# BCL-10-PROTEIININ ILMENTYMINEN PRIMAAREISSA JA SEKUNDAAREISSA KESKUSHERMOSTOLYMFOOMISSA

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Bcl-10-proteiini on normaalisti mukana NF-κB-välitteisessä signaalinvälitysketjussa, joka on tärkeä B-lymfosyyttien eloonjäännissä, erilaistumisessa ja aktivaatiossa. Normaalisti Bcl-10 ilmentyy vain sytoplasmassa. Bcl-10:n yli-ilmentyminen ja erityisesti tumailmentyminen vaikuttavat osallistuvan eräiden lymfoomien patogeneesiin.

Tutkimuksemme tavoitteena oli selvittää Bcl-10:n ja erityisesti sen tumailmentymisen yleisyyttä ja vahvuutta diffuusin suurisoluisen B-solulymfooman primaareissa ja sekundaareissa keskushermostotapauksissa. Aineistomme koostui 58 lymfoomatapauksesta Tampereen yliopistosairaalasta vuosilta 1993 – 2012. Näistä 51 oli primaareja ja 7 sekundaareja tapauksia; primaareista 45 paikallistui aivoihin ja 6 selkäytimeen.

Bcl-10 ilmentyi isossa osassa tapauksista. Ilmentyminen tumassa oli selvästi yleisempää ja vahvempaa kuin sytoplasmassa ($p<0,001$). Sekundaarit tapaukset ilmensivät Bcl-10:ä tumassa enemmän kuin primaarit ($p=0,006$). Primaarien aivo- ja selkäydinlymfoomien välillä ei havaittu tällä otoksella tilastollisesti merkittävää eroa.

Tuloksemme osoittavat, että Bcl-10:n tumailmentyminen on yleistä keskushermostolymfoomissa. Tämä luo pohjan tuleville tutkimuksille Bcl-10:n tumailmentymisen tarkemmasta roolista keskushermostolymfoomien patogeneesissa ja sen ennusteellisesta merkityksestä.

**SISÄLLYSLUETTELO**

# A DESCRIPTIVE STUDY: NUCLEAR EXPRESSION OF BCL10 IN PRIMARY AND SECONDARY CENTRAL NERVOUS SYSTEM LYMPHOMAS


## SUMMARY

Bcl10 is a signalling molecule known to play an important role in cell survival. Bcl10 expression has proved out to be common in several types of lymphomas. Further more nuclear Bcl10 expression is shown to be a sign of advanced disease in mucosa-associated lymphatic tissue (MALT) lymphomas. We have done a descriptive study of Bcl10 expression in primary and secondary central nervous system (CNS) lymphomas with an emphasis on nuclear expression. Bcl10 was immunostained in 58 diffuse large B cell CNS lymphoma cases (51 primary and 7 secondary) from Tampere University Hospital from the years 1993-2012. They showed a great portion of nuclear Bcl10 expression, secondary cases even more than primary ones (p=0.006). To a lesser extent also cytoplasmic Bcl10 expression was observed. So far little is known about Bcl10 expression in central nervous system lymphomas. This study shows a significant overall expression of Bcl10 in CNS lymphomas, which might play an important role in their pathogenesis. Moreover, there seems to be a significant difference of cytoplasmic and nuclear staining when compared to systemic lymphomas based on published data.


## 1 INTRODUCTION

Although central nervous system lymphoma is a rare disease, during the last decades its incidence has been growing (1). In Finland there are approximately 1300 new lymphoma cases diagnosed every year (1), and 1 – 2 % of them are primary central nervous system lymphomas (PCNSL) (2). Most of PCNSLs (97 %) are diffuse large B-cell lymphomas (DLBCL) (1). Primary spinal cord lymphoma is a rare form of PCNSL: 1 % to 2 % of PCNSLs locate in the spinal cord (3). On the other hand, 5 % of systemic DLBCLs metastasize in the central nervous system (4).

Bcl10 molecule is part of the lymphocyte activation and immune response through B cell receptors. Normally Bcl10 acts together with MALT1 and CARMA1 proteins in the cytoplasm as a part of a signalling pathway that activates NF-κB transcription which leads to prolonged cell survival (5).

