisemaan PM-DM – luokitukseen. Pohjoismaisessa yhteistutkimuksessa todettiin DM:iin sairastuneilla kolminkertainen riski sairastua pahanlaatuiseen sairauteen kaikissa syöpätyypeissä, miehillä SIR 3.3 (95 % luottamusväli (CI): 2.5–4.4) ja naisilla SIR 2.8 (2.2–3.6). Koska riski sairastua syöpään oli sukupuolesta riippumattomissa syövissä likimain sama, miesten ja naisten tulokset voitiin yhdistää. DM diagnoosin jälkeen suurin sairastumisriski liittyi munasarjojen, keuhkojen, haiman, mahalaukun ja paksusuolen syöpiin ja lymfoomiin, mutta myös monen muun syövän osalta riski oli kohonnut. PM:a sairastavilla miehillä oli koko seuranta-aikaa koskeva syöpäriski kohonnut, SIR 1.4 (95 % CI 1.0–1.8) ja naisilla SIR 1.2 (0.9–1.6). PM:ssa suurin riski oli sairastua non-Hodgkin lymfoomaan, keuhkosyöpään ja virtsarakon syöpään. Päinvastoin kuin DM:ssa, PM:ssa ei todettu lisääntynyttä riskiä munasarjojen, paksusuolen, mahalaukun tai haimasyövän osalta.

Suomalaisessa tutkimuksessa PM:n 5-vuotis eloonjäämisprosentti oli 75 % (95 % CI: 68–81%), DM:n 63 % (50–73%). 10-vuotis eloonjäämisprosentti oli PM:n osalta 55 % (47–62) ja DM: osalta 53 % (41–64). Mediaani elinaika oli PM:ssa 11.0 vuotta (95 % CI: 9.5–13.3) ja DM:ssa 12.3 vuotta (5.5–20.7). DM-potilailla oli 1.47 – kertainen (95 % CI: 0.99–2.12) ikä- ja sukupuolivakioitu kuolleisuus PM:iin verrattuna (p=0.08). Vakioitu kuolleisuussuhde [standardized mortality ratio (SMR)] PM ja DM:n yhteisaineistossa oli 2.92 (95 % CI: 2.48–3.44).

Kuoleman ennusteen kannalta todettiin tilastollisesti merkittävinä riskitekijöinä ikä (sekä PM:ssa että DM:ssa) ja PM:ssa myös diagnoosin viivästyminen ja kortikosteroidin aloitusannos. Syövän riski oli kohonnut erityisesti DM:ssa [riskisuhde (HR) 2.16 (95 % CI: 0.95–4.50)].

Pääasialliset peruskuolinsyyt PM-DM:iin sairastuneilla olivat verenkierto-elinsairaudet (37 % PM:ssa ja 31 % DM:ssa) sekä lihassairauden lihasheikkouteen liittyvät syyt (29 % ja 31 %). DM-potilailla todettiin lisääntynyt syöpäkuolleisuus PM-potilaisiin verrattuna (33 % vs. 9 %).

Suomalaisessa aineistossa 248 PM-DM:iin sairastuneen joukossa oli 26 (10 %) sairastanut tuberkuloosin, 19:llä PM ja 7 DM:llä. Näistä potilaista 18:lla oli maininta tuberkuloosista sairauskertomuksessa ja 8:lla oli keuhkokuvassa tuberkuloosiin sopivat muutokset.

Ainuttakaan myosiitti-diagnoosia edeltävää tuoretta tuberkuloosi-tapausta ei kuitenkaan voitu todeta.

PM-DM-diagnoosin jälkeen 13/176 (7.4 %) potilaalla todettiin olevan mykobakteeri-infektio, mutta vain yksi näistä oli aiemmin sairastanut tuberkuloosin (TB) 57 vuotta aiemmin. DM-potilaista 2/72 (2.8 %) sairastui tuberkuloosi-infektioon eikä näillä ollut aiempaa TB-historiaa. Kaiken kaikkiaan 40:lla (16 %) PM-DM potilaalla 248:sta oli ollut mykobakteeri-infektio. 5-vuoden kumulatiivinen mykobakteeri-infektion todennäköisyys PM-potilailla oli 4.8 % (95 % CI 2.4 – 9.4) ja 10-vuoden 9.3 % (95 % CI 5.4 – 15.6).

Tämän väitöskirjan löydökset tukevat sitä, että PM ja DM saattavat olla osa paraneoplastista syndroomaa. Syöpäriski on merkittävästi noussut PM-DM diagnoosin ensimmäisen vuoden aikana ja laskee seuraavien vuosien aikana. Tämä työ vahvistaa aiempia löydöksiä siitä, että pahanlaatuinen sairaus liittyy useammin DM:iin kuin PM:iin. Suomalaisessa tutkimuksessa todettiin dermatomyosiittiin sairastuneilla odotettua useammin mahasuolikanavan syöpää, keuhkosyöpää, munasarjasyöpää ja ihosyöpiä melanoomaa lukuun ottamatta. Pohjoismaisessa tutkimuksessa näiden löydösten lisäksi todettiin non-Hodgkin lymfoomaa sekä PM:ssa että DM:ssa, ja keuhkosyöpää sekä virtsarakon syöpää PM:ssa. Tämän tutkimuksen mukaan DM:n sairastuneilla on suurempi riski kuolla syöpään kuin PM:n sairastuneilla. Sekä PM:ssa että DM:ssa syövän ohella ennustetta heikentävästi vaikuttivat vanhempi sairastumisikä ja PM:ssa lisäksi hoidon viivästyminen sekä kortikosteroidin aloitusannos. PM:iin ja DM:iin sairastuneilla on lisääntynyt riski sairastua tuberkuloosiin ja muihin mykobakteeri-infektioihin, tuberkuloosin osalta myös non-endeemisissä maissa. Tuberkuloosin reaktivaation tai uuden mykobakteeri-infektion mahdollisuus tulee huomioida immunosuprimoiduilla potilailla kuten myosiittia sairastavilla.

## 3. LIST OF ORIGINAL PUBLICATIONS

I Airio A, Pukkala E and Isomäki H (1995): Elevated cancer incidence in patients with dermatomyositis: A population based study. J Rheumatol 22:1300-1303.

II Hill CL, Zhang Y, Sigurgeisson B, Pukkala E, Mellemkjaer L, Airio A, Evans SR and Felson DT (2001): Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet 357:96-100.

III Airio A, Kautiainen H and Hakala M (2006): Prognosis and mortality of polymyositis and dermatomyositis patients. Clin Rheumatol 25:234-239.

IV Airio A, Kinnula V, Kauppi M, Kautiainen H and Hakala M (2007): High association of mycobacterial infections with polymyositis in a non-endemic country for tuberculosis. Ann Rheum Dis 66:1404-1405

## 4. ABBREVIATIONS

| | |
|---|---|
| ALAT | alanine aminotransferase |
| ASAT | aspartate aminotransferase |
| ANF | antinuclear factor |
| CK | creatine kinase |
| DM | dermatomyositis |
| ECG | electrocardiography |
| EFNS | European federation of neurological societies |
| EMG | electromyography |
| ESR | erythrocyte sedimentation rate |
| IBM | inclusion body myositis |
| ICD | international classification of diseases |
| IIM | idiopathic inflammatory myopathy |
| ILD | interstitial lung disease |
| IL-1 | interleukin-1 |
| IP | interstitial pneumonitis |
| LD | lactate dehydrogenase |
| MAA | myositis-associated autoantibody |
| MRI | magnetic resonance imaging |
| MSA | myositis-specific autoantibody |
| PM | polymyositis |
| RA | rheumatoid arthritis |
| RR | relative risk |
| SGOT | serum glutamic oxaloacetic transaminase (ASAT) |
| SIR | standardized incidence ratio |
| SMR | standardized mortality ratio |
| SRP | anti-signal recognition particle |
| TNF | tumor necrosis factor |
| UIP | usual interstitial pneumonia |

## 5. INTRODUCTION

Polymyositis (PM) and dermatomyositis (DM) are rare rheumatic diseases characterised by chronic inflammation of skeletal muscles. The inflammation chiefly affects the striated muscle and usually leads to symmetrical weakness and varying grades of muscle atrophy. The aetiology of these inflammatory myopathies is unknown.

The heterogeneity of the oldest classifications of myositis makes it difficult to compare mortality between the earlier studies and the later ones. However, since the Bohan and Peter classification (Bohan and Peter 1975 part I), the comparison of mortality between epidemiological studies has been more precise and reliable. The death rate in PM and DM usually seems greater than in normal population (Carpenter et al.1977). Most studies have shown older age, delay in beginning therapy and dysphagia or severe muscle weakness to be poor signs for outcome in PM and DM (Carpenter et al. 1977).

The association between cancer and myositis was described as early as 1916 by Sterzt. The frequency with which malignancy and idiopathic myositis coexist varies in different studies and has been a subject of debate (Bohan and Peter 1975 part II).

Cardiovascular and pulmonary complications and malignancy are the most common causes of mortality related to PM and DM (Benbassat et al. 1985, Sigurgeirsson et al. 1992). The prognosis for patients with an interstitial lung disease (ILD) and myositis varies, however. ILD is considered to be a major risk factor for premature death in patients with myositis (Marie et al. 2002). Comparing mortality between PM and DM, the main difference comes from increased mortality due to cancer in DM (Sigurgeirsson et al. 1992)

The present study is a population-based one focusing on evaluating the mortality and prognosis of PM and DM and the conditions comorbid with PM and DM.

# 6. REVIEW OF LITERATURE

## 6.1. Epidemiology of polymyositis and dermatomyositis

The overall annual incidence of PM and DM in adults ranges from 0.1 to 1.0 new cases per 100.000 persons in different populations (Pearson 1963, Kurland et al. 1969, Medsger Jr et al. 1970, Benbassat et al. 1985, Lyon et al. 1989, Plotz 1989, Oddis et al. 1990, Urbano-Marquez et al. 1991, Kusumi et al. 1995, Kaipiainen-Seppänen and Aho 1996, Weitoft 1997, Patrick et al. 1999, Silman 2001, Flachenecker 2006, Gaubitz 2006). The incidence of juvenile DM is around half that seen in adult studies, i.e. 0.2-0.3 new cases per 100.000 (Pelkonen et al. 1994, Symmons et al. 1995, Silman 2001). The studies of incidence are predominantly based on ascertaining diagnosed cases attending specialist centres and relating these to the presumed catchment population of these centres. However, there has been a trend towards increasing incidence of PM and DM in several communities. It has been explained by the increased availability of skeletal muscle laboratory testing, increased physician awareness and also a true increase in incidence (Oddis et al. 1990, Cronin and Plotz 1990). The prevalence of PM and DM is estimated to be 5-10/100.000 (Kurland et al. 1969, Henriksson 1980, Kusumi et al. 1995, Wilson et al. 2008), based on epidemiological studies using the Bohan and Peter criteria (1975).

PM and DM can occur at any age; however, there is a bimodal distribution with a small peak between the ages of 10 and 15 in children and a greater one between the ages of 45 and 60 in adults. Adult PM and DM are more common in women; the female to male incidence ratio is about 2.5:1. The preponderance of female cases has been attributed in part to a greater frequency of PM and DM among black women in the U.S. (Medsger Jr et al. 1970, Oddis et al. 1990), but racial differences are not marked in all of the reported series of cases (Hochberg 1986, Lyon et al. 1989).

According to a large epidemiological study (Medsger Jr et al. 1970), genetic and hormonal factors, but not the size of family or socioeconomic or other environmental factors, may play an important role in the expression of PM and DM (Hochberg et al. 1983b, Oddis et al. 1990). Familial occurrence has only rarely been reported (Lambie et al. 1963, Lewkonia and Buxton 1973).

In their study, Hengstman et al. (2000) found a significant increase in the prevalence of DM and PM in relation to geographical latitude going from northern Europe to southern Europe. The cause of this gradient is unknown, but they emphasized that it could include environmental as well as genetic factors.

In most autoimmune diseases the strongest risk factor is the presence of particular MHC alleles. The analysis of gene expression by microarray may help in the diagnosis since PM, DM and inclusion body myositis (IBM) have a distinct gene expression pattern (Greenberg et al. 2002). Among the idiopathic inflammatory myopathy (IIM) -associated alleles published first were HLA-B8 of the MHC-I class and HLA-DR3 of the MHC type II class among juvenile DM patients (Friedman et al 1983). Later, HLA-DRB1*0301 and HLA-DQA1*0501 alleles have been described in connection with IIMs and the increased incidence of these alleles has been described in American and European Caucasoid patients (Friedman et al. 1983, Reed et al. 1991, Arnett et al. 1996, Hausmanowa-Petrusewicz et al. 1997). Genetic factors appear to identify distinct serologic subsets of PM and DM with different clinical features and, possibly, different responses to treatment and different prognoses (Love et al. 1991).

### 6.2. Aetiology

There is little definitive knowledge regarding the aetiology of PM and DM**.** It is thus possible and even likely that there are multiple etiologic factors for these diseases. Two groups of environmental factors, i.e. infection and exposure to chemicals and other agents, have been linked to the development of PM and DM.

In the study by Patrick et al. (1999) of 94 cases concerning the incidence of idiopathic inflammatory myopathies in Victoria, Australia, there was evidence of spatial clustering supporting the hypothesis that environmental factors may be important in the pathogenesis of these diseases. Leff et al. (1991) studied the geographic and seasonal clustering of 111 patients with myositis and observed significant differences according to the presence of anti-Jo-1 and anti-SRP

autoantibodies. Myositis onset in SRP-positive patients clustered significantly in the fall (58% of cases in November), in contrast to the predominancy of spring onset of IIM in anti-Jo-1 patients and summer onset in 31% of patients without myositis-specific autoantibodies.

Several hypotheses have been formulated in order to understand the possible mechanism by which pathogens may induce an autoimmune response in individuals with a particular genetic background. The microorganism could interact with cellular proteins in the host inducing changes in the proteins which are no longer recognized as "self" by the host immune system; or it could make clustered cellular antigens accessible to the immune system which has never learnt to recognize them as self proteins; or it could induce the production of human antibodies carrying pathogenetic idiotypes; or it could have antigenic sites that mimic aminoacid sequences in the normal host proteins (molecular mimicry) (Mathews and Bernstein 1983, Plotz 1983).

There is some evidence that infectious agents, the most notable among which are viruses affecting the respiratory tract (Hashimoto et al. 1971, Ben-Bassat and Machtey 1972, Gamboa et al. 1979**,** Kessler et al. 1980), may be important in the causation of PM and DM. Among the viruses suspected in the pathogenesis of IIMs, the retroviruses, HIV and HTLV-1 (Dalakas et al. 1986, Ishii et al. 1991, Caldwell et al. 1996), are implicated most strongly. Tissue is not infected directly by the virus but instead, the virus triggers a T-cell mediated inflammatory response. Although an unidentified virus may be responsible for PM or DM, viral DNA has not yet been detected in the muscle fibres of these patients. However, the possibility exists that a virus which triggers the immune response may not reside within the affected tissue but in the circulatory system or in other sites.

The role of viruses, for example picornaviruses such as Coxsackie B, has been implicated in the cause of myositis by the finding that the RNA of a murine picornavirus interacts with histidyl-tRNA synthetase, i.e., the Jo-1 antigen (Mastaglia and Walton 1970, Tang et al. 1975**,** Nishikai 1994,). Such a combination of host protein with RNA from a myotropic virus such as Coxsackie might well generate an autoimmune response and explain the link between antibody and disease (Mathews

and Bernstein 1983). Among other possible infectious agents are paramyxoviruses (Hashimoto et al. 1971), echovirus, mengovirus, adenovirus, hepatitis B (Nojima et al. 2000) and hepatitis C viruses (Nishikai et al. 1994), borrelia, Toxoplasma (Kagen et al. 1974, Phillips et al. 1979, Magid and Kagen 1983).

It has recently been shown that intracellular bacteria such as Mycobacterium tuberculosis are able to induce apoptosis in infected macrophages which deliver microbial antigens through apoptotic blebs to non-infected dendritic cells (Winau et al. 2004), which are displaying microbial antigens via MHC I and CD1 molecules as antigen-presenting cells. This apoptotically-triggered presentation of antigens activates CD8 T-cells promoting protective immunity. Thus, dysregulation of this apoptotic process may represent a potential link between infections, apoptosis and autoimmunity (Mahoney and Rosen 2005). However, there are no reports of mycobacterial infections as triggers of inflammatory myositis.

There have also been reports of onset of PM and DM after vaccination and after exposure to certain drugs (Lane and Mastaglia 1978**,** Petersen et al. 1978), but the data of Lyon et al. (1989) did not support the role of vaccinations as important antecedents to PM and DM.

The study of Lyon et al. (1989) found a negative association of upper respiratory infection, sore throat and allergic phenomena with PM and DM, whereas antecedent emotional stress and muscular exertion suggested a positive correlation with PM and DM**.** Okada (2003) found in his study that global UV light levels predict the proportion of DM around the world.

There are few reports that dermatomyositis-like cutaneous eruptions may be caused by or exacerbated by drugs. This has been best documented for hydroxyurea in the case of which de-challenges and re-challenges have been done (Dauoud et al. 1997, Oskay et al. 2002**,** Dacey and Callen 2003). Quinidine, non-steroidal anti-inflammatory drugs (Grob et al. 1989), D-penicillamine and 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors (HMGCoA), penicillins, sulphonamides, isoniazid, tamoxifen, antazoline, chlorpromazine, clemizol,

phenylbutazone and, more recently, interferon-α2B therapy (Dietrich et al. 2000) have also been linked to DM.

### 6.3. Pathophysiology

The pathophysiology of PM and DM is unknown, although immunological mechanisms are thought to be involved in their pathogenesis. Studies of their pathogenesis are controversial; some suggest that the mechanism of myopathy in these diseases differs, DM being caused by vascular inflammation (Dalakas 1998), whereas other studies on cytokines suggest that the processes are rather similar (Lundberg and Nyberg 1998). Whatever the mechanisms are that result in idiopathic inflammatory myopathies, they must be consistent with the pathology that is seen (Dalakas 2002). The pathology in the muscle, skin and other affected tissues is characterized by collections of mononuclear cells (Engel and Hohlfeld 2004). Immunohistochemical and other investigations implicate different pathogeneses in the various forms of myositis (Engel et al. 1990, Dalakas and Hohlfeld 2003, Miller 2004). It is widely accepted that polymyositis is a T-cell-mediated disease in which a cellular immune response is a key feature in promoting muscle pathology (Dawkins and Mastaglia 1973, Arahata and Engel 1986, Engel and Arahata 1986). Dermatomyositis pathology appears to be derived primarily from a humoral immune response and antibodies are directed against immune complexes deposited in blood vessel walls (Arahata and Engel 1986, Engel and Arahata 1986, Christopher-Stine and Plotz 2004). Immunohistochemical studies on muscle biopsies have shown that in PM the majority of T-cells locating in the endomysium, surrounding and invading nonnecrotic myofibres, are CD8+ T-cells. In contrast, in DM, muscle tissue specimens show mostly CD4+ and B -lymphocytes in the perimysium and in the perifascicular area (Arahata and Engel 1986, Engel and Arahata 1986). In contrast to PM and DM, abnormal immune response seems to be secondary in IBM (Dalakas 1995, Barohn 1997).

It is unlikely that the normal muscle tissue would be the site of the initiation of autoimmunity. Rather, it is more likely that damaged muscle in which there are areas of regeneration provides a source of antigen, which itself may also influence the local

inflammatory context (Casciola-Rosen et al. 2005). In their study, Casciola-Rosen et al. (2005) also found that the expression of myositis autoantigens was markedly increased in several cancers associated with autoimmune myositis compared to the levels detected in corresponding normal tissue. This finding has lead the authors to the hypothesis that undifferentiated myoblasts and tumour cells are antigenically similar and the autoimmune response directed against cancer cross-reacts with regenerating muscle cells to produce a feed-forward cycle of tissue damage and antigen selection. In addition to the influence on their autoimmune state, patients with PM and DM may be prone to have certain tumours in consequence of immunosuppressive or cytotoxic therapy (Kinlen 1992).

### 6.4. Diagnosis and classification of polymyositis and dermatomyositis

Since the original descriptions by Wagner and Unverricht in 1887, PM and DM have become well recognized disease entities. However, there have been several classifications of PM and DM that have stressed differing views of the relative importance of various clinical and pathological findings. The earliest clinical classifications were prepared to accept non-specific or even normal muscle biopsy findings on the basis that the disease may have a patchy distribution, and in occasional cases, myositis was not verified until a second biopsy (Eaton 1954, Barwick and Walton 1963, Pearson 1963, Rose and Walton 1966). Rose and Walton divided PM and DM into four groups. Myositis was classified into groups I and II also including children, cases with overlap syndromes were in group III, and myositis with malignancy was in group IV. Denny-Brown (1960) preferred a pure histological classification.

According to the Bohan and Peter classification (1975), the diagnosis of PM and DM is based on progressive, proximal symmetrical muscle weakness, an increased serum concentration of muscle enzymes, an abnormal electromyography (EMG), an abnormal muscle biopsy sample and, in the case of DM, a rash on the face, neck, anterior chest and the extensor surface of the arms. Bohan and Peter suggested five subsets of myositis – PM, DM, myositis with cancer, childhood DM and PM, and

myositis overlapping with another collagen-vascular disorder. DM and PM were thought to differ from each other only by the presence of a cutaneous disease. These categories may then be further defined as “definite” (fulfilling 4 of PM and 4-5 of DM criteria), “probable” (fulfilling 3 of PM or DM criteria) or “possible” (fulfilling 2 of PM or DM criteria) according to the presence or absence of the five criteria for diagnosis listed above. After much discussion, most authorities agreed to use the Bohan and Peter criteria for disease classification.

