Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/pjnns

Original research article

Central nervous involvement by chronic lymphocytic leukaemia

Dariusz Szczepanek [a], Ewa Wąsik-Szczepanek [b], Agnieszka Szymczyk [b,c,*], Małgorzata Wach [b], Maria Cioch [b], Monika Podhorecka [b], Ewelina Grywalska [d], Marek Hus [b]

[a] Department of Neurosurgery and Paediatric Neurosurgery, Medical University of Lublin, Poland
[b] Department of Haematooncology and Bone Marrow Transplantation, Medical University of Lublin, Poland
[c] Independent Clinical Transplantology Unit, Medical University of Lublin, Poland
[d] Department of Clinical Immunology, Medical University of Lublin, Poland

ARTICLE INFO

Article history:
Received 5 September 2017
Accepted 20 October 2017
Available online 1 November 2017

Keywords:
Chronic lymphocytic leukaemia
Central nervous system infiltration
Intraventricular treatment

ABSTRACT

Inclusion of the central nervous system (CNS) in the course of chronic lymphocytic leukaemia (CLL) is rare. At the moment no risk factors or proven treatment methods are known. The disease is described both in its early phase and during its acceleration period, thus it has been suggested that there might be independent mechanisms influencing the development of this condition. As there are no unified diagnostic procedure algorithms each patient needs to be assessed individually. CLL can manifest mostly in elderly people, for whom a possibility of development of neurological disorders with their aetiology different from leukaemia, should also be taken into consideration. The thesis presents a group of seven patients with CLL with CNS infiltration. Patients with prolymphocytic leukaemia, Richter's transformation and the original location of leukemic infiltration within the eye socket constitute an especially interesting case.

1. Introduction

Chronic lymphocytic leukaemia (CLL) is a disease that is characterised by a clonal proliferation and accumulation of mature B lymphocytes in peripheral blood, bone marrow and lymphoid tissues [1]. A different location is very rare and is usually connected with the skin and central nervous system (CNS) [2]. Despite that fact, CLL belongs to the type of proliferation in which the central nervous system involvement (CNSi) is seldom considered, contrary to infective, immunological complications or transformation of Richter syndrome (RS) [3]. At the moment no CNSi risk factors or unified proven treatment methods are determined. It results mainly from a small group of patients with such condition (in the last 40 years fewer than 100 cases of CLL and CNSi have been

* *Corresponding author at*: Department of Haematooncology and Bone Marrow Transplantation, Independent Clinical Transplantology Unit Medical, Medical University of Lublin, Staszica 11 Str., 20-081 Lublin, Poland.
E-mail address: agnieszka.szymczyk.med@wp.pl (A. Szymczyk).
https://doi.org/10.1016/j.pjnns.2017.10.012
0028-3843/

described) [3]. The most often described patients had CLL with meninges and cranial nerve, but extremely rarely with the brain and spinal cord. What is characteristic is a highly diverse clinical manifestation, although the neurological symptoms can be observed in a small number of patients, and in case of histologically confirmed affection of meninges, it concerns only 1% of the examined [4,5]. Thus, we can probably talk about a significant underestimation of the number of patients with this illness.

1.1. *Objective*

The objective of this research paper is a retrospective analysis of patients with CLL/SLL and CNS infiltration.

2. Materials and methods

The analysis included patients with CLL/SLL diagnosed in the years 2007–2016. In this timeframe, 223 CLL/SLL patients were treated. Apart from patients with inclusion of the CNS in the course of CLL, 102 women and 114 men at a median age 64.9 years (34–87 years), Rai stage 0–4 and Ann Arbor II-IV clinical stage, has been observed or treated.

Based on a retrospective analysis we have conducted an assessment of the clinical, biological and radiological parameters (magnetic resonance imaging; MRI, computed tomography; CT) of the patients with CLL and CNSi, in the period from February 2007 to March 2015. Five patients had lumbar puncture done with the collection of cerebrospinal fluid (CSF). The CSF tests included the cytological, biochemical, cytometric and microbiological evaluation. In three cases material for histopathological tests was also collected. Clinical, immunophenotyping and genetic parameters of the CLL patients at the moment of diagnosis of CNSi are shown in Table 1.

3. Results

Seven patients with CLL, who were diagnosed with CNSi were analysed. They were four men and three women aged between 43 and 76 years old. They were in the stadium 0–3 according to Rai et al. classification. The CNSi diagnosis was determined based on the flow cytometric analysis of the CSF in five patients and histopathological examination in three patients (in two patients, based on the autopsy: patient nos. 3 and 5). Three patients received intrathecal treatment, one had a neurosurgical procedure (total resection of the tumour) followed by radiotherapy. Three patients due to their serious general condition did not receive the cytostatic treatment. All patients were radiologically diagnosed (MRI/CT) and they manifested diverse neurological symptoms. Neurological disorders, radiological image, received treatment of patients with CLL and CNSi and test results of the cerebrospinal fluid are shown in Tables 2 and 3 and Figs. 1 and 2.