Nuclear expression of Bcl10 has been observed in MALT, follicular, nodal and extranodal DLBCL lymphomas and in lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (6–8 ), but its role in their pathogenesis is not known. Among normal tissues Bcl10 is expressed only in lymphoid tissue and in breast tissue, predominantly in the cytoplasm (7). Since nuclear Bcl10 staining is almost explicitly related to lymphoma cells, it seems to be of importance. In gastric MALT lymphomas nuclear Bcl10 expression is a sign of advanced disease (9).

Overall cellular Bcl10 overexpression seems to be more common in extranodal than in nodal DLBCLs (6). Expression of Bcl10 is not so far thoroughly studied in CNS lymphomas, thus data available is very limited. Courts et al. suggested that Bcl10 is underexpressed in PCNSLs when compared to normal reactive GCB cells, indicating an abnormal, Bcl10 independent activation pathway for NF-kB (10). However, nuclear and cytoplasmic Bcl10 expression was not evaluated separately, which has been shown to be of major importance when investigating its role in signalling pathways (7, 9, 11–12). Until now there have not been any publications about nuclear Bcl10 in central nervous system lymphomas, or studies comparing the expression of Bcl10 in PCNSL with that in secondary central nervous system lymphomas (SCNSL) of DLBCL type. Pathogenesis of spinal cord lymphomas has also not been documented throughly, although clinical studies and case reports are published (13–15). We have performed a descriptive study of the expression of Bcl10 in PCNSL and SCNSL and on the other hand in primary brain lymphomas and primary spinal cord lymphomas, which seems like playing an important role in pathogenesis of these disease entities.

# 2 MATERIALS AND METHODS

## 2.1 Materials

All CNS-DLBCL cases diagnosed in Tampere University Hospital during the years 1993–2012 were gathered. Of those 74 patients 14 were excluded because of lack of tissue material available, 1 because of lack of information whether it was primary or secondary case, and 1 because of technical problems, leaving 58 cases for analysis: 51 primary and 7 secondary CNS lymphomas. When we divided the PCNSLs further into subgroups according to their location, there were 45 brain lymphomas and 6 spinal cord lymphomas. Tissue biopsies were taken for diagnosis before treatment, and formalin-fixed, paraffin-embedded blocks were made. We constructed tissue microarray blocks with three representative cores per patient, diameter 1.5 mm.

16 (27.6 %) of the samples were from female patients and 42 (72.4 %) of male patients. Table 1 shows the sex and age distribution in the entire cohort and in the subgroups.

## 2.2 Immunohistochemical analysis

We used Bond-max™ automated immunostainer (Vision BioSystems Ltd, Newcastle, UK) for staining procedure. Sections were deparaffinized in Bond™ Dewax Solution, rehydrated in a graded ethanol series, and heat-induced antigen retrieval was performed in EDTA based buffer (Bond™ Epitope Retrieval Solution 2, pH 9.0, 30 min). The following mouse monoclonal antibodies were used: CD-10 (Novocastra™, dilution 1:70) Bcl-6 (Novocastra™, dilution 1:200), MUM-1 (DakoCytomation, dilution 1:200), and Bcl-10 (Zymed® Laboratories, dilution 1:80).

As positive controls we used normal appendix for CD-10 and Bcl-6, normal tonsil for Bcl-10 and extranodal marginal zone B-cell lymphoma for MUM-1. Unlabeled (negative) cases of the same tissue microarray block served as negative controls.

Tumors were categorized into four groups based on immunostaining intensity: negative (<10 % of tumor cells labeled), 1+ (10–33 %), 2+ (33–66 %) and 3+ (>66 %). We used the mean of three cores of each patient for the analysis. For Bcl-6 and MUM-1 both cytoplasmic and nuclear positivity were required, and for CD-10 only membrane staining was considered positive. For Bcl10 cytoplasmic and nuclear staining were evaluated separately.

### 2.3 Statistical analysis

The programming language R 3.0.2 was used for the analysis. Mann-Whitney U test was used to assess the differences in immunostaining of Bcl10, CD10, Bcl6 and MUM1 between the subgroups and the differences between nuclear and cytoplasmic Bcl10 expression. Spearman's rank order correlation was used to assess whether nuclear and cytoplasmic staining of Bcl10 correlated with each other. P values of <0.05 were considered statistically significant.