Recently, however, this topic has again become an object of increasing debate (Dalakas 1991, Targoff et al. 1997, Maddison 2001, Amato and Griggs 2003, Miller et al. 2003). The Bohan and Peter classification has been criticized for overdiagnosing PM (van der Meulen et al. 2003**,** Troyanov et al. 2005); for clinical, genetic, and immunologic heterogeneity in all subsets (Love et al. 1991); for loosely defining myositis in overlap with another connective tissue disease (Medsger Jr and Oddis 1995); and for being obsolete (Kissel 2002**).** Mastaglia and Phillips (2002) proposed their classification and diagnostic criteria of idiopathic inflammatory myopathies based on clinicopathologic findings including focal and diffuse varieties of IIMs. Dalakas and Hohlfeld (2003) revised the criteria including immunopathological findings and emphasized the role of the MHC/CD8 complex as a specific marker which allows differentiating the antigen-driven inflammatory cells characteristic of polymyositis and inclusion body myositis from the non-specific, secondary inflammatory response present in other muscular diseases, such as dystrophies. In a review of inflammatory myopathies, Dalakas (2004) claimed that most of the patients misdiagnosed as PM were eventually found to be suffering from IBM, dystrophic, toxic or metabolic myopathies.

It is to be noted that inclusion body myositis is now recognized as the most commonly acquired muscle disease in adults at the age of 50 or older and it accounts for up to one third of cases of inflammatory myopathy (Dalakas 1992, Dalakas and Hohlfeld 2003). In contrast to PM, patients with IBM have involvement of distal muscles such as the finger flexors more commonly. These patients are usually more resistant to corticosteroid treatment than those with PM (Siwakumar and Dalakas 1997). Also, IBM combines features of inflammation and vacuolar degeneration with

accumulation of pathological proteins similar to changes seen in Alzheimer´s disease (Oldfors and Lindberg 2005).

Although not included in Bohan and Peter's (1975) original classification, amyopathic DM was acknowledged by them in 1977. Amyopathic DM has been more fully described since (Euwer and Sontheimer 1991), and it is now routinely included in classification schemes of IIMs (Wortmann 2008). There are also other unique presentations of DM, including drug-associated DM (Dourmishev and Dourmishev 1991**,** Ruiz-Genao et al. 2002**,** Oskay et al. 2002) and the Wong type of DM (Wong 1969**,** Lupton 2000). Some rarer myositis varieties such as granulomatous, eosinophilic and angiopathic myositis and focal forms of myositis affecting the ocular or limb muscles have been described by Mastaglia and Ojeda (1985).

The discovery of the association of clinical features, immunogenetics and survival with myositis-specific autoantibodies (MSAs[1]) (Table 1) and other myositis-associated autoantibodies (MAAs[2]) (Table 2) (Bernstein et al. 1984, Hochberg et al. 1984, Reichlin and Arnett 1984, Targoff and Reichlin 1985, Targoff et al. 1988, Targoff et al. 1990, Targoff 1994, Hengstman et al. 2001) has led to the proposal of a serologic approach complementary to the Bohan and Peter classification of IIMs (Love et al. 1991, Targoff et al. 1997, Gunawardena et al. 2008, Oddis 2008). MSAs may be absent in overlap manifestations and there may be a heterogeneous group of MSA- and MAA-negative patients with undefined diagnoses, prognoses and survival (Brouwer et al. 2001). That is why Troyanov et al. (2005) proposed a modified, clinicoserologic approach to Bohan and Peter's classification, encompassing overlap-autoantibodies, autoantibodies to synthetases, systemic sclerosis-associated autoantibodies, anti-SRP and anti-nucleoporins in IIMs, and thereby showed that much of IIM is actually composed of overlap myositis. However, until now the use of these antibodies has been limited by the lack of automated tests and they have been confined mainly to research studies.

[1] MSAs such as anti-aminoacyl transfer RNA synthetases (ARS), most commonly anti-Jo 1, anti-Mi-2 directed against a nuclear helicase, anti-signal recognition particle (anti-SRP)
MAAs such as anti-polymyositis/Scl (anti-PM/Scl), anti-Ku, anti-U1-ribonucleoprotein (anti-U1-RNP) and others such as anti-U2-RNP, anti p155 and anti-MJ antibodies

### 6.5. Malignancy

The association between cancer and myositis was described as early as 1916 by Sterzt, who called attention on PM and ventricular malignancy. Improvement of DM after the treatment of an associated malignancy was first described by Bezecny (1935). The most common sites for associated neoplasms according to a literature-based study of Williams Jr (1959) were the stomach, breast, ovaries, lung, reticuloendothelial system, gall-bladder, colon and rectum and kidney, in that order. Later, in a literature-based meta-analysis of 258 cases of DM associated with malignancy, Barnes (1976) found that the distribution of tumours at various sites significantly differed from that of the general cancer population. Tumours of the ovary and the stomach were more frequently observed than in the general population, while colorectal malignancies were underrepresented. In the Asian PM/DM population the most frequent type is, however, nasopharyngeal carcinoma (Peng et al. 1995, Ang et al. 2000, Chen et al. 2001), which leads us to conclude that both the genetic background and the different nutritional habits may play a role. DM associated malignancy appears to be twice as likely in women as in men (Sparsa et al. 2002).

Although some forms of PM and DM are thought to be paraneoplastic syndromes, the elevated cancer detection may also result in part from increased cancer surveillance, selective referral practices in clinic-based studies or altered immunity of PM and DM patients (Manchul et al. 1985, Lakhanpal et al. 1986, Butler et al. 1987**,** Masi and Hochberg 1988, Callen 1991, Bernard and Bonnetblanc 1993, Zantos et al. 1994, Casciola-Rosen et al. 2005)**.** Myopathy and cancer usually appear within one year of each other (Bohan et al. 1977, Sigurgeirsson et al. 1992, Bonnetblanc et al. 1990), with most cancers seen in persons over the age of fifty (Masi and Hochberg 1988). Whitmore et al. (1996) in their case series study of DM sine myositis warranted a potential association with malignancy, similar to classic DM.

The following explanations have been given for the association between myositis and malignancy (Naschitz et al. 1999): 1) Paraneoplastic syndromes – bioactive mediators produced by the tumor - induce immune reactions against muscle fibre and skin. 2) The causal role of the compromised immune system in the outbreak of the

tumor and the myositis. 3) Malignant transformation induced by the second-line cytotoxic agents used in the treatment of myositis. 4) Common environmental factors that are carcinogenic and can play a role in triggering an immune reaction at the same time. 5) An immune reaction against the tumor transforming into an autoimmune syndrome as a consequence of cross-reactivity with skin and muscle antigens.

In earlier studies, the incidence of cancer in myositis varies from 5% to 71% (Brunsting et al. 1956, Williams Jr 1959, Arundell et al. 1960, Barwick and Walton 1963, Rose and Walton 1966, Logan et al. 1966, Winkelmann et al. 1968, DeVere and Bradley 1975). The data are, however, not reliable and comparable because patients with different classification criteria as well as juvenile and overlap cases all were included. Later on, Lyon et al. (1989) questioned the association of malignancy with PM and DM in their study of 322 patients. However, this study rested on mail survey methodology and was only a cross-sectional evaluation in terms of the cancer issue. It only covered a period of one year before disease onset and may have missed some cases of PM and DM that had early fatal courses, or additional cases with malignancy developing after the survey was completed. The authors themselves also thought it likely that their survey underestimated the true number of cancer cases. Lakhanpal et al. (1986) suggested that there may be a tenuous association only, if any, between PM and DM and malignant disease and that a diagnostic suspicion bias may contribute to this result. This opinion is supported by other investigators as well (Manchul et al. 1985). The study of Manchul et al. (1985), however, again found an association between PM and DM and malignant neoplasms, but the association was largely with malignant neoplasms diagnosed at or before the time of diagnosis of PM or DM and the authors call for more prospective studies.

More recently, in a nationwide cohort study in Denmark by Chow et al. (1995) with 539 patients with PM or DM, a significant excess was observed in cancers of the lung, the ovary, and the lymphatic and haematopoietic system. The overall cancer risk was elevated significantly among patients with DM [standardized incidence ratio (SIR) =3.8, CI=2.6-5.4] and to a lesser extent with PM (SIR=1.7, 95% CI=1.1-2.4). The term SIR here means the observed cancer cases with myositis divided by the expected number of cases according to the national age-specific, sex-specific and period-specific cancer rates.

During the first year after the diagnosis of myositis, the cancer risk was increased nearly six-fold (SIR=5.9, 95% CI=3.8-8.7). It was again lower during the second year (SIR=2.5, 95% CI=1.1-4.8), but still, from the third year onwards there was a 50% excess in the cancer risk (SIR 1.5, 95% CI 0.8-2.6). In a population-based study from Sweden (Sigurgeirsson et al. 1992), a two-fold risk of cancer compared to that in the general population was found within five years after the diagnosis of PM, and as to DM, the risk was four-fold.

The incidence of malignancy in studies after the publication of Bohan and Peter's classification (1975) is shown in Table 3.

Based on the findings above, an assessment of malignant disease should be done in all adult patients with DM in clinics (Callen 1982) and the type of assessment should be selected on the basis of the patient's age and gender (Callen 1984). A work-up for malignancy should not be overlooked in amyopathic dermatomyositis patients, either, although malignancy does not appear to occur as frequently in these patients as in those with classic DM (el-Azhary and Pakzad 2002, Chakravarty and Genovese 2003). A cutaneous finding of true leukocytoclastic vasculitis is exceedingly rare when DM occurs in adults, which supports the hypothesis that DM has a strong association with an underlying malignancy (Hunger et al. 2001, Feldman et al. 1983).

Autoantibodies that appear to be strongly associated with an increased risk of malignancy in adults with DM have recently been identified against a 155-kD protein (Targoff et al. 2006, Kaji et al. 2007)**.**

### 6.6. Clinical findings in PM and DM

#### 6.6.1.1. Clinical findings in PM

PM is best defined as a subacute myopathy that evolves over weeks or months, affects adults but rarely children, and presents with symmetrical and diffuse weakness of the proximal muscles of the body. The actual onset of PM cannot be

easily defined, unlike DM, in which the rash secures an early recognition (Dalakas 1991). Characteristically, patients complain of an inability to rise from a chair, to climb stairs and to raise the arms above their heads. Muscle pain is infrequent.

There are two types of oesophageal disease – proximal dysphagia and distal dysphagia. The former is caused by the involvement of the striated muscle of the proximal oesophagus and correlates with the severity of the muscle disease. Proximal dysphagia is responsive to steroids. Distal dysphagia is related to the involvement of the non-striated muscle and seems to be more common in those myositis patients whose disease associates with some other collagenosis such as scleroderma. The overall frequency of dysphagia has been reported to be as high as 25% to 60% in PM and DM (Marie et al. 1998, Marie et al. 1999a, Sonies 1997) and to be associated with the presence of pulmonary involvement. Dysphonia reflects the involvement of the striated muscle in the pharynx. Dysphagia and dysphonia generally signify a rapidly progressive disease course of myositis (Callen 2000).

Generalised arthralgias accompanied by morning stiffness and non-deforming arthritis of the small joints of the hands, wrists and ankles may be present in up to one quarter of patients with PM and DM.

Systemic disturbances, i.e., fever, malaise, weight loss or Raynaud´s syndrome may occur. Raynaud´s phenomenon is most commonly encountered in persons with overlap myositis. Subcutaneous or intracutaneous calcifications are sometimes seen and may be extensive and painful.

#### 6.6.1.2. Clinical findings in DM

DM affects both adults and children (Dalakas and Hohlfeld 2003). DM is identified by a characteristic rash that develops simultaneously with or follows the symptoms of myopathy or, more commonly, precedes the muscle weakness (Santmyire-Rosenberg and Dugan 2003). A heliotrope, violaceous to dusky erythematous rash around the eyelids and Gottron´s papules covering bony prominences, particularly finger joints, are characteristic and possibly

pathognomonic cutaneous features of DM. The rash may be exacerbated by exposure to sun, and a rash on the face or anterior chest, known as the V sign, may also be seen. Pruritus is common, particularly in the scalp. A disease affecting the skin only – amyopathic dermatomyositis or dermatomyositis sine myositis- may exist and amyopathic and myopathic DM are believed to be parts of the range of DM affecting skin and muscle to varying degrees (Dalakas and Hohlfeld 2003). ADM is diagnosed in patients with a typical cutaneous disease in whom there is no evidence of muscle weakness and who repeatedly have normal serum muscle-enzyme concentrations (Rockerbie et al. 1989**,** Euwer and Sontheimer 1991**,** Stonecipher et al. 1993**,** Cosnes et al. 1995).

Occasionally, when the rash is transient or poorly recognized, the term DM sine dermatitis is appropriate. In such cases, a mistaken diagnosis of PM is probable and a muscle biopsy is needed to confirm the diagnosis.

Recently, some authors have reported amyopathic dermatomyositis to be associated with ILD in the absence of other findings of the anti-synthetase syndrome (el-Azhary and Pakzad 2002).

Several other cutaneous features are characteristic of the disease, including malar erythema, a rash located over the upper back and across both shoulders (the shawl sign), violaceous erythema on the extensor surfaces, dilated capillary loops and thickened cuticles seen by magnification of fingernail bases. Some patients, particularly those with long-standing disease, develop areas of hypopigmentation, hyperpigmentation, mild atrophy, and telangiectasia known as poikiloderma.

The Wong type of DM is a rare variant of DM characterized by erythematous, hyperkeratotic, follicular papules that occur in limited or generalized distribution (Wong 1969**,** de la Tribonniere et al. 1995**,** Lister et al. 2000, Lupton et al. 2000)**.** This type of DM has been reported in adults and children both, and some reports suggest that this variant of DM may be more common in Asian patients (Lister et al. 2000).

#### 6.6.1.3. Other manifestations and complications of PM and DM

Pulmonary manifestations contribute significantly to the morbidity and mortality of patients with myositis. The symptoms may result from an intrinsic lung disease or secondary problems such as respiratory muscle weakness, aspiration pneumonia, opportunistic infection, drug-induced hypersensitivity pneumonitis or cardiac dysfunction. Dyspnoea always warrants early attention and aggressive intervention.

The overall frequency of pulmonary involvement has been reported to be as high as 5% to 46% in PM and DM (Frazier and Miller 1974, Salmeron et al. 1981, Dickey and Myers 1984, Arsura and Greenberg 1988, Tazelaar et al. 1990, Schwarz 1992, Marie et al. 1998). ILD or, more exactly, interstitial pneumonitis (IP) is a primary process seen in PM and DM. It is more frequent in patients with oesophageal involvement. IP in DM and PM can be asymptomatic, acute/subacute, or chronic. Asymptomatic IP is picked up incidentally by radiological examination. Patients with acute onset and rapidly progressive IP present with progressing dyspnoea leading to severe hypoxemia. Patients with chronic IP present a slow development of progressive respiratory failure closely resembling idiopathic usual interstitial pneumonia, i.e. UIP (Frazier and Miller 1974**,** Dickey and Myers 1984**,** Tazelaar et al. 1990, Hirakata and Nagai 2000). The rapidly progressive, diffuse alveolitis is the most worrisome complication of pulmonary diseases and may lead into adult respiratory distress syndrome (ARDS) with a poor prognosis and often a fatal outcome (Clawson and Oddis 1995). According to the results of the study of Nawata et al. (1999), corticosteroid resistant IP develops mostly in patients with DM and PM without CK elevation at onset of IP, while IP patients with CK elevation respond well to corticosteroid therapy. Idiopathic inflammatory myopathy-related ILD is closely linked to anti-synthetase antibodies. In a study, 75% of the DM patients with ILD were anti-Jo-1 positive in contrast to only 3% of those without ILD (Grau et al. 1996). The presence of the anti-Jo-1 antibody has been described as a sensitive marker of ILD in patients with PM and DM (Bernstein et al. 1984, Hochberg et al 1984, Marie et al. 1998). According to histological characterization, the most treatment-responsive conditions include bronchiolitis obliterans organizing pneumonia (BOOP), cellular interstitial pneumonitis, and alveolar haemorrhage

secondary to pulmonary capillaritis. Diffuse alveolar damage associated with ARDS is the least responsive to therapy (Fata et al. 1997, Schwarz et al. 1995)

Cardiac manifestations such as conduction defects and primarily end-rhythm disturbances may occur in up to 49% of patients (Henriksson and Sandstedt 1982), but only a small proportion of these patients have symptoms. Congestive heart failure, pericarditis and valvular disease are much less common.

### 6.6.2. Infections in PM and DM

Mainly due to therapy with corticosteroids and immunosuppressive drugs, but also due to the immune abnormalities and the organ system manifestation associated with these diseases, there is an elevated risk of opportunistic infections (Marie et al. 2005, Greenberg 2008). In case series of PM and DM patients, infectious complications have been reported in up to 30% (Callen 2000, Marie et al. 2005, Danko et al. 2004, Juarez et al 2003, Viguier et al. 2003).

There are several types of opportunistic and non-opportunistic infections that can occur in these patients. Among the non-opportunistic infections, aspiration pneumonia caused by Gram-positive and anaerobic bacteria is the most common infection, occurring in about 20% of PM and DM patients (Moore et al. 1992). Aspiration pneumonia is a potentially fatal complication of myositis related with oesophageal motor involvement and ventilatory insufficiency representing, in some cases, the principal cause of death (Marie et al. 2005, Schwarz 1998).

About 11% of PM and DM patients develop opportunistic infections (Marie et al. 2005). Fungi, Pneumocystis carini and Candida albicans, are mainly responsible for more than 50% of cases among them. Viral infections, as Herpes zoster, are usually common in PM and DM patients in the inactive phase of the disease (Nagaoka et al 1990).

Tuberculosis (TB) is a systemic disease with protean manifestations due to depressed cellular immunity. TB may either be a primary disorder or a reactivated

one associated with immunosuppression in a patient with a systemic disease or with the use of corticosteroids or immunosuppressive agents. The distinction between TB infection and TB needs to be stressed. TB infection is defined as a state in which the tubercle bacilli have become established in the body but there are no symptoms, no roentgenographic abnormalities compatible with tuberculosis, and bacteriologic studies (if done) are negative. Usually, infection can be diagnosed by demonstration of a positive tuberculin test. A definitive diagnosis of TB requires the identification of Mycobacterium (M.) tuberculosis in the patient's tissues or secretions by microscope and culture, i.e., TB indicates a state in which an infected person has an ongoing disease process which involves one or more of the organs of the body (Glassroth et al. 1980). Only about 5% to 15% of those infected ever become ill with TB (American thoracic association 1974).

According to the study of Kim et al. (1998), the most important factors linked to the development of tuberculosis are the cumulative and mean daily doses of steroid, not the patient's past history of tuberculosis or the use of cytotoxic drugs. The use of new biological drugs such as tumor necrosis-alpha (TNF-α)-blocking agents can increase the risk of patients contracting inflammations such as a latent mycobacterial infection (Jolobe 2007). There are only few small reports about co-existence of TB and PM or DM (Davidson et al. 1994), and they are predominantly from endemic countries for TB (Hernandez-Cruz et al. 1999, Mukhopadhyay et al. 2004) or deal with immigrants in a Western country (Haq and Isenberg 2002, Ravn et al. 2004). In Finland, as much as 88% of the large population of 56,417 Finnish military recruits were found to be tuberculin positive in the 1930´s, and in the 1940´s, almost 9,000 new cases of TB were detected yearly (Savonen 1937**,** Härö 2000). The systematic BCG vaccination of newborns from the 1950´s onwards has contributed to the decline of TB in Finland (Härö 1977**,** Tala-Heikkilä et al. 2001, Tala-Heikkilä 2003, Teramo 2003**).** During the recent decades the incidence of TB has progressively fallen to below 10/100000 inhabitants in 2001. While TB has become less common, new cases are detected mainly in various risk groups, the most important of which are elderly people, substance abusers, refugees and close contacts of infectious TB patients (Rajalahti et al. 2004).

There is a high proportion of extra-pulmonary TB in patients with a systemic rheumatic disease, which increases the difficulty of diagnosing and treating this infection (Hernandez-Cruz et al. 1999).

Severe immunosuppression may lead to disseminated TB such as miliary TB or other rare types of extra-pulmonary TB such as cutaneous abscesses. However, atypical mycobacteria such as M.kansasii, M.scrofulaceum, rather than M.tuberculosis are the most common etiological agents for cutaneous TB in immunocompromised patients (Mukhopadhyay et al. 2004).

Atypical mycobacterial infection is commonly seen in immunosuppressed patients. M. avium-intracellulare is a slow growing organism found in air, soil and water. Portal of entry is commonly through the gastrointestinal tract. Occasional infections caused by M. avium-intracellulare or other atypical mycobacteria have been reported in DM patients (Barcat et al. 1998, Bedlow et al. 1998, Banuls et al. 2000).

### 6.6.3. Laboratory findings

Enzymatic testing will show increases in concentrations of creatine kinase (CK), aldolase, lactate dehydrogenase (LD), aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT). CK is the most sensitive and specific test of muscle damage and the most widely used serum muscle enzyme to diagnose PM and DM and to follow the response to therapy (Bohan et al.1977, DeVere and Bradley 1975, Hudgson 1984), although some authors emphasize its unpredictability in patient management (Kagen and Aram 1987**,** Mastaglia and Laing 1996). Although most patients with PM and DM present with elevated CK, some reported series include normal CK levels at presentation (Bohan et al. 1977, DeVere and Bradley 1975, Vignos and Goldwyn 1972, Carter et al. 2001). The myocardial fraction of CK (CK-MB) may be increased in myositis without any cardiac involvement because this isoform is also released from regenerating myoblasts (Wortmann 2008). Measurements of urinary levels of creatine (Chung et al. 2003) and serum levels of myoglobin (Kagen 1977) and of soluble interleukin-2 receptors (Wolf and Baethge 1990) have also been reported to be sensitive indicators of disease activity in

idiopathic inflammatory myopathies, but they are not widely used. Fafalak et al. (1994) examined muscle strength of PM and DM patients biomechanically and found that among those who gained strength, the degree of elevation of CK correlated with greater gains.

Hidano et al. (1992) noted higher levels of ALAT in patients with PM and DM associated interstitial lung disease than in those without. In the study of Marie et al. (1998), ASAT and ferritin appeared to be significantly higher in the ILD group, particularly at the time of diagnosis of ILD. However, these findings could reflect an acute phase reaction rather than lung involvement (Marie et al 1998).