4. Discussion

Affecting the CNS in the course of non-Hodgkin's lymphomas (NHL) is observed in approx. 8% of patients [6,7]. It is mostly observed in case of the most aggressive histopathological types, such as e.g. Burkitt lymphoma or lymphomas of specific locations (testicular lymphoma, lymphoma around the paranasal sinuses) [8,9]. There are several hypotheses attempting to explain the mechanisms leading to affecting the CNS in the course of CLL. One of them indicates a possibility of the

Table 1 – Clinical characteristics, immunological and genetic parameters of patients with CLL at the time of CNSi diagnosis.

	Patient 1	Patient 2 (CLL/PLL)	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (year)/sex	63/M	43/M	54/M	70/F	76/K	56/M	70/K
Rai clinical stage	0	2	2	2	2	0	3
Stage of disease during CNSi	Stable disease	Progression		(transformation into PLL)	Progression (Richter's transformation)	Progression	Stable disease
Stable disease	Stable disease						
Prior therapy for CLL 0	0	0	COP, CHOP, FC, F,	ofatumumab + idelalisib	B, BR	0	0
Genetic aberrations	Not found	Not done	Not found	del11q	Not found	Not found	Not found
ZAP-70/CD38	ZAP-70−/CD38+	Not done	ZAP-70−/ CD38+	ZAP-70−/CD38−	ZAP-70−/CD38−	ZAP-70−/CD38+	ZAP-70+/CD38+
Time between CLL and CNSi diagnosis (month)	3	2	71	27	0	0	0
Follow up (month)	38	3	1	2	1	126	3
Status at last follow up	Alive	Death	Death	Death	Death	Alive	Death

C – cyclofosfamide; O – vincristine; H – doxorubicin; P – prednisone; F – fludarabine; B – bendamustin; R – rituximab.

Table 2 – Neurological symptoms, radiological image and treatment of patients with CLL/SLL and CNSi.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Localisation in CNS (neuroimaging)	No changes	Infiltration of hemispheres and cerebellum	Infiltration of the corpus callosum and the membrane lining the ventricles	Nodular mass in the left side part of eye socket	Infiltration of cavernous sinus		
	Infiltration of cavernous sinus	No changes					
Neurologic symptoms	Headache, behaviour disorders	Bilateral paresis, dysarthia	Headache, slowing down, orientation disorders	Headache, orientation disorders	Slowing down, orientation disorders	Impaired visual activity and limitation of movement of the left eyeball	Third left nerve palsy
Treatment of CNSi	Mtx/Ara-C/PDN intrathecal,						
radiotherapy	Mtx/Ara-C/PDN intrathecal	NA	Mtx/Ara-C/PDN intrathecal	NA	Tumour resection,		
radiotherapy	NA						
Response to treatment	CR	Progression	NA	Progression	NA	CR	NA

Mtx – methotrexate, Ara-C – cytosine arabinoside; PDN – prednisone; CR – complete remission; NA – not applicable.

Table 3 – Test results of the cerebrospinal fluid.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
CSF cellularity/μl	41	240	ND	80	ND	56	67
Percentage of leukemic cells in CSF	85.0%	87.6%	–	67.0%	–	49.0%	52.0%
Immunofenotype	CD19+/CD5+/CD23+	CD19+/CD5−/CD23−	–	CD19+/CD5+/CD23+	–	CD19+/CD5+/CD23+	CD19+/CD5+/CD23+
Red blood cells/μl	0	0	–	0	–	0	0
Protein (mg/dl)	88.0	ND	–		–		
Glucose (g/dl)	72.0	ND	–		–		
Microbiology study	Negative	ND	–	Negative	–	Negative	Negative

ND – not done.