## 3 RESULTS

Table 2 and Figure 1 show the expression of cytoplasmic and nuclear Bcl-10 in primary and secondary central nervous system lymphomas and in primary brain and spinal cord lymphomas. Approximately 2/3 of our lymphomas showed only weak or no cytoplasmic staining of Bcl10 (median=0.67). In primary cases cytoplasmic Bcl10 expression was stronger than in secondary cases (p=0.024). Among PCNSLs, brain lymphomas seemed to show more cytoplasmic staining than spinal cord lymphomas (p=0.051).

Nuclear staining of Bcl10 was overall more common and stronger than cytoplasmic (median=2) (Table 2, Table 3). All our secondary cases showed high ($x > 2$) nuclear expression of Bcl10, and the expression was thus significantly stronger than in primary ones (p=0.006). Among PCNSLs, there was no difference between brain and spinal cord cases.

Next we tried to figure out the correlation of nuclear Bcl10 positivity to cytoplasmic Bcl10 positivity. We could not find any clear correlation between nuclear and cytoplasmic expression of

Bcl10, neither in the whole sample nor in the subgroups. Thus, expression of Bcl10 nuclearly was not necessarily accompanied by cytoplasmic expression, or vice versa (Table 4).

Nuclear and cytoplasmic Bcl10 expression did not depend on age or sex (data not shown).

In addition to Bcl10, also Bcl6, MUM1 and CD10 were studied, as these markers are known to be expressed on lymphoma cells in general. Among these only significant difference was found with MUM1 expression. MUM1 is expressed more in primary brain lymphomas when compared to primary spinal cord lymphomas.

# 4 DISCUSSION

Our samples of primary and secondary CNS lymphomas showed remarkable nuclear Bcl10 expression. Although cytoplasmic Bcl10 expression was also seen in the samples, compared to the nuclear expression, it was less frequent and less intensive. Nuclear expression was stronger in secondary cases when compared to primary cases. On the other hand, cytoplasmic expression was stronger in primary cases than in secondary cases. These differences proved out to be statistically significant, despite of our small number of SCNSLs (n=7).

As the incidence and prevalence of primary spinal cord lymphomas worldwide is low, our sample collection was also small (n=6). Thus, some real differences between primary brain and primary spinal cord lymphomas may not have been shown as statistically significant. In future, hopefully international study groups will overcome this problem by combining their own sample collections for further studies.

We strongly believe that nuclear Bcl10 expression in CNS lymphomas is of great interest. So far, our information about nuclear Bcl10 expression comes mostly from MALT lymphomas. In MALT lymphomas, nuclear Bcl10 expression is partially related to the translocations t(11;18)(q21;q21) and t(1;14)(p22;q32) (16). Nakagawa et al. documented that normally MALT1 transports Bcl10 from nucleus to the cytoplasm, and suggested that nuclear Bcl10 expression is caused by failure in this transport mechanism (11). T(11;18)(q21;q21) causes the formation of API-MALT1 fusion protein,

which no longer transports Bcl10 to the cytoplasm (11, 17), and t(1;14)(p22;q32) causes overexpression of Bcl10, resulting in a relative shortage of MALT1 and thus part of Bcl10 staying in the nucleus (11). Achuthan et al. (18) suggested that t(1;14)(p22;q32) traslocation involving Bcl10 gene is limited to MALT lymphoma cases, but the small sample size (18 lymphomas, of which 4 DLBCLs and no PCNSLs) limits the cogency of their results. However, there are also MALT lymphoma cases with nuclear Bcl10 staining without above mentioned translocations (16). The molecular mechanism for nuclear Bcl10 expression in those cases still remains unclear. According to Yeh et al. (19), TNF-α induced NF-κB activation causes overexpression of Bcl10 in human breast carcinoma cells, resulting also in its nuclear location. The same mechanism could possibly explain a part of the lymphoma cases with nuclear Bcl10. Future studies will solve what causes nuclear Bcl10 in CNS lymphomas: whether it is the same translocations as in MALT lymphomas, or other reasons.

In our data nuclear and cytoplasmic Bcl10 did not correlate with each other. If nuclear location of Bcl10 were caused purely by its overexpression, it should be overexpressed both in nucleus and in cytoplasm. Thus, we suggest that not all of the nuclear Bcl10 was caused by its overexpression, but also by an aberrant nucleus-cytoplasm transport mechanism.