In the recent years, several clinical and epidemiologic studies have suggested that myositis-specific antibodies are associated with specific clinical characteristics (Love et al. 1991, Joffe et al. 1993). Serum autoantibodies, both MSAs and MAAs, have been detected in patients with idiopathic inflammatory myopathies allowing the definition of patient subsets (D´Cruz et al. 2000, Sato et al. 2005, Sordet et al. 2006). Autoantibodies to intracellular antigens are found in about 50% to 80% of patients with polymyositis or dermatomyositis (Love et al. 1991, Targoff 1992, Hengstman et al.1998). It has been suggested that antisynthetase autoantibodies can aid in the differential diagnosis between PM, DM and IBM by virtually excluding IBM in cases of anti-ARS positivity (Hengstman et al 1998). Anti-ARS autoantibodies are seen mainly in PM and DM, and hardly ever detected in patients with IBM (Love et al. 1991, Hengstman et al. 1998). The Jo-1 antibody, directed against the cytoplasmic enzyme histidyl tRNA synthetase, is found in 30% of PM patients and it is associated with ILD (Yoshida et al. 1983, Bernstein et al 1984).

It has been suggested that MSAs may identify distinct disease entities, i.e., anti-SRP is suggestive to PM (Targoff et al. 1990) and Mi-2 antibodies to DM (Targoff and Reichlin 1985)

### 6.6.4. Electromyographic and histopathologic findings

Electromyography **(**EMG) is a very sensitive but non-specific diagnostic tool. The most common abnormalities in myositis are irritability on needle insertion, and at rest, bizarre high frequency discharges, spontaneous fibrillations, positive sharp waves and decreased amplitude and duration of motor unit potentials on full concentration (Bohan et al. 1977).

Whatever the mechanisms are that are hypothesized to result in idiopathic inflammatory myopathy, the most conclusive evidence of myositis is provided by an open muscle biopsy or biopsy with a concotomy technique. Because the disease is patchy in distribution, sampling error precludes 100% sensitivity (Henriksson 1980, Mastaglia and Laing 1996). Thus, essentially normal tissue can be present next to active inflammatory lesions, which in turn can be juxtaposed with areas characterized by nearly complete fibrosis from prior inflammation (Miller 2007). Muscle biopsies of DM reveal predominantly perivascular inflammation accompanied by capillary destruction. CD4+ T-cells and B-cells predominate in the perivascular areas causing perifascicular atrophy, related to capillary depletion and dropout. In DM, muscle fibres undergo necrosis, degeneration and phagocytosis, and perivascular atrophy occurs even in the absence of inflammation. However, in PM, there is no perivascular atrophy and blood vessels are normal although endomysial infiltrates are collected within the fascicles surrounding healthy muscle fibres, causing degeneration and regeneration of muscle fibres, and CD8+T lymphocytes invade non-necrotic fibres (Arahata and Engel 1984, Engel and Arahata 1984, Engel and Arahata 1986, Dalakas 2002).

In addition to myonecrosis, inflammation and regeneration seen in inflammatory myopathies, three other features make inclusion body myositis histologically distinct from other IIMs, i.e., rimmed vacuoles, intranuclear and cytoplasmic inclusion bodies, and deposits of amyloidogenic proteins in rimmed vacuoles (Calabrese and Chou 1994). In IBM, inflammatory cells invade non-vacuolated fibres, whereas vacuolated fibres are not invaded by T-cells, which implies two independent processes, i.e. a primary immune process with antigen-driven T-cells identical to

polymyositis, and a degenerative process in which beta-amyloid and amyloid-related proteins participate in vacuolar degeneration (Dalakas 2004).

The biopsy of skin lesions suggestive of DM is essential for an accurate and timely diagnosis, especially in cases where skin manifestations are the initial or only finding. The characteristic cutaneous histopathologic findings of DM include vacuolar alteration of the epidermal basal layer, necrotic keratinocytes, vascular dilatation, and a perivascular lymphocytic infiltrate (Santmyire-Rosenberg and Dugan 2003). These findings mimic changes found in systemic lupus erythematosus.

### 6.6.5. Magnetic resonance imaging

The magnetic resonance imaging (MRI) technique is non-invasive and may be used to document myositis or a disease flare, distinguish chronic active from chronic inactive myositis and noninvasively direct the site of biopsy. MRI is not a substitute for muscle biopsy, except perhaps in isolated cases. T1-weighted images provide excellent anatomical detail, whereas T2-weighted images with fat suppression or STIR (short tau inversion recovery) sequences can identify oedema indicating active inflammation. Limitations of MRI include the expense of the procedure and the nonspecifity of oedema that may be found in other inflammatory processes, toxic myopathies or dystrophic conditions (Virta et al. 1998, Scott and Kingsley 2004).

### 6.6.6. Assessment of health status and muscle strength

Several validated and extensively used outcome measures of disease activity and damage have been developed for rheumatic diseases including the Disease Activity score (DAS), the Health Assessment Questionnaire (HAQ) and the Visual Analogue Scale (VAS) (Dayal and Isenberg 2001).

Functional assessment tools such as the HAQ show increasing scores for adult patients with PM and DM as the disease progresses, and thus, in patients with longstanding disease, they may also reflect measures of disease damage or chronicity (Clarke et al. 1995).

However, measures for IIM have proved elusive and difficult to develop because of the difficulties in distinguishing the disease activity from damage in the skeletal muscle. Also, there have been difficulties in agreeing which additional organs or systems should be assessed.

Manual muscle strength testing, based on the Medical Research Council War Memorandum scale, is the most widely used clinical method for serial strength evaluation in therapeutic trials, but it has not been validated (Rider 1996).

Two other unvalidated functional assessment tools have been developed for adult IIM patients and used in clinical trials. The Myositis Functional Index measures distal muscle strength and peak expiratory flow (Josefson et al. 1996). The modified Convery Activities of Daily Living assessment tool has been used in outcome measurements in recent IIM trials (Villalba et al. 1998).

### 6.7. Treatment of PM and DM

Before pharmacologic intervention, patients should receive information about their disease and treatment options. Due to the evidence that immunopathological mechanisms are involved, drug therapy of PM and DM consists of immunosuppressive drugs to decrease tissue inflammation. Because target antigens are unknown, these therapies are non-selective. Although corticosteroids have not been adequately tested and proved beneficial in a controlled manner (Metzger et al. 1974), these drugs have been the mainstay of treatment for PM and DM (Pearson 1963, Briemberg and Amato 2003, Dalakas 2003, Oddis 2002). On clinical grounds, corticosteroids are the most effective and prevalent therapy of PM and DM.

The concept of quantity of life versus quality of life has been discussed in relation to the use of potentially lethal drugs in nonfatal connective tissue disorders (Steinberg 1973). The use of these immunosuppressive agents is argued to be justified because they help relieve suffering even though they may shorten the patient's life. The study of Carpenter et al. (1977), however, showed that prednisone does not seem to shorten survival.

There are controversial results as to the use of other immunosuppressive drugs. More potent and more toxic immunosuppressive drugs have been used in PM with encouraging results (Malaviya et al. 1968, Metzger et al. 1974, Benson and Aldo 1973). In the past, there was the concern whether the use of immunosuppressive therapies would predispose the patient to an increased risk of cancer. Methotrexate (MTX), azathioprine (AZA) and cyclophosphamide have been implicated in the development of subsequent malignancy, in particular, lymphoreticular neoplasia (Wishart 1973, Kinlen et al. 1979, Mashaly et al. 1981**,** Weiss and Serushan 1982, Callen 1983, Radis et al. 1995, Matteson et al. 1991), in patients treated for more than six years compared to those treated for less than one year (Asten et al. 1999), whereas cancers associated with myopathy are mostly diagnosed within the first three years after the diagnosis of myopathy.

### 6.7.1. Corticosteroids

Randomized controlled studies on the effect of corticosteroids on the morbidity and mortality of patients with PM and DM are lacking (Bohan and Peter 1975 I-II). In their review, DeVere and Bradley (1975) pointed out that there already is enough evidence of the effect of corticosteroid therapy so that a controlled study to show the effect of corticosteroids on the outcome of PM and DM is not needed. Their opinion has been, however, criticized because their conclusion seems to be based on a very heterogeneous group of patients, many of whom had a normal muscle biopsy (43%), i.e., the diagnosis of PM was questionable in many of those patients (Carpenter et al. 1977). In a survival analysis by Carpenter et al (1977) and another one by Medsger et al. (1971), there was no statistically significant difference between patients treated with low-dose (lower than 10mg of prednisone or equivalent per day) or high-dose (20mg or more of prednisone or equivalent per day) corticosteroids and non-users. However, compared with historical controls, there is so much clinical evidence today to show the effect of corticosteroids on these diseases that a placebo-controlled study is not justified from an ethical point of view.

Corticosteroids have anti-inflammatory and immunosuppressive effects, and they may inhibit the movement of lymphocytes to areas of inflammation and interfere

with the production of lymphokines. The immunosuppressive effects of corticosteroids occur with doses of prednisolone over 20mg/day and include a reduction in numbers of circulating monocytes and lymphocytes, T-cells being more affected than B-cells (Fauci and Dale 1974). Corticosteroids inhibit the synthesis of most cytokines and that of several cell surface molecules and interfere with both antigen-induced and mitogen-induced proliferative lymphocyte responses (Auphan et al. 1995, Horst and Flad 1987).

Factors important for achieving responses to corticosteroid therapy in myositis include the adequacy of the initial dose, i.e., prednisone >1mg/kg/day or 1g intravenous bolus once a month, the use of high-dose therapy until or after CK normalization and a slow tapering ca 5 to 10mg/month (0.25mg/kg/day or every other day over months). The usual practice is to begin oral daily therapy of 60mg to 80mg prednisone or equivalent as a single daily morning dose or divided into two doses (Dalakas 2003, Dalakas and Hohlfeld 2003). The improvement in muscle strength may lag behind CK improvement by weeks or months.

Well-known problems of the use of corticosteroids are cushingoid facial appearance, weight gain, easy bruisability, emotional lability, insomnia, and nocturnal sweating. More serious corticosteroid-related side effects are cataract, peptic ulcer disease, hypertension, diabetes mellitus, increased susceptibility to infection, osteoporosis and avascular necrosis of bone (Benson and Aldo 1973, Ansell 1985).

The long-term use of steroids may theoretically cause worsening of muscle strength associated with normal or unchanged CK levels, referred to as “steroid myopathy”. This condition is suggested by continued or increasing proximal muscle weakness involving predominantly the lower extremities at a time CK has normalized and a clinical response would be expected. Actually, the term “steroid myopathy” is a misnomer because steroids do not cause histological signs of myopathy but, rather, selective atrophy of type II muscle fibres. Contrary to what is believed, the condition is not common (Dalakas 2003). This myopathy improves with steroid dose reduction. The data are controversial concerning the improvement in muscle strength during corticosteroid treatment in patients with malignancy

associated myositis. It is reported that if any treatment response is achieved at all, it is of a shorter duration than in PM and DM patients without malignancy (Barnes 1976, Talbott 1977, Bohan et al. 1977, Williams 1959), but according to the study by Hochberg et al (1986) the response does not differ from what is seen in patients with malignancy.

### 6.7.2. Immunosuppressive and cytotoxic drugs

#### 6.7.2.1. Methotrexate and azathioprine

Although most patients will respond to corticosteroids, there are some (up to 20% to 40%) in whom steroids are ineffective or who cannot tolerate them due to toxicity (Cherin 1997). MTX and AZA are the immunosuppressive drugs most frequently prescribed for corticosteroid-resistant patients, but cyclosporine A (CyA) and combinations of these agents (Metzger et al. 1974, Villalba et al 1998) are increasingly used. The patients who are considered to be particularly prone to develop steroid side effects or who evince poor prognostic factors should be considered for a more aggressive therapy from the beginning of their disease (Mastaglia et al. 1993). However, there are no double-blind, placebo-controlled studies that would show the effectiveness of any of these agents.

The most extensive experience has been acquired from MTX. The oral dosage of MTX is 5-25mg once a week or 0.5 to 0.8mg/kg bodyweight (30 to 50mg) by subcutaneous or intravenous routes, if no toxicity is encountered. MTX up to 35mg/week can also be useful for the cutaneous lesions in patients with DM (Zieglschmid-Adams et al. 1995**,** Kasteler and Callen 1997). In addition to regular haematogical monitoring while receiving MTX, patients should be questioned and examined for the presence of stomatitis, sore throat, skin rash, fever or gastrointestinal complaints. Acute drug-induced pneumonitis is treated by the discontinuation of the drug and a short course of high-dose corticosteroids. Liver biopsy is suggested by some authors after a cumulative dose of 1500mg. MTX may be superior to AZA in patients with the antisynthetase syndrome (fever, interstitial lung disease, arthritis, Raynaud´s and mechanic's hands and poor response to

treatment) and in men (Joffe et al. 1993). The term mechanic's hands means cracking, fissuring, or both, of the lateral and palmar digital skin pads.

On the basis of clinical experience, AZA is well-tolerated and effective (Benson and Aldo 1973) for long-term therapy although its benefits do not become apparent for three to six months (Bunch 1981). The daily dose of AZA is 50–200mg orally. Important toxicities due to AZA include gastrointestinal intolerance, leucopoenia from bone marrow suppression, susceptibility to various infections and development of malignant disease later on. The combination of MTX with AZA may improve patients unresponsive to either agent alone (Villalba et al. 1998). In a small, randomized, controlled trial, AZA combined with prednisone was shown to be superior to prednisone alone in the control of myositis in PM with respect to functional disability (Bunch 1981).

CyA has been used with good clinical results in patients with steroid- and immunosuppressive resistant myositis and in ILD in doses of 2-4mg and up to 7.5 to 10mg/kg/day in combination with corticosteroids or MTX (Nawata et al. 1999, Jones et al. 1987, Dawson et al. 1996, Zabel et al. 1984, Goei The et al. 1985, Van der Meer et al. 1986, Vencovský et al. 2000). In corticosteroid resistant polymyositis and dermatomyositis patients with interstitial pneumonitis, CyA was reported to significantly prolong the survival in a series (Nawata et al. 1999). This drug interferes with the function of interleukin-1 (IL-1), thereby blocking T-lymphocyte-mediated responses and the elaboratorion of inflammatory lymphokines. The use of CyA requires follow-up of renal function.

#### 6.7.2.2. Other cytotoxic drugs and new immunomodulators

Other immunosuppressive drugs, such as cyclophosphamide 0.5-1g/$m^2$ intravenously every 1-4 weeks or orally in a daily dose of 2-2.5mg/kg, may be the most effective therapy in PM and DM with an interstitial lung disease or with features of vasculitis (Bombardieri et al. 1989, al-Janadi et al 1989, Mok et al. 2003). However, intermittent intravenous pulse cyclophosphamide has been reported to be ineffective and frequently toxic in treatment of PM (Cronin et al. 1989)**.** Its toxicity

and serious side effects are notable and include haemorrhagic cystitis, bone marrow suppression, infertility, increased susceptibility to infection and delayed malignancies (Bernatsky et al. 2008).

Also chlorambucil 2-6mg orally daily and Tacrolimus are used in some therapy-resistant patients. Chlorambucil is a potentially carcinogenic agent and its use is recommended to be restricted to short periods of time only.

Successful treatment results in PM have been reported from using prednisone in combination with chlorambucil or cyclophosphamide and MTX (Tiliakos 1987, Wallace et al. 1985)

Leflunomide is a relatively new immunosuppressive drug introduced into the treatment of rheumatoid arthritis and psoriatic arthritis. A few case reports describing successful treatment with leflunomide have been reported concerning patients with PM and DM (Lange et al. 2006, Boswell and Costner 2008).

Mycophenolate mofetil (MMF) is a relatively new drug which inhibits lymphocyte proliferation and is indicated as antirejection therapy for renal and cardiac transplantation (Lipsky 1996). Recent reports suggest that MMF may be effective in autoimmune diseases, such as treatment-resistant DM (Gelber et al. 2000), diminishing cutaneous activity, giving a sense of generalized improvement and the opportunity of tapering the steroid dose.

Fludarabine, an adenine analogue and antineoplastic agent, was studied in a group of 16 patients with refractory PM and DM. Using less stringent criteria of manual muscle testing and functional assessment tools, the investigators reported that 8 of the 11 patients who completed the trial would have been classified as improved (Adams et al. 1999).

### 6.7.3. Biological drugs

Anti-TNF agent therapy with etanercept and infliximab or anti-B-cell therapy with rituximab may help some patients whose disease is refractory to other agents (Efthimiou et al. 2006). However, there is the risk of reactivation of TB related to the use of biologics that specifically inhibit TNF-α. The risk exists because TNF-α is a crucial cytokine in the body's defence against TB. Infliximab causes the highest risk of TB reactivating, adalimumab causes an intermediate risk and etanercept causes the lowest one, but the risk associated with the use of all three is higher than in the general population (Gardam et al. 2003, Tubach et al. 2008).

### 6.7.4. Intravenous gammaglobulin

There is some evidence that intravenous gammaglobulin (IVIG) may be more useful and cost-effective in adult and juvenile DM than in PM and it is recommended also for severely ill, immunosuppressed or infected patients (Dalakas et al. 1993, Dalakas 1996, Marie et al. 1999b). According to the recent guidelines of European Federation of Neurological Societies for treatment of neurological diseases (Elovaara et al. 2008), IVIG is recommended as a second-line treatment in combination with prednisone for such patients with DM who have not adequately responded to corticosteroids. It is also recommended as a measure in combination with immunosuppressive medication to lower the dose of steroids in patients with DM. IVIG is not recommended as monotherapy for DM. IVIG may be considered a first-line treatment in severe, life-threatening DM together with some other immunosuppressive therapy. IVIG may be considered amongst the treatment options for patients with PM not responding to first-line immunosuppressive treatment.

IVIG exerts its action in IIM by 1) inhibiting myotoxic cytokines such as TNF-α and IL-1; 2) blockading Fc receptors on endomysial macrophages interfering with Fc receptor-mediated phagocytosis and 3) inhibiting the uptake of C3 and intercepting the formation and deposition of the membranolytic attack complex on the endomysial capillaries. More recently, a theory has been proposed of the action of IVIG in autoantibody-mediated diseases (Yu and Lennon 1999). A new transport receptor for

IgG has been discovered, called the MHC-1 related Fc receptor (FcRn). This protein protects pinocytosed IgG from catabolism. IVIG treatment leads to transient hypergammaglobulinemia and saturates FcRn. In this state, a higher proportion of endogenous, pathologic autoantibodies is available to be catabolized, leading to a reduction in autoantibodies and disease activity.

The dose of IVIG is 2g/kg, given in two to five divided daily doses, every 5 to 8 weeks as clinically required (Dalakas 2003). The obvious advantage of IVIG is the lack of serious side effects.

### 6.7.5. Plasmapheresis and cytapheresis

Plasmapheresis and leukapheresis have been effective on occasion in patients with active DM when combined with immunosuppressive drugs (Dau 1981**,** Khatri et al. 1982), but not as the single treatment for corticosteroid-resistant PM or DM (Miller et al. 1992). The goal of plasmapheresis is to reduce the amount of circulating antibodies, thus potentially reducing the tissue deposition of immunoglobulins.

The effective mechanism of cytapheresis in immune disorders is controversial. However, the removal of the leukocyte including the granulocyte, lymphocyte, and monocyte may play a crucial role in correcting the imbalance of the immune system. A session of cytapheresis including leukocytapheresis (LCAP) and granulocytapheresis (GCAP) may not create a sufficient amount of cell removal for the human body. However, the cell removal and the reaction from blood contacting with medical device materials may play a role in the immunomodulation of immune disorders (Yamaji et al. 2001).

### 6.7.6. Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation has been increasingly performed in patients with severe and refractory autoimmune diseases. High-dose cyclophosphamide is used as myeloablative conditioning before infusion of autologous stem cells (Baron et al. 2000).

### 6.7.7. Total body irradiation

Total body irradiation with 150 rads administered in fractionated doses over a 5-week period is an extreme method in intractable or life-threatening myositis and should be considered only as the last resort (Engel et al. 1981, Hubbard et al. 1982, Morgan et al. 1985**,** Kelly et al. 1988). However, this therapy includes an increased risk of bone marrow suppression and it potentially develops later malignancy. Total body irradiation should, therefore, be considered only for patients who are unable to tolerate or who fail to respond to all other available forms of treatment and who are seriously incapacitated by their disease (Mastaglia et al. 1997).

### 6.7.8. Rehabilitation and other treatment modalities

During the active inflammatory stage of the disease, while CK elevation is present, normal physical activities may be pursued by the patient as he or she tolerates (Alexandersson et al. 2000). However, bed rest is valuable for patients with progressive weakness, but it must be combined with a range-of-motion (ROM) exercise programme to prevent contractures. Rehabilitation and physical therapy are used to maintain ROM and to improve muscle strength and endurance during a remission. Graded isotonic exercises may increase muscle strength without myositis flares during the recovery phase of the disease (Wiesinger et al. 1998).

Dysphagia can occur due to involvement of posterior pharyngeal muscles and it is usually associated with dysphonia. This will need to be treated by a semisolid diet or tube feeding until improvement occurs. In more severe dysphagia, especially when a mechanical obstruction is present, interventional procedures such as cricopharyngeal myotomy or percutaneous endoscopic gastrostomy are available (Oh et al. 2007). Injections of botulinum toxin have been found to be of therapeutic value in the treatment of a variety of neurological disorders causing cricopharyngeal dysfunction; they are most commonly used in patients with IBM (Haapaniemi et al. 2001, Oh et al. 2008).

Palatal and respiratory muscle weakness must be carefully monitored. Ventilatory failure due to muscle weakness may need to be treated for some time and Haskard (1983) recorded a successful outcome in a patient requiring 18 days of intermittent positive pressure ventilation.

Photoprotection, topical steroids and hydroxycloroquine are important adjunct therapies in severe DM.