Yeh et al. (19) found that overexpressed and nuclearly located Bcl10 in their data further acted as a transcriptional activator of NF-κB. Also Liu et al. (12) suggested that Bcl10 has transactivation activity and thus could cause tumorgenesis by acting as a transcription factor, and Nakagawa et al. (11) documented that nuclear Bcl10 and MALT1 location was associated with increased NF-κB activation in a cell culture. It is shown that nuclear Bcl10 and NF-κB activation correlate in MALT lymphomas (20), but seemingly not in lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (8). To the best of our knowledge, correlation between nuclear Bcl10 and NF-κB activation in other lymphomas has not been studied. It should be investigated, whether nuclear Bcl10 expression correlates with NF-κB activation in CNS lymphomas, and if it does, whether there is causality and what the causal direction is. Regardless of the molecular mechanism, however, it has been proved that nuclear Bcl10 is associated with advanced tumor in gastric MALT lymphomas, i.e. non-responsiveness to Helicobacter pylori eradication (9, 21). Thus, nuclear Bcl10 certainly affects the tumorgenesis of MALT lymphomas, and probably also other lymphomas with nuclear Bcl10 expression.

Little is known about the biology of systemic DLBCLs invading the brain. Although clinical studies and even a guideline on the prevention of SCNSLs are published (22–23), so far no biological markers for the probability of a brain recurrence of a systemic DLBCL are known. Our study suggests that Bcl10 might have a role in SCNSLs, since all our cases showed strong nuclear Bcl10 expression. In systemic DLBCLs outside the brain nuclear Bcl10 is an existent but not a common phenomenon (7, 24). Future studies should be performed to compare Bcl10 expression in SCNSLs and other DLBCLs in general. Moreover, it would be interesting to know if the expression profile of Bcl10 changes when a systemic DLBCL metastasizes to the CNS. If nuclear Bcl10 proves out to be more common in SNCSLs than in other DLBCLs as it now seems, it might be a biological marker predicting a CNS involvement of a systemic DLBCL.

The median overall survival time for non-Hodgkin's lymphoma with CNS involvement has been only approximately 2 months in several studies (25–27), while for PCNSLs it is as much as 29 to 51 months when treated with combined high-dose methotrexate-based chemotherapy and radiation therapy (28–29). Because of the heterogeneity of treatments of our patient sample, we could not perform any prognostic analysis of nuclear Bcl10. Since all our SCNSLs showed strong nuclear Bcl10 expression and they generally have a poor prognosis, we still suggest that it might be a prognostic marker in CNS lymphomas and in DLBCLs in general. This will be a subject of future studies with a nationwide, more homogeneously treated patient sample.

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# REFERENCES

1. Kuittinen, O. Primaarinen keskushermostolymfooma. *Focus Oncologiae* 2011:25–29.
2. Jyrkkiö, S. Ekstranodaaliset lymfoomat. *Focus Oncologiae* 2012:38-41.
3. Mechtler LL, Nandigam K. Spinal Cord Tumors. Neurol Clin 2013;31(1):241-68.