### 6.8. Outcome and prognostic factors of outcome

#### 6.8.1. Mortality

Mortality in different disorders is usually expressed in three different ways: 1) as a relative risk (RR) or standardized mortality ratio (SMR); 2) as survival curves; or 3) as survival years. RR denotes the death rate as ratios between the observed and the expected in populations with and without a certain disease, whereas the SMR compares the death rates in the population with the disease with those in the population as a whole. Also, the excess of mortality is related to disease severity and the SMRs are higher in clinically-based than in population-based series because hospitalized patients have the disease more severe.

The heterogeneity of earlier disease classifications without differentiation between DM and PM or paediatric cases makes it difficult to compare mortality between the historical studies of PM and DM and the recent ones. Ethnic differences should also be considered when comparing results from different series (Hidano et al. 1986, Medsger Jr et al. 1971).

There are several earlier studies of survival in PM and DM where the overall survival rate varies between 39% and 75% (Steiner 1903, O´Leary and Waisman 1940, Sheard Jr 1951, Pearson 1963, Rose and Walton 1966, Winkelman et al. 1968, Medsger Jr et al. 1970, Logan et al. 1966, Medsger Jr et al.1971, Riddoch and Morgan-Hughes 1975, DeVere and Bradley 1975) (Table 4a).

Table 4b shows the cumulative mortality rate in different PM and DM studies in which the disease classification is based on the Bohan and Peter criteria.

### 6.8.2. Causes of death

The three major causes of deaths in PM and DM are cardiovascular (DeVere and Bradley 1975, Gottdiener et al. 1978, Askari and Huettner 1982, Haupt and Hutchins 1982, Henriksson and Sandstedt 1982, Benbassat et al. 1985, Ramirez et al. 1990), pulmonary (Henriksson and Sandstedt 1982, Benbassat et al. 1985, Hochberg et al. 1986, Lakhanpal et al. 1987, Maugars et al. 1996, Ascherman 2002) and carcinomatous disorders (DeVere and Bradley 1975, Barnes 1976, Bohan et al. 1977, Benbassat et al. 1985, Basset-Seguin et al. 1990). The main types of pulmonary disorders are ventilatory insufficiency associated with bronchopneumonia, alveolitis and ILD. Marie et al. (1998) found a rate of 40% morbidity and a 27% rate of mortality from pulmonary disorders in their study of 55 consecutive patients seen at the University of Lille medical centre.

Before Bohan and Peter's classification criteria (1975), there were several studies concerning causes of death. According to DeVere and Bradley (1975), in a series of 118 patients with PM and DM death could be directly related to PM and another connective tissue disease or there was evidence that PM had contributed in some way to the death in 24% of all autopsies. A common mechanism for death was that severe disability resulted in respiratory complications such as pneumonia. In 44% of the autopsied cases of the above series the cause of death was apparently unrelated to PM or its associated diseases: two-thirds were due to coronary thrombosis which is 16 times more than in the data of Registrar-General for the general population, suggesting that PM predisposes to myocardial infarction. Carcinoma was responsible for 18% of the deaths.

In a nationwide U.S. study from 1968 through to 1978, based on death certificates and using the International Classification of Diseases, Eighth Revision (ICD-8), Hochberg et al. (1983) identified a total of 1986 deaths in patients with PM and DM. The mortality data represented cases with either PM or DM coded as the underlying

cause of death on death certificates, but it is likely that a systematic underestimation of mortality occurred especially in the age groups above the age of 45 because of the accepted association of PM and DM with malignancy (Bohan et al. 1977). There was an increasing mortality with increasing age for non-whites from the age of 64 onwards. The mortality rate was the lowest among white males regardless of their age group.

Table 5 shows the causes of death in the studies relying on Bohan and Peter's disease classification. In their representative nationwide population-based study with 396 patients with PM and 392 with DM, Sigurgeirsson et al (1992) found slightly increased mortality in male but not in female patients with PM. The main cause of death was cancer in 14% of patients, 13% died of PM and 46% of circulatory diseases. The mortality was clearly increased in patients with DM, particularly in the females, in whom the risk was doubled with the increase mainly due to deaths from cancer (40%); 10% died of DM and 26% of circulatory diseases.

Iatrogenic causes are reported to account for 4% to 32% of deaths in patients with PM and DM (O´Leary and Waisman 1940, DeVere and Bradley 1975, Bohan et al. 1977, Henriksson and Sandstedt 1982, Hoffman et al. 1983, Tymms and Webb 1985, Maugars et al 1996). Infections due to immunosuppressive drugs, gastrointestinal haemorrhage and perforations and osteoporosis due to high dosages of corticosteroids are the most frequent iatrogenic causes of death (O´Leary and Waisman 1940, Bohan et al. 1977, Henriksson and Sandstedt 1982, Hoffman et al. 1983, Tymms and Webb 1985, Hochberg et al. 1986, Maugars et al. 1996).

### 6.8.3. Prognostic factors of outcome

#### 6.8.3.1. Prognostic factors in general

There is much controversy over the results of studies that have assessed prognostic factors for survival in PM and DM. The correct comparison of prognostic data requires assessments based on survival rates that also take into account the follow-up, cases lost from sight, and deaths. Most studies have found older age to be

the most important risk factor for death in PM and DM (Logan et al. 1966, DeVere and Bradley 1975, Bohan et al. 1977, Henriksson and Sandstedt 1982, Hochberg et al. 1983a, Benbassat et al. 1985, Tymms and Webb 1985, Hidano et al. 1986, Hochberg et al. 1986, McKendry Jr 1987, Love et al. 1991, Maugars et al. 1996).

Associated malignancy is another often mentioned prognostic factor (Barnes 1976, Bohan et al. 1977, Henriksson and Sandstedt 1982, Benbassat et al. 1985, Hidano et al. 1986, Ramirez et al.1990, Maugars et al. 1996) especially concerning DM (Basset-Seguin et al. 1990). In addition, delayed diagnosis and therapy have been reported as prognostic factors (Bohan et al. 1977, Henriksson and Sandstedt 1982, Benbassat et al 1985, Joffe et al. 1993, Fafalak et al. 1994).

There is scant evidence on the prognostic significance of histological findings in affected muscles. However, Bohan et al. (1977) mentioned that irreversible fibrosis and widespread muscle fibre degeneration mean a poorer prognosis. No association between the degree of inflammation or the biopsy picture and outcome has been found (Riddoch and Morgan-Hughes 1975, Carpenter et al. 1977, Maugars et al. 1996).

In an Israeli retrospective study of prognostic factors in PM and DM from 1956-1976 using the Bohan and Peter criteria, Benbassat et al. (1985) reported a failure to induce remission, leucocytosis, fever, older age, a short disease history and dysphagia as unfavourable prognostic signs . A lack of muscle improvement is significantly associated with death (Hochberg et al. 1983, Maugars et al. 1996). The efficacy of corticosteroids is a good prognostic factor in several studies (Medsger Jr et al. 1971, Riddoch and Morgan-Hughes 1975, Henriksson and Sandstedt 1982, Benbassat et al. 1985, Maugars et al.1996). Table 6 shows results of studies of prognostic factors for survival in patients with PM and DM according to the Bohan and Peter criteria (1975).

The following findings have also been reported as unfavourable prognostic factors for PM: the presence of an underlying collagen-vascular disease, especially rheumatoid arthritis and progressive systemic sclerosis, age at presentation, a low

corticosteroid dosage and a delay of therapy of more than a year. In addition, carcinoma has prognostic importance in classic DM (DeVere and Bradley 1975).

Medsger Jr et al. (1971) reported several clinical variables - decreased urinary creatine, low serum album, and SGOT elevation - which correlated with reduced survival in adult PM. When account was taken of the presence or absence of dysphagia, decreased urine creatine was the only independent variable contributing to mortality. Dysphagia has been reported as a prognostic factor for death mainly in older series (Medsger Jr et al. 1971, Carpenter et al. 1977, McKendry Jr 1987).

Winkelmann et al. (1968) found a higher death-rate in PM and DM when the course of the disease was rapid and progressive and if the patients had either Raynaud´s phenomenon or sclerosis of the skin.

It has been anything but clear recently whether serum markers – MSAs and MAAs - could have prognostic value. Alveolitis is a frequent manifestation in patients with anti-Jo-1 and the other anti-aminoacyl-tRNA synthetase autoantibodies. The presence of anti-Jo1 antibodies does not appear to have prognostic value for outcome when ILD has already developed (Douglas et al. 2001, Marie et al. 2002, Späth et al. 2004); however, the overall prognosis seems to be worse for patients with anti-Jo1 antibodies compared to patients without these antibodies (Love et al. 1991). The study of Troyanov et al. (2005) found that anti-synthetase, anti-SRP, and nucleoporin autoantibodies are markers of chronic myositis, whereas anti-U1RNP, Pm-Scl and Ku are markers of monophasic myositis. According to these findings (Troyanov et al. 2005) and other similar ones (Rider and Miller 2000), it has been suggested that the initial use of a second-line therapy agent such as methotrexate, concurrent with adequate initial corticosteroid therapy, should be strongly considered in patients with PM or DM and in overlap myositis patients with autoantibodies to synthetases, nucleoporins, or SRP. Among the serum autoantibodies, anti-SRP is the worst prognostic marker; the antisynthetases are also associated with recurrent disease flares and lower survival. Conversely, the 5-year survival rates among the subsets with anti-PM-Scl and anti-Mi-2 antibodies approach 95% (Oddis et al. 1992).

Other features, such as CK, have been more frequently contested than confirmed in the literature. Fudman and Schnitzer (1986) reported seven DM patients with normal CK activity associated with either malignancy or ILD and suggested that this

laboratory feature may be a poor prognostic sign. However, some authors have criticized this opinion (Nicholls 1987). In the studies of Marie et al. (1998) and Fernandez-Sola et al. (1991), for example, no correlation was shown between the CK levels in patients with PM and those with DM and ILD.

Chen et al. (2001) found in their study two independent predictive factors for PM and DM with malignancy, i.e. older age at onset (>45 years) and male gender. In addition, patients who had the complication of interstitial lung disease had a significantly lower frequency of malignancy.

#### 6.8.3.2. Interstitial lung disease as a prognostic factor

Interstitial lung disease is considered to be a major risk factor for premature death in patients with myositis. Today, the overall survival appears to be better than in the historical controls with idiopathic UIP (Douglas et al. 2001). In a study of Marie et al. (2002), the 5-year survival of patients with PM and DM with ILD was 60.4%. In a study of Douglas et al (2001), the survivals for 1, 3 and 5 years were 94.4%-90.4%-86.5%, respectively. Negative prognostic factors for survival of patients with ILD included Hamman-Rich –like syndrome (acute interstitial pneumonia), initial diffusing capacity of carbon monoxide less than 45%, neutrophil alveolitis and histopathologic features of UIP (Marie et al. 2002).

Some histopathologic features including diffuse alveolar damage (Tazelaar et al. 1990, Marie et al. 2002), UIP (Marie et al. 2002), neutrophil alveolitis (Marie et al. 2002, Schnabel et al. 2003), digital infarcts showing microangiopathy in DM (Tjiu et al. 2004), and amyopathic DM (Lee et al. 2002, High et al. 2003, Sontheimer and Miyagawa 2003 Sakamoto et al. 2004) have been reported as risk factors for poor outcome. Rapidly progressive interstitial pneumonitis has been shown to be mostly resistant to high-dose corticosteroid therapy, and when it occurs, patients die of respiratory failure in a relatively short time (Dickey and Myers 1984, Tazelaar et al. 1990). About 40% of patients with a slower presentation of IP died (Tazelaar et al. 1990). Characteristic nailfold capillaroscopic microangiopathy is more frequent in patients with lung involvement, particularly ILD (80%) (Marie et al. 1998).

Though presence of the anti-Jo-1 antibody is associated with ILD, it does not seem to alter the prognosis of ILD. In a study of 70 patients with PM and DM-related ILD (Douglas et al 2001), the survival did not differ significantly between the Jo-1 positive and negative groups.

It is uncertain whether the prognosis of ILD differs between patients with PM and DM. In a study by Fujisawa et al. (2005), patients with DM and associated ILD were less responsive to corticosteroid therapy than patients with PM-associated ILD, resulting in a poor prognosis for the DM group.

### 6.8.4. Drug-related outcome

In the pre-corticosteroid-era the overall mortality rates in PM and DM rose up to 50% (Steiner 1903, O´Leary and Waisman 1940). An indirect piece of evidence on the effect of corticosteroids on the mortality of these diseases is given by the common impression of the patient outcome having been better since the 1940's compared to the historical controls from pre-corticosteroid-era. In their review Bohan and Peter (1975 I-II), however, pointed out that there is actually no firm evidence to show that corticosteroids improve survival or lessen the severity of the disease in patients with PM. According to the survival analyses of Carpenter et al. (1977) and Medsger Jr et al. (1971) there were no statistically significant differences between low-dose/no-users and recipients of high-dose corticosteroid treatment in PM or DM.

Immunosuppressive drugs showed no significant effect on survival in the study of Maugars et al. (1996). CyA has been used with good results in patients with corticosteroid- and immunosuppressive-resistant myositis and ILD in combination with corticosteroids (Nawata et al. 1999, Jones et al. 1987) including better survival (Nawata et al. 1999).

## 7. AIMS OF THE STUDY

The purpose of the present study was to assess the following aspects in a hospital-based series of patients with PM and DM:

- incidence of different types of cancer in Finland and in the Scandinavian countries (I, II)
- prognostic factors and outcome (III)
- history of TB and incidence of mycobacterial infections (IV)

## 8. SUBJECTS AND METHODS

### 8.1. Selection of patients and study design

Because of the rarity of PM and DM, the studies of these diseases often originate from minor individual centres. In countries with well-established disease registers it is possible to study the epidemiology of rare diseases reliably. The Finnish National Board of Health has collected nationwide information about hospitalized patients since 1969. These data contain the unique identification number of each person, the diagnosis and the dates of admission and discharge of each hospitalization period.

It has been customary in Finland for all patients with a suspicion of PM and especially with that of DM to be admitted to hospital for examination. We used the national hospital discharge registry as a source for our case selection for the present series (study I, III and IV). The files of the Finnish Cancer Register were used to assess cancer incidence in these patients (study I). The patients were followed up until death or till the end of August 1995, whichever occurred first, using the national mortality files of Statistics Finland.

In order to have sufficient power to test the association between myositis and specific cancer types, a pooled analysis of published national data from Sweden, Denmark and Finland (Sigurgeirsson et al. 1992, Chow et al. 1995, study I) was done (study II). The data of the original publications were based on national registries. All the Scandinavian countries have hospital discharge registries maintained by the

authorities; i.e., the Swedish National Board of Health, the Danish Hospital Discharge Registry and the Finnish National Board of Health. The discharge data was cross-linked to national cancer registries and registries of cause of death. Each country has a cancer registry to which treating physicians and pathology and haematology laboratories must report all cancers. The cancer registries of the three countries have been validated and have over 95% completion rates (Mattsson et al. 1984, Teppo et al. 1994, Storm et al. 1997). For this study, cancers were classified according to the International Classification of Diseases.

### 8.1.1. Subjects in a nationwide survey for cumulative incidence of malignancies in PM and DM (study I)

For this study, all the patients with a code for PM or DM in the period of 1969-1985 were selected from the hospital discharge registry. The codes 716.00 and 716.10 of the ICD-8 were used. Altogether, 731 patients with the codes for PM or DM were identified from 5 Finnish university hospitals, 18 general county hospitals and 32 local hospitals including 2 rehabilitation centres.

The medical records of each patient were requested from the local physicians. Twenty patients fell outside the follow-up period. The medical records of 84 patients (11%) were not available. After an in-depth examination of the remaining 627 medical records, a total of 316 cases were excluded from the study: 115 because of an incorrectly classified neuromuscular disease, 20 because of exposure to myotoxic drugs or toxins, 16 because of other incorrectly classified diseases, and 90 patients because they did not fulfil the Bohan and Peter diagnostic criteria for PM and DM. Among the 311 accepted cases (103 men and 208 women), there were 191 definite, 107 probable, and 13 possible cases of PM or DM as defined by Bohan and Peter. Of these, 30 patients aged under 15 were excluded and so were 35 who had an associated connective tissue disease (Figure 1).

The patient selection of this study was conducted with care and the patients' inclusion, as they were divided into groups according to the Bohan and Peter criteria (1975), was considered to be homogenous. The fact that the great majority of the

patients was classified as definite/probable PM or DM (95.8%) and only 4.2% of the cases was classified as possible points out the homogeneity of the patients and the importance of critical patient selection. These thirteen possible cases, however, were clinically obvious and included those that were not completely investigated (no biopsy 7/13, EMG not done 9/13, muscle enzymes not elevated 10/13) for various reasons when the PM or DM diagnosis was made. Of these thirteen patients two had dermatomyositis, two had overlap myositis and the remaining nine had polymyositis.

The median follow-up period of the series was 11 (10 to 26) years. The follow-up procedure relied on the personal identification code given to every Finnish citizen and foreign resident in Finland. The underlying cause of death was determined from the data of Statistics Finland in accordance with the internationally established norm.

### 8.1.2. Subjects in a multinational survey for cumulative incidence of malignancies in PM and DM (study II)

The data from three follow-up studies conducted in Sweden, Denmark and Finland (Sigurgeisson et al. 1992, Chow et al. 1995, study I) were used for this substudy. Only adult patients (≥ 15 years) in whom the diagnoses of PM and DM were based on hospital examinations were included, i.e., the cases were identified by the discharge diagnoses (ICD 7 and/or ICD-8 codes) from discharge registries. From Sweden, 389 patients with PM and 329 with DM were included in the study, while the corresponding figures from Denmark were 350 and 218 and, from Finland 175 and 71. Altogether, the multinational survey covers 914 cases of PM and 618 cases of DM.

### 8.1.3. Subjects in a national survey for prognosis and outcome in PM and DM (study III)

During the follow-up, the total amount of cases represented in study I increased from 311 to 316. The explanation is that we excluded one case of IBM from the study and included six outpatient cases (three PM and one DM) from the University

Hospitals of Helsinki and Turku (Figure 1). Later on, one PM case proved to be associated with another connective tissue disease. This explains the difference in the number of subjects (changing from 175 to 176 cases for PM and from 71 to 72 cases for DM) between articles I-II and III-IV. The remaining cases out of the 316 were classified as myositis with another collagen disease, or juvenile cases.

The baseline demographic and clinical characteristics of 248 patients are shown in Table 7. The patients with PM were somewhat older than those with DM, but the difference did not reach statistical significance. The median delay in diagnosis was calculated from the onset of first symptoms compatible to myositis. The delay was greater in the PM group than in the DM group ($p<0.001$). During the follow-up period of over 20 years, the normal reference limits of laboratory values changed several times. Therefore, we analyzed the values of muscle enzymes as x-fold of their normal upper limits. Due to the insufficiency of data available, no uniform analysis of chest X-ray findings could be done.

### 8.1.4. Subjects in a nationwide survey on the incidence of mycobacterial infections in PM and DM (study IV)

The patients in this substudy represent the same patient series as in study III. Earlier histories of mycobacterial infections, incidences of these infections after the diagnosis of PM or DM and causes of death were assessed from medical records.

No uniform baseline analysis on chest X-ray findings could be done for this study. Each diagnosis of TB and its type is reported as documented in medical records.

## 8.2. Statistical analyses

Study I. The person-years at risk and follow-up for cancer started when the patient was admitted to hospital for diagnosis of PM or DM, and ended at the time of death or end of follow-up. The observed numbers of cancer cases were compared with those expected on the basis of the sex- and age-specific incidence rates for the whole

Finnish population. The standardized incidence ratio (SIR) was expressed as an age- and sex-specific ratio of the observed and expected numbers of cases. The statistical significance of the SIR was estimated by using Poisson distribution. A similar calculation was also made for the prevalence of cancer at the time of the PM or DM diagnosis using the average prevalence of the whole population in 1969-85 for reference.

Study II. The relationship between PM or DM and cancer was expressed with a standardized incidence ratio (SIR).

Study III. Descriptive values of variables with a normal (Gaussian) distribution were expressed by mean and standard deviations (SD); the statistical comparison between the groups was made using the t-test. If the variables did not have a normal distribution, then the descriptive values were expressed by median and interquartile range (IQR); the statistical comparison between the groups was made by using the Mann-Whitney test. Measures with a discrete distribution are expressed as counts (%) and analysed by the Chi-Square test. The normality of variables was evaluated by Shapiro-Wilk statistics. The Kaplan-Meier curve was used to illustrate information on the cumulative proportions of survival and the difference between the groups was tested by using the Log-rank test. The prognostic factors predicting survival were analysed using proportional hazard regression models, called Cox's regression models (Cox 1972). The number of deaths is expressed as proportion of deaths that would have been expected if the age- and sex-specific rates in a 'standard' population had applied; the Standardized Mortality Ratio (SMR) was calculated with 95% confidence intervals, assuming a Poisson distribution.

Study IV. The time-to-event analysis was based on the product limit estimate (bootstrap estimation) to derive the cumulative probability (95% CI) of the mycobacterial infections.

# 9. RESULTS

## 9.1. Cumulative incidence of cancer in PM and DM

### 9.1.1. Results from the nationwide Finnish series (I)

There were 63 cases of cancer among the 311 PM and DM patients by the end of 1990. The total number of person-years at risk was 2,712 and the mean follow-up time 8.7 years. After excluding patients with cancers preceding the diagnosis of myositis (N=12) and those with basal cell carcinomas (N=14), carcinoma in situ of cervix uteri, myelofibrosis, and polycythemia vera (N=1 in each group), there were 34 cases of cancer versus the 16.4 expected. In the PM group there were 4 haematological cancers versus the 1.1 expected (SIR 3.8, 95% CI 1.0-9.8), otherwise all the excess risk was attributable to DM.

The SIR among patients with DM was increased both in men (8.3, 3.0-1.8) and women (6.0, 3.2-10). The excess risk was observed only in patients older than 50 at the time of the DM diagnosis. The risk was increased for cancers of the gastrointestinal tract (SIR 9.0, 3.6-19), for lung cancer (SIR 10, 2.1-29), ovarian cancer (SIR 32, 8.7-82), and for non-melanoma skin cancer (SIR 29, 3.6-106).