4. Ferreri AJM, DeAngelis LM. Central nervous system lymphomas. In: Marcus R, Sweetenham JW, Williams ME (edit.). Lymphoma: Pathology, Diagnosis, and Treatment. Cambridge University Press 2013, p. 208-24.
5. Thome, M. CARMA1, BCL-10 and MALT1 in lymphocyte development and activation. *Nature Reviews Immunology* 2004;4:348-59.
6. Ohshima K, Kawasaki C, Muta H, Deyev V, Haraoka S, Suzumiya J, et al. CD10 and Bcl10 expression in diffuse large B-cell lymphoma: CD10 is a marker of improved prognosis. *Histopathology* 2001;39:156-62.
7. Ye H, Dogan A, Karran L, Willis TG, Chen L, Wlodarska I, et al. Bcl10 expression in normal and neoplastic lymphoid tissue. Nuclear localization in MALT lymphoma. *Am J Pathol* 2000;157(4):1147-54.
8. Merzianu M, Jiang L, Wang X, Weber DM, Vadhan-Raj S, Nguyen MH, et al. Nuclear Bcl-10 expression is commoin lymphoplasmacytic lymphoma/Waldenström macroglobulinemia and does not correlate with p65 NF-κB activation. *Mod Pathol* 2006;19:891-8.
9. Liu H, Ye H, Dogan A, Ranaldi R, Hamoudi RA, Bearzi I, et al. T(11;18)(q21;q21) is associated with advanced mucosa-associated lymphoid tissue lymphoma that expresses nuclear Bcl10. *Blood* 2001;98:1182-7.
10. Courts C, Montesinos-Rongen M, Martin-Subero JI, Brunn A, Siemer D, Zühlke-Jenisch R, et al. Transcriptional profiling of the nuclear factor-kappaB pathway identifies a subgroup of primary lymphoma of the central nervous system with low BCL10 expression. *J Neuropathol Exp Neurol* 2007;66(3):230-7.
11. Nakagawa M, Hosokawa Y, Yonezumi M, Izumiyama K, Suzuki R, Tsuzuki S, et al. MALT1 contains nuclear export signals and regulates cytoplasmic localization of Bcl10. *Blood* 2005;106:4210-6.
12. Liu Y, Dong W, Chen L, Zhang P, Qi Y. Characterization of Bcl10 as a potential transcriptional activator that interacts with general transcription factor TFIIB. *Biochem Biophys Res Comm* 2004;320:1-6.
13. Flanagan EP, O'Neill BP, Porter AB, Lanzino G, Haberman TM, Keegan BM. Primary intermedullary spinal cord lymphoma. *Neurology* 2011;77:784-91.
14. Schild SE, Wharen RE Jr, Menke DM, Folger WN, Colon-Otero G. Primary lymphoma of the spinal cord. *Mayo Clin Proc* 1995;70:256-60.
15. Herrlinger U, Weller M, Kuker W. Primary CNS lymphoma in the spinal cord: clinical manifestations may precede MRI detectability. *Neuroradiology* 2002;44:239-44.
16. Sagaert X, Laurent M, Baens M, Wlodarska I, De Wolf-Peeters C. MALT1 and Bcl10 aberrations in MALT lymphomas and their effect on the expression of Bcl10 in the tumour cells. *Modern Pathol* 2006;19:225-32.
17. Maes B, Demunter A, Peeters B, De Wolf-Peeters C. BCL10 mutation does not represent an important pathogenic mechanism in gastric MALT-type lymphoma, and the presence of the API2-MLT fusion is associated with aberrant nuclear BCL10 expression. *Blood* 2002;99:1398-404.
18. Achuthan R, Bell SM, Carr IM, Leek JP, Roberts P, Horgan K, et al. Bcl10 in malignant lymphomas – an evaluation using fluorescence in situ hybridization. *J pathol* 2002;196:59-66.
19. Yeh PY, Kuo S-H, Yeh K-H, Chuang S-E, Hsu C-H, et al. A pathway for tumor necrosis factor-α-induced Bcl10 nuclear translocation. Bcl10 is up-regulated by NF-κB and phosporylated by Akt1 and then complexes with Bcl3 to enter the nucleus. *J Biol Chem* 2006;281(1):167-75.
20. Ohshima K, Muta H, Kawasaki C, Muta K, Deyev V, Kanda M, et al. Bcl10 expression, rearrangement and mutation in MALT lymphoma: correlation with expression of nuclear factor-kappaB. *Int J Oncol* 2001;19(2):283-9.