The risk of cancer was lower among patients who had received cytotoxic therapy. In the DM group, the SIR among the patients who had taken cytotoxic drugs was 3.8 (0.8-11) and among those who had not, 7.6 (4.3-12). Regardless of cytotoxic treatment, the relative risk of cancer decreased with time after the PM and DM diagnosis.

The relative risk of cancer among the patients with DM was very high (SIR 26, 12-48) in the first year after the diagnosis of DM. Also, the prevalence of cancer at the time of the DM diagnosis (7 cases) was significantly higher than among the population at large (standardized prevalence ratio 3.7, 95% CI 1.5-7.6). The prevalence of cancer was not raised at the time of the PM diagnosis (5 cases, standardized prevalence ratio 1.0, 0.3-2.2).

### 9.1.2. Results from the combined study from the Scandinavian countries (II)

The mean age of the patients with DM at diagnosis was 55.6 (SD 18.4) for men and 55.4 (17.1) for women, and that of the PM patients, 56.2 (16.2) for men and 57.5 (16.3) for women. Among the patients with DM, a total of 198 cancers were identified, of which 115 developed after the diagnosis. Among those with PM, 137 cancers were identified, of which 95 developed after the diagnosis.

#### Association between PM and DM and cancer

For all cancer types, there was a three-fold increase in the risk of malignant disease after the diagnosis of DM. The SIRs for men and women with DM were 3.3 (95% 2.5-4.4.) and 2.8 (2.2-3.6), respectively. Since SIRs were almost the same for sex-neutral cancers, the results for men and women were combined. The highest risks after the diagnosis of DM were for ovarian, lung, pancreatic, stomach, and colorectal cancers, and for lymphomas. However, the relative risk of many other malignant diseases was also raised. The SIR for the entire follow-up for PM was 1.4 (95% CI 1.0-1.8) for men and 1.2 (0.9-1.6) for women. The greatest increased risks were for non-Hodgkin lymphoma and lung and bladder cancers. In contrast with DM, there was no increased risk of ovarian, colorectal, stomach, or pancreatic cancers.

#### Association between histological types of cancer and myositis

It was examined whether or not myositis was associated with specific histological subtypes. In DM, although adenocarcinomas were the most common type of cancer recorded, there was an increased risk associated with all histological types. The risk of squamous cell cancers and adenocarcinomas was not increased in patients with PM; however, the risk of haematological and lymphatic malignant diseases was increased two-fold.

### Length of follow-up and the risk of cancer

The risk of cancer was highest within the first year after the myositis diagnosis, and dropped substantially thereafter. In patients with PM, the risk fell to the expected rates 5 years after diagnosis; however, the risk in DM did not return to the expected population values for most cancers. The risk of ovarian, pancreatic, and lung cancer remained high up to 5 years after the diagnosis, while the risk of pancreatic and colorectal cancer extended past the 5 years of follow-up. The risk of non-Hodgkin's lymphoma was increased in the first year but not subsequently.

### Cancers arising before the diagnosis of myositis

Most cancers diagnosed before DM preceded myositis by 2 years or less (71%). In contrast in PM, most cancers were diagnosed more than 5 years before the diagnosis. In the year before the diagnosis of DM, 43 cancers were recorded (adjusted SIR 9.8, 95% CI 7.3-15.3). Lung (43.2, 26.1-71.7) ovarian (28.6, 10.7-76.1), colorectal (10.5, 7.7-23.3), and breast cancers (10.7, 5.1-22.5) were associated with increased adjusted risks. In the 1-2 years before the DM diagnosis, 16 cancers were recorded, giving an adjusted SIR of 4.6 (95% CI 2.8-8.7). In the PM patients, 11 cancers were seen in the year before the diagnosis (1.6, 0.9-2.9), and only the risk of lung cancer was increased (4.4, 1.4-13.6). In the 1-2 years before the PM diagnosis, three cancers were recorded, giving an adjusted SIR of 0.5 (0.2-1.7).

## 9.2. Prognosis and mortality in PM and DM (III)

In the nationwide series, the five-year survival rate for PM was 75% (95 % CI: 68 to 81%) and that for DM 63 % (50 to 73 %), and the ten-year survival rates were 55 % (47to 62 %) and 53 % (41 to 64 %), respectively (Figure 2). The median time of survival for PM was 11.0 (95 % CI: 9.5 to 13.3) years and that for DM 12.3 (5.5 to 20.7) years. The patients with DM had a 1.47- fold (95 % CI: 0.99 to 2.12) age- and sex-adjusted mortality rate compared to those with PM (p=0.08). The SMR for the combined group of PM and DM was 2.92 (95 % CI: 2.48 to 3.44).

With the exceptions of age in both diagnosis groups and the delay in diagnosis and initial dose of corticosteroid in the PM group, no other individual factor reached significance as prognostic of death. However, cancer had a HR of 2.16 (95% CI: 0.95 to 4.50) in the DM group and a HR of 1.99 (95% CI: 1.01 to 3.94) in the PM group (Table 8).

During the follow-up, 107 of the 176 patients with PM and 42 of the 72 patients with DM died. The main causes of death are shown in Table 9. The most common main causes of death for both PM and DM patients were circulatory diseases (37 and 31%, respectively) and the musculoskeletal disease itself (29 and 31%, respectively). The patients with DM had excess mortality from cancer compared to the patients with PM, cancer being the main cause of death in 33% and 9% of the patients, respectively. Among the 14 cancer deaths in the DM patients, the most common malignancies were lung cancer (N=4), ovarian cancer (N=3) and gastric cancer (N=3), while breast cancer was the most common malignancy (N=3) in the 10 cancer deaths in the PM patients.

In the group of patients with a musculoskeletal disease as the main cause of death (N=44), pneumonia was the most common immediate cause of death, accounting for 14 (45%) of the 31 PM deaths and 4 (31%) of the 13 DM deaths. In the whole series, pneumonia was either the immediate or the main cause of death in 23 cases (21%) out of the 107 PM deaths and in five (12%) of the 42 DM deaths.

Septicaemia was coded as the immediate cause of death in three patients, one of whom was a user of azathioprine. Five patients died from gastrointestinal perforation or bleeding; the colon was involved in three and the stomach in two cases.

Figure 3 presents a forest plot comparing the age- and sex-adjusted risks for patients with PM or DM to die from different main causes of death. Cancer was the only cause of death that differentiated the groups, i.e., the DM patients were at a greater risk to die from cancer with a HR of 5.11 (95% CI: 2.31 to 11.30).

Figure 4 demonstrates the difference in survival between DM patients with and without cancer ($p<0.001$; log-rank test). The age-adjusted HR was 1.68 (95% CI: 0.87 to 3.24).

### 9.3. Mycobacterial infections in PM and DM (IV)

Twenty-six (10 %) of the whole series of 248 patients with myositis had a history of tuberculosis; nineteen of them had PM and seven had DM. Eighteen out of the 26 patients had TB in their disease history and eight additional subjects had chest radiological signs suggestive of earlier TB. However, there were no cases with recent TB before the diagnosis of myositis.

After the diagnosis of myositis, 13/176 (7.4%) patients with PM were documented to have a mycobacterial infection, but only one of them was in the group with a history of TB, in this case as long as 57 years earlier. 2/72 (2.8%) patients with DM had a TB infection (without an earlier history of TB). This means that altogether 40 (16%) of all the 248 patients with PM/DM had suffered from mycobacterial infections. The cumulative probability of mycobacterial infections among the patients with PM was 4.8% (95% CI 2.4 to 9.4%) in 5 years and 9.3% (95% CI 5.4 to 15.6%) in 10 years (Figure 5).

Detailed data on bacteriology, type of infection and patients' characteristics are shown in Table 10. At the time of diagnosis of a mycobacterial infection, all of the patients used corticosteroids, and four PM patients also used azathioprine. In addition, there were three ex-users of azathioprine among those with PM. Overall, no risk factor for tuberculosis could be identified in the PM patients (Table 8). TB was coded as the main cause of death for three patients with PM, the disseminated type for one and miliary TB for two. TB represented 2.8% of the total number of 107 PM deaths. Additionally, there was one PM case with disseminated TB as the immediate cause of death. None of the four patients with tuberculosis were users of cytotoxic drugs.

## 10. DISCUSSION

### 10.1. General

There are only few studies (Oka and Raassakka 1978, Oka et al.1988) about PM and DM in Finland; there are also some case reports (Salmi et al. 1978, Jula and Haataja 1982, Jalava et al. 1983, Vilppula and Aine 1984, Meretoja et al. 1994, Saario et al. 1994, Koskela and Kaipiainen-Seppänen 2006) and reviews (Pirskanen 1978, Sivenius and Riekkinen 1979, Kalimo et al. 1993) and one doctoral thesis concerning connective tissue diseases including PM and DM (Vilppula 1972). The limitations of a retrospective and hospital-based study like this are well recognized. This method of collection and identification of patients relies on accurate coding of discharge diagnoses. In addition, it is difficult to attain complete case ascertainment from community health care. In their editorial, McCarty et al. (1992) highlighted the importance of population-based incidence registries for rare connective tissue diseases. The validity of these data depends on there being a uniform definition of disease, confirmation of a high level of case ascertainment, and verification of the disease diagnosis.

In Finland, the Finnish National Board of Health has collected nationwide information about hospitalized patients into the hospital discharge register since 1969. At the beginning of this registration, i.e., from 1969 to 1971, the register seldom contained the complete identification number for the patient. However, PM and DM are disabling diseases which are difficult to diagnose and treat, and a very high proportion of patients (95%) have a hospital diagnosis at some time during the course of their disease (Oddis et al. 1990). Thus it was possible to identify patients retrospectively although they had incomplete personal codes in the register early in their disease course. In addition, our case identification was certified by registers of individual hospitals when needed. The data were also completed by a detailed review of medical records to ensure a reliable classification of diseases. It can be concluded that this approach provides a rather good accuracy to investigate the epidemiology of rare diseases, such as PM and DM.

In Finland, sickness insurance statistics may provide a good source for epidemiological studies (Kaipiainen-Seppänen and Aho 1996), but the use of this register may also lead to an underestimation of the true number of PM and DM patients. When the patient needs prolonged antirheumatic medication, a drug reimbursement certificate is written, but if the patient dies from this disease soon after the diagnosis is established, i.e. before the doctor's certificate is written, she or he is not included in the register. Combining the data from sickness insurance statistics with hospital discharge registries and reviewing the medical records of these patients would probably be the most reliable way of collecting epidemiological data.

There are also some points to remember concerning the diagnosis of myositis. Aminotransferase abnormalities do not always indicate liver disease, also drugs and toxins can cause a muscle disease, and fatigue and weakness may be present in the muscles as well as in the head. A family history of a similar illness, neurological signs, asymmetry and an onset of symptoms related to exercise or eating all contradict a diagnosis of myositis.

No data of MSAs or MAAs were available that would have been helpful in the classification of patients with IIM at that time the present series was recruited for 1969-1985.

The use of the Bohan and Peter criteria may increase the risk of misclassification of myositis, e.g. the typical histologic features of DM can be seen in patients with no rash or a mild rash (Hilton-Jones and Squier 1992). Thus PM or DM might have been misclassified as another connective tissue disease, a neurological disorder, or IBM, toxic/metabolic myopathies or muscular dystrophy might have been included (van der Meulen et al. 2003) in our series. However, a large number of cases misclassified as PM or DM were excluded simply by reviewing the hospital records. A great proportion of misclassifications as other neuromuscular diseases was attributable to polymyalgia rheumatica and can be explained simply by the fact that an incorrect ICD-code was used. The collection material also shows (Figure 1) that PM and DM patients are managed by and referred to several specialists such as dermatologists, neurologists, rheumatologists and specialists in internal medicine, which still increases heterogeneity in the diagnostics of these diseases.

As to the validity of death certificates, the correct data of mortality is related to different factors such as the way to examine the principal cause of death with or without autopsy, the coding procedure and the care taken in filling in the certificates. In fact, in Finland, autopsies are performed in 30% of deaths (Statistics Finland 1993). Actually, the lack of systematic autopsies may be one of the factors at work in the underestimation of causes of death other than the musculoskeletal disorder, e.g. myocardial involvement (Maugars et al 1996).

The non-melanoma skin cancer was excluded from the multinational combined study conducted in the Scandinavian countries, because this cancer type was reported on differently. This may be one source of bias leading to the lack of detection between immunosuppressive therapy and cancer (Kinlen et al. 1979). However, it is possible that skin cancers may be detected more often and earlier in patients who are under hospital follow-up and this exclusion is therefore justified (Matteson et al 1991).

### 10.2. Malignancy in PM and DM (Studies I and II)

The frequency with which malignancy and IIM coexist varies between different studies and has been a subject of debate (Bohan 1975 part II). There are studies where the incidence of malignancy in PM and DM is relatively low, 6.1-8.5% (DeVere and Bradley 1975, Bohan et al. 1977, Henriksson and Sandstedt 1982, Hoffmann et al. 1983, Hochberg et al.1986, Love et al. 1991), but rates similar to ours have been published by others (Benbassat et al. 1985, Tymms and Webb 1985, Oddis et al 1990, Ramirez et al. 1990, Sigurgeirsson et al. 1992, Maugars et al. 1996).

Caldwell and McCallum (1986) suggested that a clue to an associated malignancy often rises from history, physical examination, or routine laboratory studies. Many authorities (Ansell 1985, Schulman et al. 1991) recommend that patients with myositis should always be investigated for the presence of an occult malignancy, especially if the patient is over the age of 40, male, or has DM (DeVere and Bradley 1975, Maugars et al. 1996). However, beyond a thorough history and physical

examination, chest radiographs and routine blood studies, data are too few and controversial to support the cost-effectiveness of exhaustive workups for occult malignancy (Moss and Hanelin 1977, Callen et al. 1980, Hoffman et al. 1983). However, the number of patients in these studies is small and more extensive studies are needed for evaluation.

The association of PM and DM with different cancer types raises the question of the type of connection between the etiopathogeneses of these diseases. Among the patients with DM in the present population-based study, the most frequent histological cancer type was ovarian adenocarcinoma. It can be speculated that, at least in some of these cases, myositis could have been a feature of the paraneoplastic syndrome. It is also possible that myositis and malignancy occur coincidentally, especially if myositis precedes or follows the tumour by many years or does not relapse with reappearance of the tumour. Related occurrence should be considered probable when myositis improves with tumour therapy and relapses with the recurrence of the tumour.

The role of immunosuppressive agents in the development of cancer may be significant especially in patients with long-lasting myositis and concomitant therapy with these drugs or when myositis develops years after the treatment of a malignant disease (Callen 1983, Rider and Miller 2000).

Scandinavian studies, including the present ones, have documented an increased rate of malignant disease associated with DM over that observed in the general population (Sigurgeirsson et al. 1992, Chow et al. 1995). Gynaecological malignant disease, in particular ovarian carcinoma, was highly overrepresented in patients with DM in our Scandinavian study (II), with the SIR at 72.0 (95% CI 37.5-138.4) at one-year follow-up, and in the Finnish study (I), with the SIR at 32 (95% CI 8.7-82), respectively.

Several studies have documented a slightly increased rate of malignancies in patients with PM, although the increase is not highly significant and might be partly explained by diagnostic suspicion bias, i.e., by more active procedures to search for cancer. Our study from Finland did not support this finding, giving a SIR of 1.0 (95%

CI 0.5-1.8) for PM, but in the study from the Nordic countries the SIR was 2.6 (95%CI 1.6-4.0).

More recent studies suggest that extensive malignancy workup, including abdominal and pelvic CT scans and age-appropriate cancer screening, is warranted in at least a subset of patients with DM or PM (Callen 2002, Sparsa et al. 2002) and the workup should be tailored to the patient's gender and ethnicity. In women, ovarian and breast cancer are the commonest types (Callen 2002). In our Finnish study (I) they presented 26% of all cancer cases, and in the Scandinavian study (II), 21.7%. According to the study of Whitmore et al. (1994) ovarian cancer is very difficult to detect with routine examinations or intermittent ultrasound or CT scans. They suggested as useful screening test serum CA-125 or variations on the presently available monoclonal antibody systems especially targeted at histologically nonmucinous ovarian cancers. The site of the malignant disease is associated with the patient's age, e.g., malignancy in a young man is more commonly testicular cancer, whereas in an older man colon or prostate cancer is more common (Callen 2000).

Cancer seems to be among the three main causes of death in PM and DM according to several studies (Bohan and Peter 1977, Baron and Small 1985, Benbassat et al. 1985, Basset-Seguin et al. 1990, Maugars et al. 1996). In the literature, the frequency of death due to associated cancer is strictly correlated with the size of the group. In our study among circulatory and musculoskeletal causes, cancer was the third, causing 16% of the deaths.

### 10.3. Prognostic factors and outcome in PM and DM (study III)

As early as 1975, Bohan and Peter highlighted the need of classification of homogeneous patient groups using diagnostic criteria including confidence limits and exclusions, which makes it possible to analyze prognostic factors and outcome more reliably. In their study, Bohan and Peter (1977) found older age, malignancy and prolonged duration prior to therapy to be unfavourable prognostic signs. Later, most reports have presented older age as a prognostic factor (Henriksson and Sandstedt 1982, Benbassat et al. 1985, Tymms and Webb 1985, Hochberg et al 1986, Basset-

Seguin et al 1985, Maugars et al. 1996, Marie et al. 2001). Our study supports this finding. Delay in diagnosis and malignancy have been suggested as prognostic factors in several studies since 1977 (Henriksson and Sandstedt 1982, Tymms and Webb 1986, Marie et al. 2001), whereas we found these to be prognostic for PM only. We also found the initial dose of corticosteroid in the PM group a risk factor prognostic of death, but except the factors mentioned above, no other individual factor reached statistical significance. Similar to our series, previous studies of Maugars et al. (1996) and Marie et al. (2001) did not find immunosuppressive therapy a prognostic factor.

Compared with the historical controls, patients with PM and DM live longer today and are more aggressively treated with immunosuppressive agents. The 5-year survival rate in PM and DM was 67% in a study in 1996 (Maugars et al.), and in a cohort of 46 patients in 2000, thus without malignancy-associated disease, it was 95% (Sultan et al. 2002). As early as in 1983, Hochberg et al found that between the years 1968 and 1978 the mean age of death in patients with PM and DM increased significantly in the U.S.; the mean age for white males increasing from 58 to 67 and for white females from 56 to 63, for non-white males from 41 to 57 and for non-white females from 41 to 52.

In the previous series, analyzing the survival of PM and DM patients, survival ranged from 34-73% and 42-85% at 5 and 10 years, respectively. Hochberg et al. (1986) found an improvement in the cumulative survival rate of their PM and DM patients compared with the data by Medsger et al. (1971) 15 years earlier, i.e., 73% after 8 years and 53% after 7 years of follow-up. However, the long-term prognosis of PM or DM after more than 5 years of follow-up cannot be accurately assessed concerning studies collected before 1996, because too few patients were still alive at that point and the confidence interval is too large (Hochberg et al 1986, Love et al 1991, Medsger et al 1971).

The three major causes of death (cardiovascular, musculoskeletal and carcinomatous) accounted for 81% of all deaths in the present series. This study also shows that PM and DM are associated with decreased survival. The differences in

previous mortality data may partly be explained by the better management of PM and DM patients today as compared with the older series.

While the survival of patients with PM and DM is improving due to the administration of modern immunosuppressive therapy, among other things, the survival data of patients of PM and DM with cancer is still unfavourable (Wakata et al. 2002, Danko et al. 2004). The lack of systematic autopsies in previous studies may be one of the factors in the underestimation of myocardial involvement (Benbassat et al. 1985, Tymms and Webb 1985, Maugars et al. 1996).

Mortality due to mycobacterial infections, especially TB, was high in the present series. This may be due to the low level of suspicion of TB in its early phase. In addition, the immunosuppressive state makes the individual more prone to extrapulmonary TB and more active infection.

It seems that the prognosis of PM and DM has improved during the 20$^{st}$ century (Hochberg et al. 1983a, Hochberg et al. 1986, Maugars et al. 1996, Sultan et al. 2000). The explanation might be partly due to the more exact diagnostic criteria, and hence early treatment, and also due to the development of more efficacious methods of treatment. Early recognition and prompt treatment of disease-related complications may further improve the morbidity and mortality of these diseases. The identification of certain serum autoantibodies in patients with IIMs can solidify the diagnosis of myositis in patients with atypical clinical features, and it may also provide clues to early discovery of systemic complications and better selection of different therapies, thereby leading to a more favourable disease course (Amoura et al. 2005).

### 10.4. Incidence of mycobacterial infections in PM and DM (study IV)

It is thought that one third of the world population has latent infection with M.tuberculosis (Hernandez-Pando et al. 2000), and in areas of low endemicity, most infections are due to reactivation of latent bacilli. As TB case rates have fallen, so has general awareness about this disease. In addition, the clinical spectrum of the disease has changed: extra-pulmonary disease represents an increasing proportion of all cases (Farer et al. 1979).

The efficacy of bacillus Calmette-Guerin (BCG) vaccine has ranged from 0 to 80 per cent due to several reasons (Glassroth et al. 1980). Even if vaccines of proved efficacy were available, the benefits of vaccination would decrease as the incidence of TB fell. In Finland, BCG vaccination ended 1 September 2006. During the time period of the present study, the BCG vaccination had evident benefits in Finland, although the benefits were questioned later (Tala-Heikkilä et al. 1998). Furthermore, the BCG vaccination provides protection against non-tuberculous (atypical) mycobacteria. These infections are more common in immunodeficient persons and especially in patients with pre-existing lung diseases. It is highly likely that these (non-tuberculous) infections did not play a significant role in BCG vaccinated PM and DM patients, although knowledge of their exact numbers remains unknown. It is always worth considering atypical infection in patients with PM and DM who present with musculoskeletal symptoms that do not settle with conservative treatment.

Our study was conducted in Finland which is a nonendemic country for tuberculosis. In the 60´s, when this study was started, the incidence of TB was remarkably high compared to today but had already been in decline for years. The risk factors, as well, were different at that time compared to those today. TB was more common in younger age groups then, both in women and men, than during the present decade. The incidence of TB in Finland in 1969 when the first patients of the present study had been diagnosed was 110/100 000, it was 47/100 000 in 1980 and 11/100 000 at the end of the follow-up period of this study (http://www.stat.fi). The declining trend can be seen in older age groups also. If we look at the incidence of TB in patients at the age of around 60 – corresponding to the mean age of our series – in the general population, considering the decline of TB over the period of this study, it can be noted that the incidence of TB in PM patients is remarkably high.

It is difficult to believe that so many myositis patients had a TB infection by chance in a country with very low TB incidence. The high frequency (16%) of patients with myositis and with a history of TB or an active TB infection may even suggest that in some cases TB has a causal association with myositis, i.e. “reactive myositis” due to latent TB. All in all, there is a significant risk of a TB infection during the first 6 months after the diagnosis and also later during the follow-up.

There is some evidence of the role of mycobacteria in other diseases also, the pathophysiology of which is thought to be mainly derived through immunological mechanisms. Actually, Autschbach et al. (2005) found a high prevalence of M. avium subspecies paratuberculosis DNA in gut tissues from individuals with Crohn´s disease but not in non-inflamed control tissues.

## 11. CONCLUSIONS

The results of this study on the epidemiology of PM and DM in the Finnish population confirm earlier findings from other ethnic populations:

- PM and DM may occur as a paraneoplastic syndrome.
- The risk of cancer is significantly increased during the first year and declines steadily with subsequent years following the initial diagnosis of PM or DM.
- DM, rather than PM, is more commonly associated with malignancy.
- The cancers of the gastrointestinal tract, lung cancer, ovarian cancer and non-melanoma skin cancer are the cancers most often noted in patients with DM.
- In addition, the multinational Scandinavian study completed these national findings with non-Hodgkin lymphoma for both DM and PM and lung and bladder cancer for PM.
- Patients with DM have a greater risk of dying from malignancy than patients with PM.
- Besides malignancy, factors associated with poor survival are older age in both PM and DM, and delay in the initiation of therapy and initial corticosteroid dose in PM.

The special findings of this study:

- Patients with PM are at an increased risk of TB and other mycobacterial infections also in non- endemic countries for TB.
- The possibility of the reactivation of TB or a new mycobacterial infection must be noted in immunosupprimized patients including those with myositis.
- This study raises the question of the role of a mycobacterial infection as an aetiological factor of myositis.

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## 14. APPENDICES

Table 1. Myositis-specific autoantibodies (MSA). Modified by the author from tables by Targoff (1994), Hengstman et al. (2001), Gunawardena et al. (2008) and Oddis (2008)

| Autoantibody | Antigenic target | Frequency in IIM (%) | Clinical associations |
|---|---|---|---|
| Anti-Jo-1 | Histidyl-tRNA synthetase | 11-20 | ASS*) |
| Anti-PL-7 | Threonyl-tRNA synthetase | 2 | ASS |
| Anti-PL-12 | Alanyl-tRNA synthetase | 1-2 | ASS; lower frequency of myositis |
| Anti-OJ | Isoleucyl-tRNA synthetase | 1 | ASS |
| Anti-EJ | Glycyl-tRNA synthetase | 1 | ASS; DM>PM |
| Anti-KS | Asparaginyl-tRNA synthetase | <1 | ASS. Rare; most patients have ILD |
| Anti-tRNA | Histidyl-tRNA | 7 | ASS. In about 30% of patients with anti-Jo-1 |
| Anti-tRNA | Alanyl-tRNA | 1 | ASS. In the sera of most patients with anti-PL-12 |
| Anti-Mi-2 | Nuclear helicase | 4-14 | Classic DM with good response to treatment. PM in 10% |
| Anti-SRP | Signal recognition particle-complex | 4-5 | Severe necrotizing myopathy; cardiac complications; |
| Anti-p155/140 | p155-transcription intermediary factor 1-gamma | 13-21 | CAM in adults. Severe cutaneous disease in adult and juvenile DM. |
| Anti-KJ | Unidentified translation factor | <1 | PM. ILD. Raynaud´s phenomenon- |
| Anti-MJ | Nuclear matrix protein NXP-2 | not given | CAM in adults. |
| Anti-SAE | small-ubiquitin-like modifier enzyme | 4-8 | Adult DM. May present with CADM first |
| Anti-CADM-140 | unknown | 19 | CADM. Interstitial pneumonia |
| Anti-PMS1 | PMS1 | not given | Myositis. Specific phenotype not described |

*) myositis with fever, idiopathic interstitial lung disease, arthritis, Raynaud´s and mechanic's hands and poor response to treatment; ASS, antisynthetase syndrome; CAM, cancer-associated myositis; ILD, interstitial lung disease; CADM , clinically amyopathic dermatomyositis;

Table 2. Myositis-associated autoantibodies (MAA). Modified by the author from tables by Targoff (1994), Hengstman et al. (2001) and Oddis (2008).

| Autoantibody | Antigenic target | Frequency in IIM(%) | Clinical associations |
|---|---|---|---|
| Anti-PM-Scl | Exosome proteins; multiprotein complex | 5-10 | Overlap myositis with limited systemic sclerosis; myositis less severe |
| Anti-U1RNP | U1 small nuclear ribonucleoprotein | 5-10 | MCTD or overlapping myositis syndromes |
| Anti-U2RNP | U2 small nuclear ribonucleoprotein | <3 | Myositis, SSc. Usually with anti-U1RNP |
| Anti-Ku | DNA binding complex | 1 | PM-SSc overlapping; occasionally SLE |
| Anti-Ro/SSA | Ro60 and Ro52 | 10-20 | Sjögren´s; SLE; seen with antisynthetases |
| Anti-Wa | tRNA | not given | Resembling antisynthetase syndrome. Especially in patients with SSc |
| Anti-FER | Elongation factor 1a | <1 | Clinical specificity uncertain. Myositis |
| Anti-Mas | tRNAser and? related protein | 1 | Myositis |

Abbreviations: CTD, connective tissue disease; IIM, idiopathic inflammatory myopathy; MCTD, mixed connective tissue disease; SSc, systemic sclerosis

Table 3. Incidence of malignancy (%) in patients with PM and DM.

| | DM (%) | PM (%) | PM and DM together (%) | Total number of patients |
|---|---|---|---|---|
| Bohan et al. (1977)* | 11 | 6 | 9 | 142 |
| Callen et al. (1980) | 26 | 3 | 13.5 | 58 |
| Vesterager et al. (1980) | 50 | NI | NI | 18 |
| Henriksson and Sandstedt (1982) * | 15.5 | 7.5 | 8 | 86 |
| Herson et al.(1982) | NA | NA | 22 | 50 |
| Black et al. (1982) | NA | 18 | NA | 27 |
| Manchul et al. (1982) | NA | NA | 24 | 71 |
| Hoffman et al. (1983) | 16.5 | 9 | 7.5 | 27 |
| Baron and Small | 46 | 18 | 32 | 22 |
| Benbassat et al. (1985) | 25.5 | 14.5 | 14 | 89 |
| Holden et al. (1985) | NA | NA | 11 | 36 |
| Manchul et al. (1985) | NA | NA | 24 | 71 |
| Tymms and Webb (1985) | 16.5 | 8 | 15 | 105 |
| Hochberg et al. (1986) | 12.5 | 8.5 | 8.5 | 76 |
| Lakhanpal et al. (1986) | 22 | 28 | 25 | 115 |
| Hidano et al. (1986)* | 30 | NI | NI | 569 |
| Lakhanpal et al. (1987) | 12 | 12.5 | NA | 65 |
| Bonnetblanc et al. (1990) | 28 | NI | NA | 118 |
| Basset-Seguin et al. (1990) | 41 | NI | NA | 32 |
| Love et al.(1991) | NA | NA | 6.1 | 212 |
| Sigurgeirsson et al. (1992) | 15 | 9 | NA | 788 |
| Maugars et al. (1996)** | 20.5 | 13.5 | 18.5 | 49 |
| Marie et al. (2001) | 42 | 2 | 21 | 77 |
| Stockton et al. (2001) | 27 | 17 | 21 | 705 |
| Buchbinder et al. (2001) | 42 | 18 | 22 | 537 |
| András et al. (2008) | 29 | 3.5 | 12 | 309 |

Abbreviations: DM, dermatomyositis with malignancy; PM, polymyositis with malignancy; PM or DM, malignancy with polymyositis or dermatomyositis or myositis undefined; NA, not given; NI, not included; *, including only adult patients; **, excluding juvenile and overlap myositis

Table 4a. Overall mortality in published series of patients with polymyositis and dermatomyositis, not classified according to Bohan and Peter (1975).

| Study | Mortality % | surveyed time interval | Number of patients |
|---|---|---|---|
| Steiner (1903) | 60.7 | not given | 28 |
| O´Leary and Waisman (1940) | 50.0 | 1925-1938 | 40 |
| Sheard Jr (1951) | 52.0 | 1927-1947 | 25 |
| Pearson (1963) | 25.0 | not given | 48 |
| Rose et al (1966) | 30.3 | 1954-1964 | 89 |
| Logan et al (1966) | 41.1 | 1950-1963 | 63 |
| Winkelman et al (1968) | 27.6 | not given | 289 |
| Medsger et al (1971) | 47 | 1947-1968 | 124 |
| Riddoch and Morgan-Hughes (1975) | 40.0 | 1960-1970 | 20 |
| DeVere and Bradley (1975) | 27.9 | 1954-1974 | 118 |
| Carpenter et al (1977) | 45.2 | 1947-1971 | 62 |
| Hochberg et al (1983) | 27.2 | 1970-1981 | 76 |

Table 4b. Cumulative survival rates of patients with PM and DM according to the original or modified criteria of Bohan and Peter (1975).

| Study | 1-year survival rate in PM/DM % | 5-year survival rate in PM/DM % | 10-year survival rate in PM/DM % | follow-up yrs (range) | Number of patients |
|---|---|---|---|---|---|
| Bohan et al (1977)* | NA | 86 | NA | 4.3 (0.2-21.1) | 153 |
| Baron and Small (1985) | NA | NA | 68 | 5.6 | 22 |
| Benbassat et al. (1985) | 66 (M) 72 (F) | 50 (M) 52 (F) | NA | 21 | 92 |
| Hochberg et al. (1986) | 94 | 80 | NA | 8 | 76 |
| Lakhanpal et al. (1986) | 76 | 57 | 42 | 15 | 115 |
| Basset-Seguin et al. (1990) | 66 | 48 | NA | 3.4 (0.1-17) | 32 |
| Ehrenstein et al. (1992) | NA | 88 | NA | 8 (3-21) | 25 |
| Sigurgeisson et al. (1992) | 90 | 65/60 | 52/50 | 11.4 | 788 |
| Maugars et al. (1996) | 83 | 81/60 | NA | 11.6 (6.3-21.7) | 69 |
| Xue et al. (1997) | NA | 53 | NA | NA | 119 |
| Marie et al. (2001) | NA | 95 | 84 | 4 (0.1–24) | 77 |
| Sultan et al. (2002) | NA | 95 | 84 | 20 | 46 |
| András et al. (2008) | 95 | 92 | 89 | 21 (8-190) | 309 |

*=children are included in study; DM=dermatomyositis; PM=polymyositis; NA=not given; M= male; F= female

Table 5. Cause of death in patients with PM and DM in studies using the criteria of Bohan and Peter (1975).

| CAUSE OF DEATH | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Study | infection % | musculoskeletal % | cardiovascular % | respiratory % | cancer % | other % | all deaths (N) | Total (N) |
| Bohan and Peter (1977) | 19 | 9.5 | 9.5 | not given | 24 | 38 | 21 | 153 |
| Baron et al. (1985) | 14.3 | not given | not given | not given | 71.4 | 14.3 | 7 | 22 |
| Benbassat et al.(1985)* | not given | not given | 19.9 | 26.7 | 16.7 | 36.7 | 30 | 92 |
| Tymms and Webb (1985) | 21.0 | 26.3 | 15.8 | not given | 21.1 | 15.8 | 19 | 105 |
| Hidano et al. (1986)** | 10.2 | 2.4 | 1.9 | 18.5 | 54.6 | 12.4 | 205 | 569 |
| Basset-Seguin et al. (1990) | 21.4 | not given | 14.3 | not given | 64.3 | not given | 14 | 32 |
| Ramirez et al. (1990) | 100 | 0 | 0 | 0 | 0 | 0 | 1 | 25 |
| Sigurgeirsson et al. (1992) | 0.9 | 18.1 | 36.0 | 4.5 | 27.1 | 13.4 | 336 | 750 |
| Maugars et al. (1996) | 6 | 3 | 27 | 27 | 17 | 20 | 30 | 69 |
| Marie et al. (2001) | not given | 5.9 | not given | 35.3 | 47.1 | 11.7 | 17 | 77 |

*=including children and overlap syndromes

**=including only adults and DM

***=according to autopsy reports

Table 6. Prognostic factors in published series of patients with PM and DM using the criteria of Bohan and Peter (1975).

| N | Study | Unfavourable prognostic. signs | Signs not shown to have any prognostic significance |
|---|---|---|---|
| 153 | Bohan et al. (1977) | Malignancy, older age, prolonged duration prior to treatment | Severity of activity, scleroderma, Raynaud´s phenomenon |
| 107 | Henriksson and Sandstedt (1982) | Older age, prolonged duration prior to treatment, cardiac manifestations, malignancy, no response to treatment | |
| 92 | Benbassat et al. (1985) | Independent risk factors: older age, fever, leukocytosis, failure to induce remission. Comorbid factors: malignancy, skin rash, dysphagia, shorter disease history | Arthritis, ESR, abnormal muscle histopathology, EMG abnormalities, Raynaud´s phenomenon, haemoglobin level, blood pressure, ECG abnormalities, splenomegaly, sex, ANA, level of muscle enzymes |
| 105 | Tymms and Webb (1985) | Older age, muscle weakness exceeds 4 months before diagnosis | |
| 76 | Hochberg et al. (1986) | Age, cardiac involvement, dysphagia | Malignancy, white and non-white race, gender |
| 32 | Basset-Seguin et al. (1990) | Malignancy, higher age, dysphagia, extensive cutaneous lesions on the trunk, elevated erythrocyte sedimentation rate | Low level of CK |
| 69 | Maugars et al. (1996) | For DM: Old age, malignancy, pulmonary interstitial fibrosis, asthenia-anorexia, lack of muscle improvement For PM: Old age, failure to improve muscle strength in response to treatment in one month, lack of myalgia as presenting symptom For DM and PM: dysphonia, absence of dysphagia | Immunosuppressive drugs, diagnostic delay, cardiac manifestations at onset, inflammatory changes in muscle biopsy. |
| 77 | Marie et al. (2001) | Older age, treatment delay, pulmonary involvement, malignancy | CK, therapy with methotrexate, azathioprine, cyclophosphamide or IVIG |

Figure 1. The procedure and concept of PM and DM patients selection and follow-up**.**

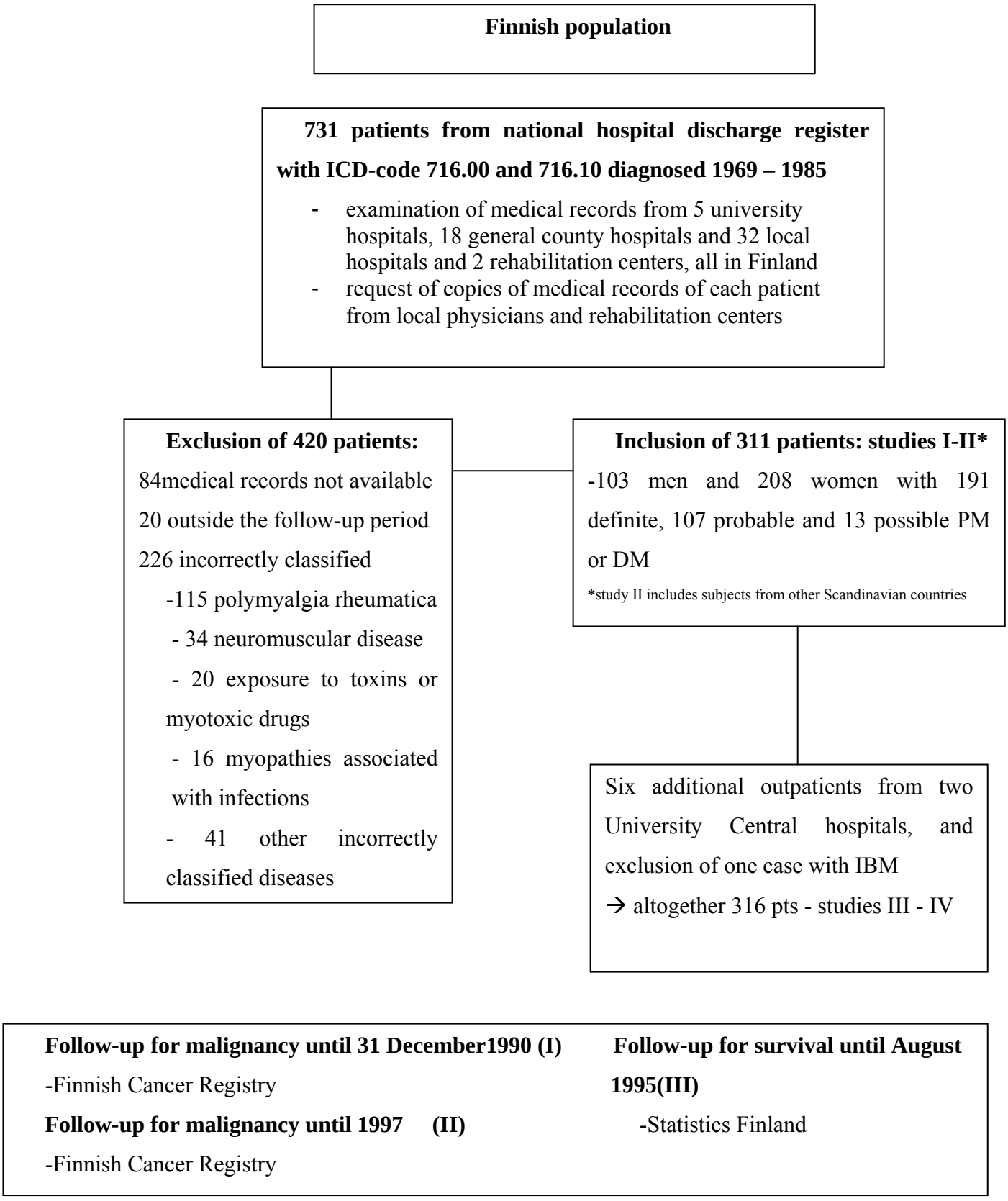

Table 7. Baseline demographic and clinical characteristics of PM and DM patients (III).

| | PM<br>N=176 | DM<br>N=72 | P-value |
|---|---|---|---|
| Number of female, (%) | 110 (63) | 53 (74) | 0.094 |
| Mean age, (SD) | 56 (14) | 53 (17) | 0.13 |
| Median S-CK†, (IQR) | 50 (20 , 162) | 44 (10 , 87) | 0.058 |
| Median ESR, (IQR) | 27 (13 , 45) | 27 (13 , 46) | 0.97 |
| Median delay of diagnosis, (IQR) | 7 (3 , 24) | 4 (1 , 7) | <0.001 |
| Median initial dose of corticosteroids‡, (IQR) | 0.7 (0.4 , 1.0) | 0.8 (0.4 , 1.0) | 0.51 |
| Number on cytostatic drugs, (%)<br>median time used, months, (IQR) | 66 (38)<br>19 (2 , 58) | 22 (31)<br>13 (4 , 50) | 0.29 |

† x-fold of upper limit normal.
‡ mg/kg/day.
IQR = interquartile range

Table 8. Cox regression models for patients with PM and DM (III).

| Risk factor | Polymyositis (N=154) | | Dermatomyositis (N=62) | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | P-value | Hazard ratio (95% CI) | P-value |
| Male sex | 1.29 (0.83 to 2.02) | 0.26 | 1.35 (0.54 to 3.70) | 0.51 |
| Age, yrs | 1.09 (1.06 to 1.11) | <0.001 | 1.07 (1.03 to 1.11) | <0.001 |
| Delay of diagnosis, mo | 1.01 (1.00 to 1.02) | 0.006 | 1.00 (0.96 to 1.05) | 0.86 |
| CK | | | | |
| Normal | 1.00 | | 1.00 | |
| >1xULN | 1.04 (0.57 to 1.88) | 0.91 | 1.61 (0.56 to 3.42) | 0.29 |
| >10xULN | 1.00 (0.53 to 2.00) | 0.99 | 3.04 (0.81 to 7.52) | 0.037 |
| ESR | 1.00 (0.99 to 1.01) | 0.60 | 1.00 (0.99 to 1.01) | 0.85 |
| Cancer | 1.99 (1.01 to 3.94) | 0.047 | 2.16 (0.95 to 4.50) | 0.052 |
| Initial dose of corticosteroids mg/kg | 1.06 (1.00 to 1.11) | 0.035 | 1.03 (0.73 to 2.43) | 0.36 |
| Use of cytostatics | 1.03 (0.65 to 1.64) | 0.90 | 0.93 (0.36 to 2.40) | 0.87 |

ULN=Upper limit normal
CK= Creatine phosphokinase
ESR= Erythrocyte sedimentation rate

Table 9. Main causes of death of 149 deceased patients with PM and DM (III).

| Main cause of death | PM (N=107) Number (%) | DM (N=42) Number (%) | Total (N=149) Number (%) |
|---|---|---|---|
| Infection | 4 (4) | 0 (0) | 4 (2.5) |
| Urogenital | 1 (1) | 0 (0) | 1 (1) |
| Musculoskeletal | 31(29) | 13 (31) | 44 (30) |
| Unidentified | 1 (1) | 0 (0) | 1 (0.5) |
| Accident | 2 (2) | 0 (0) | 2 (1) |
| Cancer | 10 (9) | 14 (33) | 24 (16) |
| Endocrine or metabolic | 1 (1) | 0 (0) | 1 (0.5) |
| Psychiatric | 2 (2) | 0 (0) | 2 (1) |
| Neurologic | 4 (4) | 1 (2) | 5 (3) |
| Circulatory | 40 (37) | 13 (31) | 53 (36) |
| Respiratory | 6 (6) | 1 (2) | 7 (5) |
| Gastrointestinal | 5 (5) | 0 (0) | 5 (3) |