21. Dong G, Liu C, Ye H, Gong L, Zheng J, Li M, et al. BCL10 nuclear expression and t(11;18)(q21;q21) indicate nonresponsiveness to Helicobacter pylori eradication of Chinese primary gastric MALT lymphoma. *Int J Hematol* 2008;88:516-23.
22. Tomita N, Kodama F, Kanamori H, Motomura S, Ishigatsubo Y. Secondary central nervous system lymphoma. *Int J Hematol* 2006;84:128-35.
23. McMillan A, Ardeshna K, Cwynarski K, Lyttelton M, McKay P, Montoto S. Guideline on the prevention of secondary central nervous system lymphoma: British Committee for Standards in Haematology. *British J Haematol* 2013;163:168-81.
24. Ye H, Gesk S, Martin-Subero JI, Nader A, Du M-Q, Sibert R. Bcl10 gene amplification associated with strong nuclear Bcl10 expression in a diffuse large B cell lymphoma with IGH-BCL2 fusion. *Haematologica* 2006;91(6)e81-2.
25. Björkholm M, Hagberg H, Holte H, Kvaloy S, Teerenhovi L, Anderson H, et al. Central nervous system occurence in elderly patients with aggressive lymphoma and a long-term follow-up. *Annals of Oncology* 2007;18:1085-9.
26. Boehme V, Schmitz N, Zeynalova S, Loeffler M, Pfreundschuh M. CNS events in elderly patients with aggressive lymphoma treated with modern chemotherapy (CHOP-14) with or without rituximab: an analysis of patients treated in the RICOVER-60 trial of the German High-Grade-Non-Hodgkin Lymphoma Study Group (DSHNHL). *Blood* 2009;113:3896-902.
27. Machintosh FR, Colby TV, Podolsky WJ, Burke JS, Hoppe RT, Rosenfelt FP, et al. Central nervous system involvement in non-Hodgkin's lymphoma: an analysis of 105 cases. *Cancer* 1982;29:586-95.
28. Gavrilovic IT, Hormigo A, ahalomo J, DeAngelis LM, Abrey LE. Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. *J Clin Oncol* 2006;24:2570-4.
29. Thiel E, Korfel A, Martus P, Kanz L, Griesinger F, Rauch M, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *Lancet Oncol* 2010;11:1036-47.

Table 1. Sex and age distributions.

| | All cases (58) | PCNSL (51) | Secondary (7) | PCNSL brain (45) | PCNSL spinal cord (6) |
|---|---|---|---|---|---|
| Age, md (range) | 65.5 (21-79) | 66 (39-79) | 56 (21-77) | 66 (39-78) | 65.5 (44-79) |
| Women | 27.6 % | 29.4 % | 14.3 % | 31.1 % | 16.7 % |
| Men | 72.4 % | 70.6 % | 85.7 % | 68.9 % | 83.3 % |

Table 2. Bcl10, CD10, Bcl6 and MUM1 expression in the subgroups.

| | All cases (58) | | | PCNSL (51) | | | All cases (58) |
|---|---|---|---|---|---|---|---|
| | PCNSL (51) md (range) | SCNSL (7) md (range) | P value | Brain (45) md (range) | Spinal (6) md (range) | P value | md (range) |
| Bcl10 nuclear | 2 (0-3) | 3 (2.33-3) | 0.006 | 2 (0-3) | 2.83 (1-3) | 0.18 | 2 (0 – 3) |
| Bcl10 cytopl. | 1 (0-3) | 0 (0-2.33) | 0.024 | 1 (0-3) | 0 (0-1.5) | 0.051 | 0.67 (0 – 3) |
| CD10 | 0 (0-3) | 0.33 (0-3) | 0.13 | 0 (0-3) | 0.96 (0-3) | 0.025 | 0 (0 – 3) |
| Bcl6 | 2 (0-3) | 1.67 (0-3) | 0.27 | 2 (0-3) | 2 (0-3) | 0.77 | 2 (0 - 3) |
| MUM1 | 2 (0-3) | 2.33 (0-3) | 0.78 | 2 (0-3) | 0.5 (0-1) | <0.001 | 2 (0 – 3) |

Table 3. Nuclear and cytoplasmic Bcl10 expression.

| | Nuclear (md) | Cytoplasmic (md) | P value |
|---|---|---|---|
| All | 2 | 0.67 | <0.001 |
| PCNSL | 2 | 1 | <0.001 |
| SNCSL | 3 | 0 | 0.001 |
| Primary brain | 2 | 1 | 0.001 |
| Primary spinal cord | 2.83 | 0 | 0.011 |

Table 4. Correlation between nuclear and cytoplasmic Bcl10.

| | Spearman correlation | P value |
|---|---|---|
| All | 0.09 | 0.49 |
| PCNSL | 0.25 | 0.081 |
| SCNSL | 0.39 | 0.39 |
| Primary brain | 0.41 | 0.006 |
| Primary spinal cord | -0.36 | 0.48 |