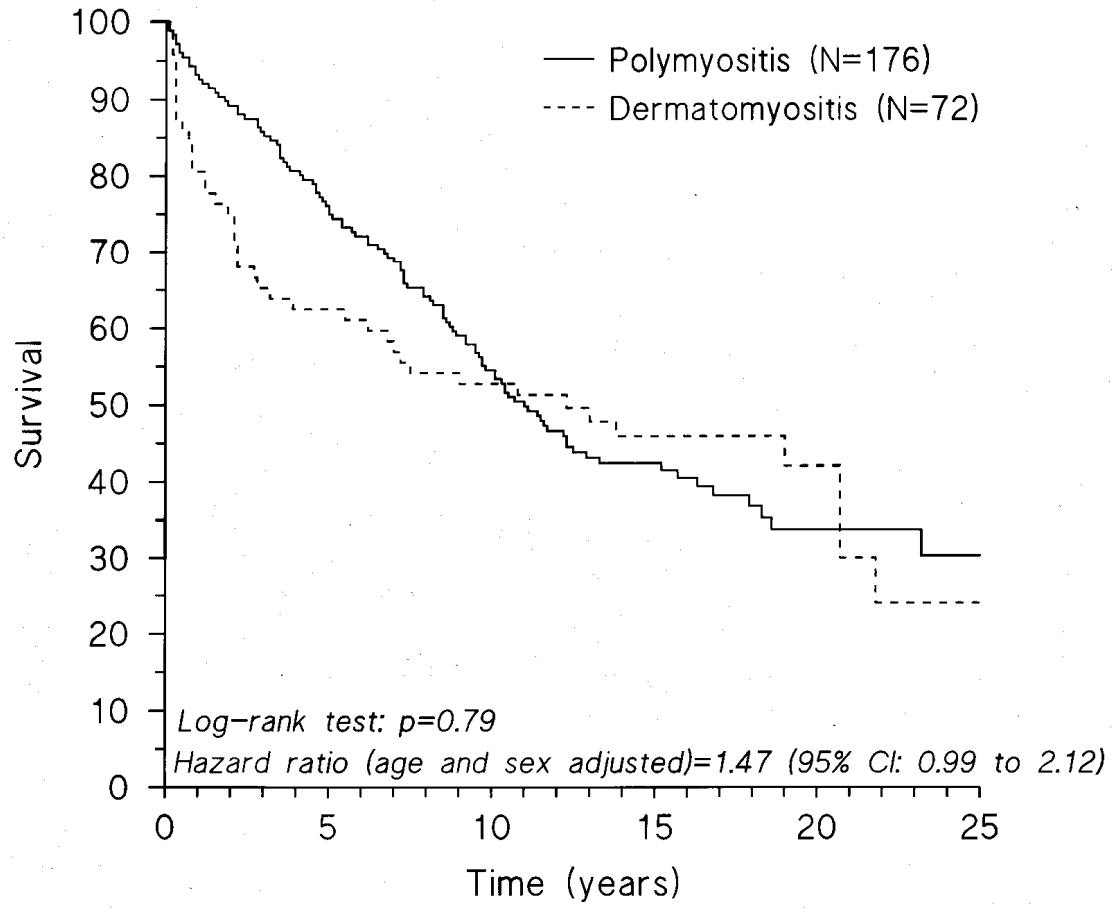


Figure 2. Product-limit survival curves for PM and DM patients

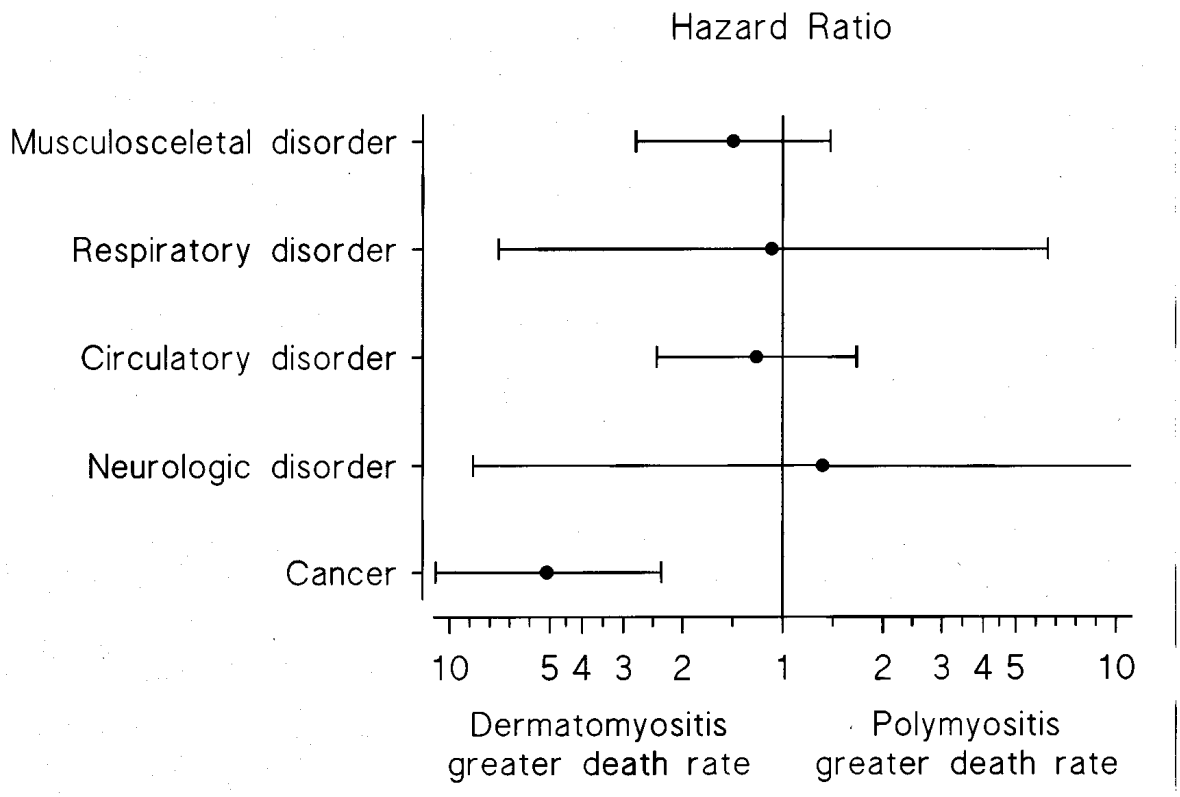


Figure 3. Age- and sex-adjusted risks of PM and DM patients to die from various main causes of death as shown by a forest plot

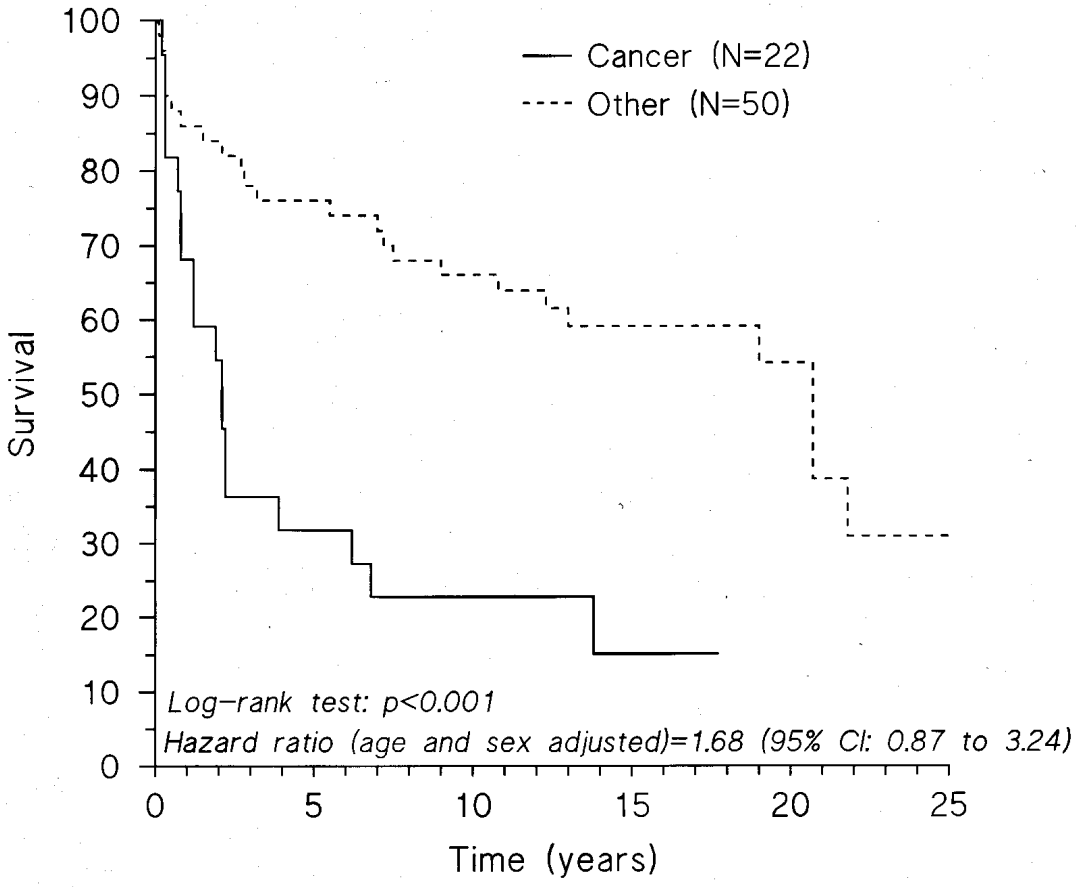


Figure 4. Product-limit survival curves for DM patients with and without cancer.

Table 10. Data on PM and DM patients with TB-infection (IV).

| Myositis type | Sex | Age at diagnosis of myositis | Time from dg of myositis to TB (months) | Bacterial type | Type of infection | Use of cytostatics (months)/drug | TB as a cause of death (N/Y) |
|---|---|---|---|---|---|---|---|
| PM | F | 21 | 97 | M. atypica | dermal abscess | 2/aza | Alive |
| PM | M | 62 | 111 | M. tub | pleuritis | 17/aza | N |
| PM | M | 75 | 3 | M. tub | disseminated | N | Y |
| PM | F | 65 | 12 | M. tub | pulmonary | N | N |
| PM | F | 62 | 10 | M. tub | disseminated | 1/aza | N |
| PM | F | 60 | 89 | M. tub | pulmonary, miliary | N | Y |
| PM | F | 74 | 6 | M. tub | disseminated | N | Y * |
| PM | F | 55 | 4 | M. atypica | pulmonary | 1/aza | Alive |
| PM | M | 77 | 20 | M. tub | pulmonary | N | Alive |
| PM | M | 66 | 104 | M. tub | pulmonary, miliary | N | Y |
| PM | F | 48 | 37 | M. atypica | pulmonary, axillary abscess | 28/aza | Alive |
| PM | F | 57 | 94 | M. atypica | glenohumeral joint | 38/aza | Alive |
| PM | F | 36 | 18 | M. tub | cervical | 4/aza | Alive |
| DM | M | 42 | 19 | M. tub | pulmonary | N | Alive |
| DM | M | 62 | 8 | M. tub | disseminated | N | Y |

F = female, M = male; dg = diagnosis; M. atypical = atypical mycobacteria; M. tub = *Mycobacterium tuberculosis;* aza= azathioprine; N = no, Y = yes. * Immediate cause of death (Ia)

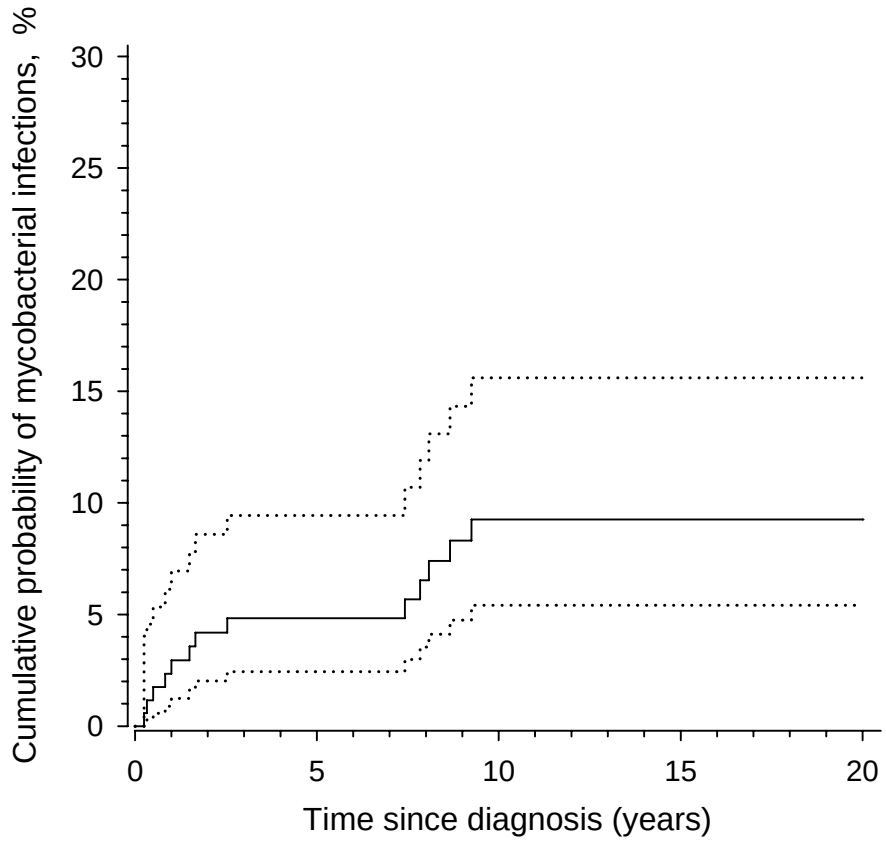


Figure 5. Cumulative probability of mycobacterial infections in 176 patients with polymyositis after the diagnosis of myositis.

## 14. ORIGINAL PUBLICATIONS I-IV

# Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study

*Catherine L Hill, Yuqing Zhang, Bardur Sigurgeirsson, Eero Pukkala, Lene Mellemkjaer, Antti Airio, Stephen R Evans, David T Felson*

## Summary

**Background** Dermatomyositis and polymyositis are associated with cancer, but previous nationwide studies have not had sufficient cases to test the association between myositis and specific cancer types. Our aim was to investigate the risk of specific cancer types in individuals with dermatomyositis and polymyositis.

**Methods** We did a pooled analysis of published national data from Sweden, Denmark, and Finland. All patients with dermatomyositis and polymyositis (⩾15 years old) were identified by discharge diagnosis from the Swedish National Board of Health (1964–83), Danish Hospital Discharge Registry (1977–89), and Finnish National Board of Health (1969–85). Personal details were matched to national cancer registries, to identify all cases of cancer up to 1987 in Sweden, 1995 in Denmark, and 1997 in Finland, and to national death registries for the same periods. We calculated standardised incidence ratios (SIR) for individual cancer sites for dermatomyositis and polymyositis separately, using national cancer rates by country, sex, age, and date.

**Findings** We identified 618 cases of dermatomyositis, of whom 198 had cancer. 115 of the 198 developed cancer after diagnosis of dermatomyositis. This disease was strongly associated with malignant disease (SIR 3·0, 95% CI 2·5–3·6), particularly ovarian (10·5, 6·1–18·1), lung (5·9, 3·7–9·2), pancreatic (3·8, 1·6–9·0), stomach (3·5, 1·7–7·3), and colorectal (2·5, 1·4–4·4) cancers, and non-Hodgkin lymphoma (3·6, 1·2–11·1). 137 of the 914 cases of polymyositis had cancer, which developed after diagnosis of polymyositis in 95. Polymyositis was associated with a raised risk of non-Hodgkin lymphoma (3·7, 1·7–8·2), and lung (2·8, 1·8–4·4) and bladder cancers (2·4, 1·3–4·7). In both dermatomyositis and polymyositis, risk of malignant disease was highest at time of myositis diagnosis.

**Interpretation** Our results provide evidence that dermatomyositis is strongly associated with a wide range of cancers. The overall risk of malignant disease is also modestly increased among patients with polymyositis, with an excess for some cancers.

*Lancet* 2001; **357:** 96–100
*See Commentary page pg 85*

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## Introduction

Previous epidemiological studies have shown an increased rate of cancer in people with dermatomyositis and polymyositis.[1–4] However, these studies have had too few myositis cases with each cancer type to examine the associations with specific cancers.[1–4] Paraneoplastic syndromes such as Eaton-Lambert syndrome, limbic encephalitis, and cerebellar ataxia are mediated by cancer-associated antibodies and are usually linked with particular cancer types.[5] Identification of an association with specific cancer types would both enhance our understanding of the causes of myositis and help to identify appropriate diagnostic workup for cancer screening in affected patients.[6] Epidemiological studies and case series of dermatomyositis and polymyositis suggest an association with ovarian, lung, and gastric cancers in the former disease.[1,7,8]

Our aim was to investigate risk of specific cancer types in dermatomyositis and polymyositis by pooled analysis of published national data from Sweden, Denmark, and Finland. We studied cancers that arose before and after development of myositis.

## Methods

### *Patients*

We used data from three published studies.[1–3] Additionally, more recent follow-up data were available from Denmark and Finland. Only patients in hospital who had polymyositis and dermatomyositis were included. Each country has a cancer registry to which reporting of cancers is mandatory for treating physicians and pathology and haematology laboratories. All cancers were classified according to the International Classification of Diseases (ICD-7). Each country records all deaths. The cancer registries of the three countries have been validated, and have over 95% completion rates.[9–11]

In Sweden, all adults (⩾15 years) with dermatomyositis and polymyositis were identified by discharge diagnosis from the National Board of Health, with ICD-7 codes 710.00, 710.01, and 726.30 from 1964 to 1968, and ICD-8 codes 716.00 and 716.10 from 1969 to 1983. Patients with myositis were matched to the cancer registry to identify cases of cancer diagnosed in 1987, and unique personal identification numbers were issued. To provide information on censoring after myositis, personal identification numbers were matched to the Cause-of-Death Registry, which includes information on all deaths whether they took place in Sweden or elsewhere. Two dermatologists reviewed a random sample of 10% (76) of hospital records of patients diagnosed with myositis who were classified according to Bohan and Peter's criteria.[12] This system defines polymyosis as an inflammatory myositis with no rash, and dermatomyositis as an inflammatory myositis with dermatological features (including heliotrope rash, scaly erythematous rash over dorsum of hands, or involvement of the knees, elbows, and medial malleoli, face, neck, and upper torso). Of those reviewed, 72% (50) were classified as definitely, and 20% (14) as probably, having either dermatomyositis or polymyositis.

In Denmark, all adults (≥15 years) with dermatomyositis or polymyositis were identified by discharge diagnosis (ICD-8 codes) from the hospital registry between 1977 and 1989. A unique personal identification number was issued, and all those with myositis were linked to the national cancer registry to identify all cases of cancer until 1995. Myositis patients were also matched to the Central Population Register, which contains information about death and migration of all residents.

In Finland, all adults (≥15 years) with dermatomyositis or polymyositis were identified by discharge diagnosis (ICD-8 codes) from the National Board of Health between 1969 and 1985. The medical records of each patient with a myositis diagnosis were requested, and a rheumatologist reviewed those available (89%, 627). Of these records, 50% (311) of cases were excluded because of incorrectly classified disease or failure to fulfil Bohan and Peter's diagnostic criteria.[12] The remaining patients were issued with personal identifiers, which were subsequently matched to the national cancer registry and the national mortality files of Statistics Finland until 1997.

### *Analysis*

Our main aim was to determine risk of developing cancer after diagnosis of myositis. For this analysis, patients diagnosed with dermatomyositis or polymyositis before age 15 years were excluded. Patients with non-melanoma skin cancer were also excluded, because this cancer type is reported differently in the three Nordic countries. Finally, in-situ cancers were excluded from the Swedish and Danish data sets because these cancers are not included in the national rates. In-situ cancers (apart from skin and cervix) were included in the Finnish data. Second and subsequent cancers that constituted the first cancer diagnosed after myositis were included. We established the number of years of follow-up for each patient with myositis, beginning at the date of diagnosis and ending at the date of censorship—ie, date of diagnosis of cancer, death, or end of follow-up period.

We examined the association between dermatomyositis and polymyositis and all cancer types combined and specific types of cancer individually with standardised incidence ratios (SIR)—ie, the number of cancer cases that arose among dermatomyositis or polymyositis patients divided by the expected number of cancer cases according to national age-specific, sex-specific, and period-specific cancer rates. Because certain histological subtypes of cancer share the ability to produce substances that cause paraneoplastic syndromes, we assessed the risk of histological types of cancer developing in myositis. We used three broad categories: squamous carcinomas (head and neck cancers, oesophageal cancer, and carcinoma of the cervix), adenocarcinomas (stomach, colorectal, pancreas, thyroid, breast, ovary, uterus, and prostate), and haemopoietic and lymphatic malignant diseases (non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and leukaemia). Categories for squamous carcinomas and adenocarcinomas were based on the most common histological type at each cancer site. Lung cancers were not included in any of these categories, since histology was unknown for a substantial proportion of cases in the Swedish and Danish data sets, and this site has equally common histological subtypes.

To assess whether associations varied according to time after myositis diagnosis, we divided follow-up into three periods: 1 year or less; 2–5 years, and more than 5 years. A further analysis was done to assess the risk of malignant disease among those aged between 15 and 44 years and 45 years and over at myositis diagnosis, separately for dermatomyositis and polymyositis.

Cancers identified before diagnosis of myositis were classified according to cancer site (ICD-7 codes), and by numbers of years before diagnosis of myositis. To provide an estimate of the risk of cancer in myositis patients in the 2 years before myositis diagnosis, we calculated SIRs by observed and expected cancers in all myositis patients in two periods: 0–11 and 12–23 months before myositis diagnosis. Only people surviving cancer could be diagnosed with myositis; thus, the expected rates had to be adjusted for cancer survival. To make this adjustment, risks were divided by Finnish site-specific cancer survival rates.[13] For relative risks at 0–11 and 12–23 months before diagnosis of myositis, we used 6 and 18 month survival rates, respectively, and made this survival adjustment for relative risks significantly ($p<0.05$) raised in non-adjusted analyses.

## Results

We identified 618 patients with dermatomyositis (Sweden n=329, Denmark n=218, Finland n=71) and 914 with polymyositis (Sweden n=389, Denmark n=350, Finland n=175). The mean age at diagnosis of dermatomyositis was 55·6 (SD 18·4) years for men and 55·4 (17·1) for women, and for polymyositis was 56·2 (16·2) for men, and 57·5 (16·3) for women. Among those with dermatomyositis, a total of 198 cancers were identified, of which 115 developed after diagnosis. Among those with polymyositis, 137 cancers were identified, of which 95 developed after diagnosis.

### *Association between dermatomyositis and polymyositis, and cancer*

For all cancer types, there was a three-fold increase in risk of malignant disease after diagnosis of dermatomyositis. The SIRs for men and women with dermatomyositis were 3·3 (95% CI 2·5–4·4) and 2·8 (2·2–3·6), respectively. Since SIRs were almost the same for sex-neutral cancers, results for men and women were combined (table 1). The highest risks after diagnosis of dermatomyositis were for ovarian, lung, pancreatic, stomach, and colorectal cancers, and for lymphomas. However, the relative risk of many other malignant diseases was also raised. Polymyositis increased risk of cancers by 30%. The SIR for the entire follow-up for polymyositis was 1·4 (95% CI 1·0–1·8) for men and 1·2 (0·9–1·6) for women. The greatest increased risks were for non-Hodgkin lymphoma and lung and bladder cancers. By contrast with

| Cancer type (ICD-7 code) | Dermatomyositis (n=618) | | Polymyositis (n=914) | |
|---|---|---|---|---|
| | Number | SIR (95% CI) | Number | SIR (95% CI) |
| All (140–205) | 115 | 3·0 (2·5–3·6) | 95 | 1·3 (1·0–1·6) |
| Oesophagus (150) | 1 | 2·9 (0·4–20·8) | 1 | 1·3 (0·2–9·4) |
| Stomach (151) | 7 | 3·5 (1·7–7·3) | 1 | 0·3 (0·04–1·9) |
| Colorectal (153, 154) | 12 | 2·5 (1·4–4·4) | 10 | 1·1 (0·6–2·0) |
| Pancreas (157) | 5 | 3·8 (1·6–9·0) | 1 | 0·4 (0·1–2·7) |
| Lung, trachea, and bronchus (162) | 19 | 5·9 (3·7–9·2) | 20 | 2·8 (1·8–4·4) |
| Breast (170) | 12 | 2·2 (1·2–3·9) | 12 | 1·4 (0·8–2·5) |
| Cervix (171) | 2 | 2·7 (0·7–10·8) | 0 | 0 (0–2·9) |
| Ovary (175) | 13 | 10·5 (6·1–18·1) | 2 | 1·1 (0·3–4·2) |
| Prostate (177) | 5 | 1·8 (0·8–4·4) | 4 | 0·6 (0·2–1·6) |
| Kidney (180) | 2 | 1·7 (0·4–6·7) | 4 | 1·5 (0·6–3·9) |
| Bladder (181) | 3 | 1·8 (0·6–5·6) | 9 | 2·4 (1·3–4·7) |
| Non-Hodgkin lymphoma (200) | 3 | 3·6 (1·2–11·1) | 6 | 3·7 (1·7–8·2) |
| Hodgkin's lymphoma (201) | 1 | 5·9 (0·8–42·0) | 0 | 0 (0–11·1) |
| Myeloma (203) | 1 | 1·5 (0·2–10·5) | 2 | 2·1 (0·5–8·5) |
| Leukaemia (204) | 2 | 2·6 (0·7–10·5) | 2 | 1·4 (0·3–5·4) |

Table 1: **Standardised incidence ratios (SIR) and 95% CIs for cancer after diagnosis of dermatomyositis or polymyositis**

| | Squamous* | | Adenocarcinoma† | | Haematological and lymphatic‡ | |
|---|---|---|---|---|---|---|
| | Number | SIR (95% CI) | Number | SIR (95% CI) | Number | SIR (95% CI) |
| **Dermatomyositis** | | | | | | |
| Men | 4 | 8·1 (3·0–21·6) | 15 | 2·6 (1·6–4·3) | 4 | 4·0 (1·5–10·6) |
| Women | 3 | 2·3 (0·7–7·1) | 40 | 3·4 (2·5–4·6) | 3 | 2·1 (0·7–6·5) |
| **Polymyositis** | | | | | | |
| Men | 2 | 1·6 (0·4–6·4) | 10 | 0·6 (0·3–1·2) | 5 | 2·3 (0·9–5·5) |
| Women | 1 | 1·0 (0·7–1·6) | 20 | 1·0 (0·7–1·6) | 5 | 2·2 (1·0–5·5) |

*Includes head and neck cancers and oesophageal and cervical cancer. †Includes stomach, colorectal, pancreas, thyroid, ovarian, breast, and prostate cancer. ‡Includes non-Hodgkin lymphoma, Hodgkin's lymphoma, myeloma, and leukaemia.

Table 2: **Standardised incidence ratios (SIR) and 95% CIs for cancers of different histological type in dermatomyositis and polymyositis**

dermatomyositis, there was no increased risk of ovarian, colorectal, stomach, or pancreatic cancers (table 1).

*Association between histological types of cancer and myositis*

We examined whether or not myositis was associated with specific histological subtypes (table 2). In dermatomyositis, although adenocarcinomas were the most common type of cancer recorded, there was an increased risk associated with all histological types. Risk of squamous cell cancers and adenocarcinomas was not increased in patients with polymyositis; however, risk of haematological and lymphatic malignant diseases was increased two-fold.

*Length of follow-up and risk of cancer*

The risk of cancer was highest within the first year of myositis diagnosis, and dropped substantially thereafter (table 3). In those with polymyositis, the risk fell to expected rates 5 years after diagnosis; however, the risk in dermatomyositis did not return to expected population values for most cancers. The risks of ovarian, pancreatic, and lung cancer remained high up to 5 years after diagnosis of dermatomyositis, and the increased risk of pancreatic and colorectal cancer extended past the 5 years follow-up. The risk of non-Hodgkin's lymphoma was increased in the first year but not subsequently.

*Age and risk of cancer*

Although there was a raised risk of malignant disease in people aged 15–44 years at time of dermatomyositis diagnosis (SIR 2·2, 95% CI 1·1–4·2), and in those aged 45 and older (3·1, 2·6–3·7), the number of cancers recorded after diagnosis in the younger age group was small (nine cancers in 153 patients). There was no increase in the risk of cancer in patients diagnosed with polymyositis aged 15–44 years (SIR 1·2, 95% CI 0·5–2·6), but a small increased risk of malignant disease in those aged 45 years and older (1·3, 1·1–1·6) was recorded.

*Cancers arising before diagnosis of myositis*

Of cancers diagnosed before dermatomyositis, most preceded myositis by 2 years or less (71%). By contrast, most cancers were diagnosed greater than 5 years before polymyositis diagnosis. In the year before diagnosis of dermatomyositis, 43 cancers were recorded (adjusted SIR 9·8, 95% CI 7·3–15·3). Lung (43·2, 26·1–71·7), ovarian (28·6, 10·7–76·1), colorectal (10·5, 7·7–23·3), and breast cancers (10·7, 5·1–22·5) were associated with increased adjusted risks. In the 1–2 years before dermatomyositis diagnosis, 16 cancers were recorded, giving an adjusted SIR of 4·6 (95% CI 2·8–8·7). In polymyositis patients, 11 cancers were seen in the year before diagnosis (1·6, 0·9–2·9), and only risk of lung cancer was increased (4·4, 1·4–13·6). In the 1–2 years before polymyositis diagnosis, three cancers were recorded, giving an adjusted SIR of 0·5 (0·2–1·7).

## Discussion

We have confirmed that both dermatomyositis and polymyositis are associated with an increased risk of malignant disease, but that this risk is substantially greater for dermatomyositis. The cancers most strongly associated with dermatomyositis are ovarian, lung, gastric, colorectal, and pancreatic cancers, and non-Hodgkin's lymphoma. However, there was also an association with a broad range of other malignant diseases. In patients with polymyositis, there was a raised risk of lung and bladder cancers, and non-Hodgkin's lymphoma. Our results emphasise that dermatomyositis and polymyositis are different diseases, in respect of the magnitude of risk and types of associated malignant disease.

Our study is one of the largest of its kind, and has allowed us to estimate fairly precisely specific cancer risks. To assess the relations between specific cancer types and myositis a large population sample is needed, because dermatomyositis and polymyositis are rare, and individual cancer types uncommon. Despite our use of data from three countries, the number of cancer cases in each category was small, underscoring the difficulty of epidemiological studies in rare diseases.

| Type of cancer | 0–1 year follow-up | | 2–5 years follow-up | | >5 years follow-up | |
|---|---|---|---|---|---|---|
| | Number | SIR (95% CI) | Number | SIR (95% CI) | Number | SIR (95% CI) |
| **Dermatomyositis** | | | | | | |
| All | 55 | 13·5 (10·4–17·6) | 30 | 2·5 (1·7–3·5) | 30 | 1·4 (1·0–2·0) |
| Stomach | 6 | 27·5 (12·4–61·3) | 0 | 0 (0–4·7) | 1 | 1·9 (0·3–13·3) |
| Colorectal | 4 | 8·6 (3·2–22·8) | 2 | 1·2 (0·3–5·0) | 6 | 2·3 (1·03–5·1) |
| Pancreas | 1 | 7·1 (1·0–50·4) | 2 | 4·1 (1·03–16·5) | 3 | 4·1 (1·3–12·6) |
| Lung | 10 | 28·3 (15·2–52·5) | 5 | 4·7 (2·0–11·4) | 4 | 2·2 (0·8–5·9) |
| Non-Hodgkin lymphoma | 3 | 42·3 (13·6–131·0) | 0 | 0 (0–12·3) | 0 | 0 (0–6·2) |
| Breast | 5 | 9·9 (4·1–23·8) | 4 | 2·4 (0·9–6·3) | 4 | 1·3 (0·5–3·4) |
| Ovary | 9 | 72·0 (37·5–138·4) | 3 | 7·3 (2·4–22·6) | 1 | 1·5 (0·2–10·6) |
| Prostate | 3 | 9·6 (3·1–29·7) | 0 | 0 (0–3·2) | 2 | 1·4 (0·4–5·6) |
| **Polymyositis** | | | | | | |
| All | 19 | 2·6 (1·6–4·0) | 40 | 1·5 (1·1–2·1) | 36 | 0·9 (0·6–1·3) |
| Colorectal | 0 | 0 (0–3·3) | 6 | 1·8 (0·8–4·1) | 4 | 0·8 (0·3–2·2) |
| Pancreas | 2 | 7·5 (1·9–30·1) | 0 | 0 (0–3·2) | 0 | 0 (0–2·2) |
| Bladder | 1 | 2·7 (0·4–18·8) | 5 | 3·8 (1·6–9·0) | 1 | 0·5 (0·1–3·7) |
| Lung | 2 | 2·3 (0·6–9·3) | 10 | 3·4 (1·8–6·4) | 6 | 1·4 (0·7–3·2) |
| Non-Hodgkin lymphoma | 2 | 12·6 (3·2–50·3) | 1 | 1·8 (0·3–12·7) | 2 | 2·2 (0·6–8·8) |
| Breast | 1 | 1·3 (0·2–8·9) | 5 | 1·7 (0·7–4·0) | 6 | 1·3 (0·6–2·8) |

Table 3: **Standardised incidence ratios (SIR) and 95% CIs of cancer by year after diagnosis of myositis**

We have shown an increase in risk of malignant disease in the period around diagnosis of myositis suggesting that heightened surveillance for cancer is likely at this time, resulting in some detection bias. However, in dermatomyositis, the raised risk of malignant disease persisted through all years of follow-up, which suggests that detection bias would explain only a small part of this association, and that a true link with cancer does exist. The clustering of cancer cases before diagnosis of myositis further suggests that the association is not merely a result of increased cancer surveillance after this diagnosis. Also, a previous analysis of the Swedish data set indicated that mortality due to cancer was increased in individuals with dermatomyositis, which would not be affected by better diagnosis of malignant disease.[1]

The small overall magnitude of association in polymyositis, the increased risk in the first year after polymyositis diagnosis, and the reduced risk after 5 years of follow-up all suggest that detection bias could account for a large part of the recorded association in polymyositis. A previous meta-analysis of case-control and cohort studies of myositis and malignant disease showed no increase in cancer detection before diagnosis of polymyositis, despite a raised risk after diagnosis.[14] Misclassification of dermatomyositis cases as polymyositis could also contribute to this apparent high risk in polymyositis.

We assessed the case records according to Bohan and Peter's criteria.[12] This classification has been criticised because diagnosis of dermatomyositis is based both on the presence of a rash and myositis.[15] More recent evidence shows that changes in muscle characteristic of dermatomyositis can take place with little or no rash being evident.[16] The only cohort study to classify myositis on the basis of histological diagnosis, and therefore less likely to have misclassified dermatomyositis as polymyositis, showed a small but significant increased risk of malignant disease in polymyositis.[4] Furthermore, cancers with increased risk in polymyositis differ from those in dermatomyositis. Therefore, a small increased risk of malignant disease in polymyositis seems likely.

Dermatomyositis is probably a paraneoplastic event in some patients. Ovarian, lung, and colorectal cancers were diagnosed frequently both before and after diagnosis of dermatomyositis, suggesting that these could be candidate cancers associated with the disease. Dermatomyositis has been noted to improve after treatment of cancer, with recurrence of muscle weakness taking place at relapse of malignant disease, further suggesting a paraneoplastic origin.[17,18] There also seem to be differences in clinical features of dermatomyositis associated with malignant disease. Patients with cancer-associated dermatomyositis are more likely to have normal creatinine kinase values and digital vasculitis, and less likely to have myositis-specific autoantibodies than those without cancer.[19,20] Generally, paraneoplastic features are associated with certain histological types of cancer;[5,6] however, different cancers seem to be associated with dermatomyositis. Although we noted an increased risk of cancers diagnosed before dermatomyositis, the method of calculation, by expected cancer survival, was imprecise.

Our results also suggest that the common assumption that malignant disease is a feature only in older people developing dermatomyositis is incorrect.[21] Although the absolute number of cancer cases is small, the risk of malignant disease is increased even in dermatomyositis patents aged 45 or younger.

Our study is based on information from three Nordic countries with little ethnic diversity, suggesting that our results are mainly relevant to whites. However, case series indicate that other types of cancer might be commonly associated with myositis among Asians.[22]

A limitation of registry-based data is the possibility of some misclassification of myositis. Although a subset of case records in Sweden and all those in Finland, were reviewed, no Danish case records were inspected; however, when we did analyses excluding Danish data, results remained unchanged. Additionally, there could be a small group of patients misclassified with dermatomyositis or polymyositis rather than other forms of muscle disease, which would mean that the calculated risks of malignant disease are underestimated.

Amyopathic dermatomyositis has been identified,[21] but any such cases are unlikely to have been included in our study. Although there are case reports of amyopathic dermatomyositis associated with malignant disease,[23,24] there are no population data on the increased risk of cancer for this subtype of dermatomyositis.

The importance of our study lies partly in its implications for the malignant disease workup of myositis patients, which could potentially reduce mortality in these individuals. Rheumatology textbooks and reviews cite personal experience and scant data on the cancer types associated with dermatomyositis and polymyositis in their recommendations for investigation of malignant disease.[20,25,26] Consequently, recommendations vary widely, and range from advising careful clinical examination and routine laboratory screening,[25] to extensive invasive investigations.[20] In view of the increased risk of ovarian, lung, gastric, colorectal, pancreatic, and breast cancer, and non-Hodgkin lymphoma, our findings suggest that, in addition to routine examination and laboratory screening, chest computed tomography (CT) scan, faecal blood testing, abdominal ultrasound or CT scan; mammography, pelvic CT scan, or ultrasound, and gynaecological examination, are justified in those with dermatomyositis. Since the risk of malignant disease remains high for many years after diagnosis, vigilance needs to be maintained. Even if mortality is not prevented, or survival prolonged, for these malignant diseases, disability from myositis could be alleviated if cancers are detected and treated early enough. In those with polymyositis, investigation should be targeted to the commonest sites of cancer (including lung, bladder, and non-Hodgkin's lymphoma).

*Contributors*

Catherine Hill and Yuqing Zhang were responsible for study design and execution, and analysis and interpretation of results. Bardur Sigurgeirsson, Lene Mellemkjaer, Eero Pukkala, and Antti Airio recorded data and helped with analysis and interpretation of results. Stephen Evans contributed to data analysis and David Felson provided the conceptual basis for the study. All authors were involved in writing the manuscript.

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# High association of mycobacterial infections with polymyositis in a non-endemic country for tuberculosis

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The susceptibility to mycobacterial infections of immunosuppressed subjects, for example, those treated actively for rheumatic diseases, is widely recognized.[1 2] However, the co-existence of mycobacterial infection (caused either by *Mycobacterium tuberculosis* or other mycobacterial infections) and polymyositis (PM) has been reported only in small series of patients [2 5] predominantly from countries where tuberculosis (TB) is endemic [2 3] or in immigrants in a Western country.[4 5]

We assessed the frequency of mycobacterial infections in patients with PM and dermatomyositis (DM) in Finland, a non-endemic country for TB that has kept detailed registry for TB. All patients with an ICD-8 code for PM (716.00) and DM (716.10) who had been discharged from any Finnish hospital during the years 1969 to 1985 were identified by using the information from the National Discharge Registry. During this period, diagnostic studies for PM and DM were usually performed on inpatients. Therefore, the present series of patients represents the vast majority of PM and DM cases in Finland during this period.

We found 176 patients with PM and 72 with DM who fulfilled the diagnostic criteria of Bohan and Peter. [6 7] We followed their progress by studying the records until they died or until the end of August 1995. At the time of the diagnosis of myositis, 26 (10%; 19 with PM and 7 with DM) of the whole series of 248 patients had a history of TB. In addition, 13 out of 176 patients (7.4%) with PM and 2 out of 72 patients (2.8%) with DM were documented to have a mycobacterial infection after a median time (range) of 20 (3–111) months from the diagnosis of myositis. Only one of them (who had PM) was in the group with a history of TB (57 years earlier).

Cumulative probability of mycobacterial infections among patients with PM was 4.8% (95% CI 2.4 to 9.4%) in 5 years and 9.3% (95% CI 5.4 to 15.6%) in 10 years (fig 1). On the basis of acid fast stain and mycobacterial culture, we determined that 11 out of the 15 mycobacterial infections were caused by *M. tuberculosis* (nine of them in PM patients) and four by other mycobacteria (*M. avium intracellulare* or mycobacteria group IV). At the time of the diagnosis of the mycobacterial infection, all the patients used corticosteroids, and seven PM patients also used or had used azathioprine. The risk factors for developing mycobacterial infections did not differ between patients with and without the infection.

Altogether, in 40 out of 248 (16%) patients with myositis — in 31 out of 176 (18%) with PM and 9 out of 72 (13%) with DM there was a former or diagnosed mycobacterial infection noticed during the follow up. To the best of our knowledge, the present study is the first one reporting a high frequency of mycobacterial infections in a large, systematically collected population of subjects with PM and DM in a Western non-endemic area for TB .

It may be supposed that, at least in part, the high incidence of mycobacterial infections during the treatment of myositis is caused by the reactivation of a former infection. The association

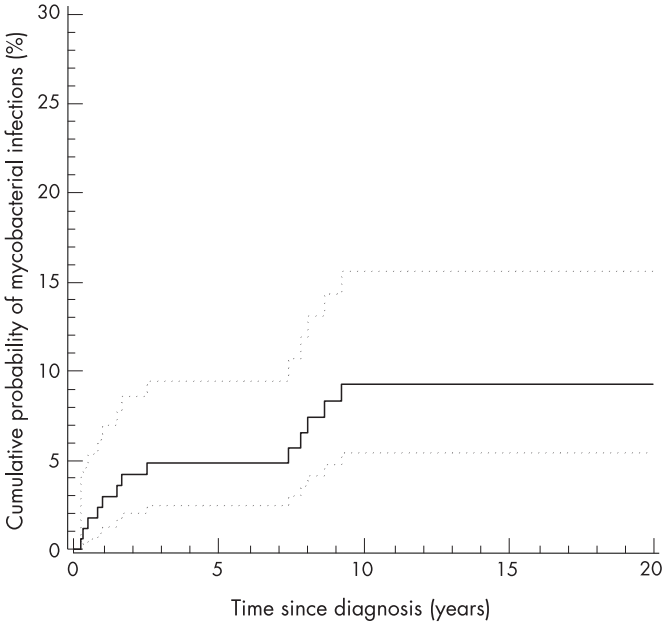


**Figure 1** Cumulative probability of mycobacterial infections in 176 patients with polymyositis after the diagnosis of myositis. The incidence of tuberculosis was 110 out of 100 000 people in Finland in 1969. It was 47 out of 100 000 in 1980, and 11 out of 100 000 in 1995.[8] The incidence of mycobacterial infections (*M. tuberculosis* and other mycobacteria) in PM patients was remarkably high when compared with that in the general population, especially considering the downward trend in infection over the period of this study. The risk of infection even seems to increase during the follow up after the diagnosis of PM. *M. tuberculosis* had been coded as either the main cause (N = 3) or immediate cause (N = 1) of death for four patients with PM.

between mycobacterial infections and PM is interesting, especially if there was a latent infection present in most of the cases, although this cannot be confirmed from their records. A weak causal relationship with 'reactive myositis' caused by a former or latent mycobacterial infection cannot be ruled out.

We conclude that the possibility of mycobacterial infection has to be kept in mind when diagnosing and treating patients with myositis.


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