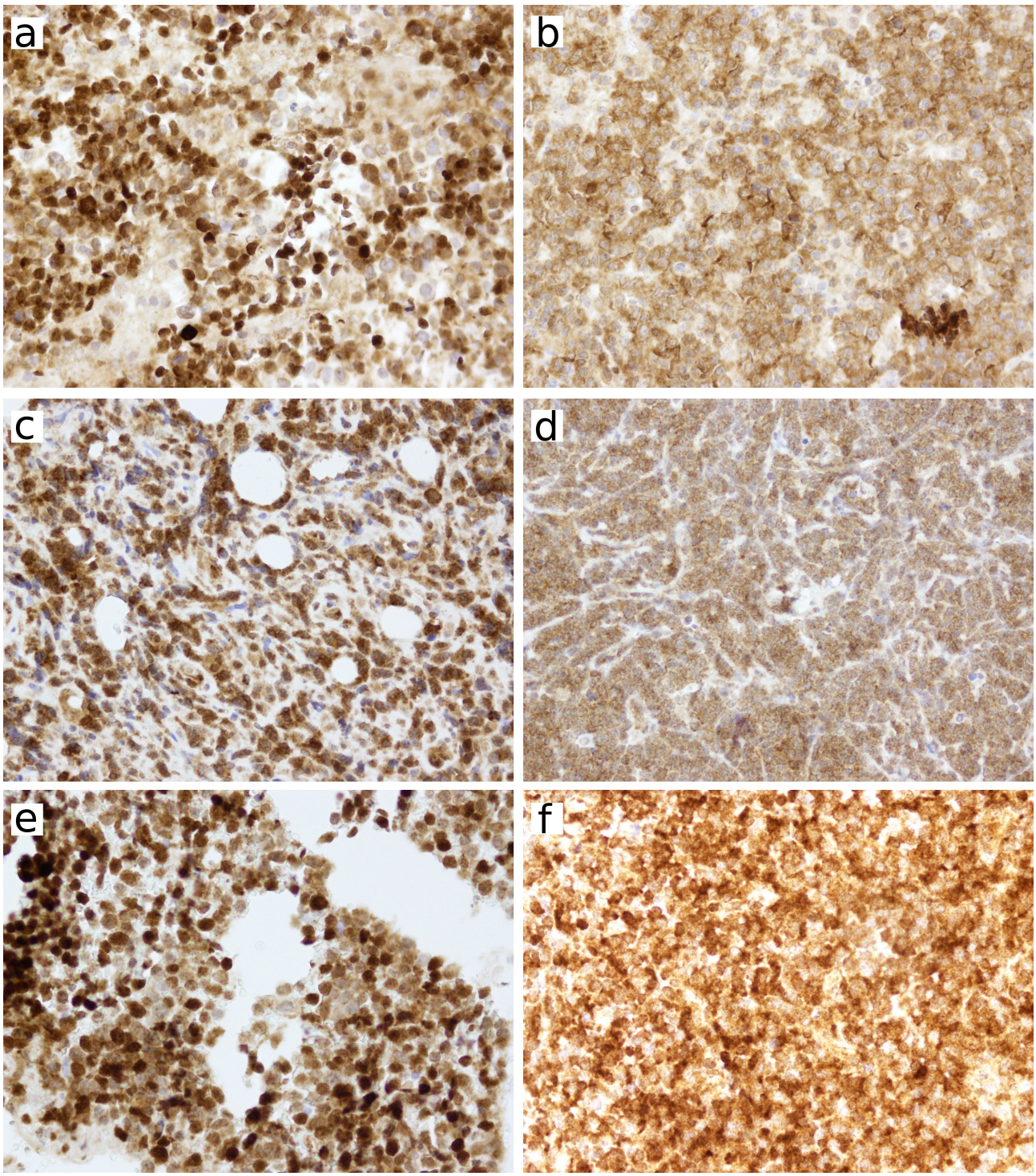


Figure 1. Bcl10 positive primary brain (a, b), primary spinal cord (c, d) and secondary brain (e, f) lymphoma cases. Original magnification x200.

a, c and e) nuclear +++ b) nuclear +, cytoplasmic +++ d) cytoplasmic ++ f) cytoplasmic +++, nuclear +++.