migration of the leukemic cells to the subarachnoid space through damaged blood vessels and perineural sheath of the cranial nerves and spinal nerve roots [6]. CLL is a disease that is characterised by complex immunological disorders, concerning both the cellular and humoral response. CNS and the peripheral nerves might be places connected with the leukemic complications [10,11]. De Vito et al. described paraneoplastic syndrome, which is present in a patient with small lymphocytic lymphoma (SLL), involving demyelination of the CNS. Conducted diagnostic tests: MRI, CSF test did not indicate the leukemic infiltration. According to the authors, it is the only such case described, connected with the presence of unknown antibodies [12]. CLL can manifest mostly in elderly people, for whom a possibility of development of neurological disorders with their aetiology different from leukaemia, should also be taken into consideration. In an extensive work dedicated to the neurological disorders in patients with CLL, Silva describes a range of causes that may potentially trigger them. Those include i.e. retinopathy, optic neuropathy, secondary brain tumours (meningiomas, gliomas), intracranial bleeding, infections, neurotoxicity caused by prescribed drugs [13]. It might seem that CNSi in the course of CLL should appear in leukaemia progression phase. Moazzam et al. based on one of largest study demonstrated a lack of relevant connection of this pathology with more aggressive course of CLL, age and sex of the patients, clinical stage and type of neurological symptoms [3]. In our study (four patients) the leukemic infiltration of the CNS most often occurred in the period of acceleration (i.e. prolymphocytic leukaemia, Richter's syndrome), but also in the phase of stabilisation and even in the moment of diagnosis of CLL. This may prove an existence of different mechanisms influencing the develop-

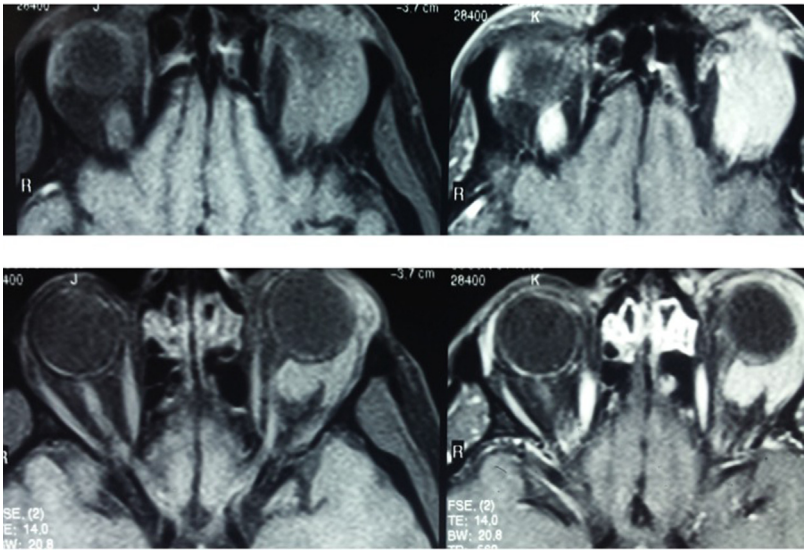

Fig. 1 – Nodular mass in the left side part of eye socket (patient 6).

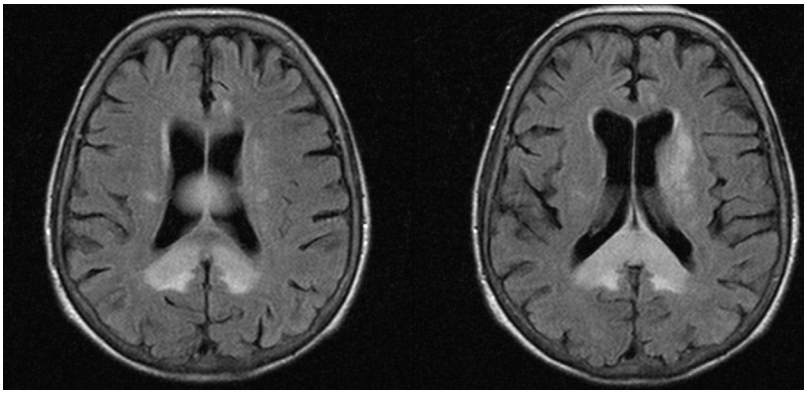

Fig. 2 – Infiltration of the corpus callosum and the membrane lining the ventricles (patient 5).

ment of this condition, proceeding independently of those which are characteristic of the natural course of leukaemia. As can be seen, CNSi may appear in all stages of the disease, regardless of its dynamics.

A lot of controversies is posed by the issue of diagnosing the CNSi, which at the moment is based on morphological, cytometric [14], and cytogenetic [15] evaluation of the CSF cells and imaging studies, referred to as MRI. A certain amount of caution is advised in clear interpretation of the presence of lymphocyte population of monoclonal antibodies in CSF. It does not have to constitute a clear proof of leukemic infiltration of the CNS. It is believed that in certain situations they may move to CSF and similarly to normal lymphocytes, they may be ''mobilised'' to the inflammatory foci [16].

Due to that fact, a possible presence of the inflammatory processes or autoimmune complications must be taken into consideration in every situation. Another possible mechanism is ''contamination'' of CSF by the leukemic cells during lumbar puncture. In every case studied by us, the CSF indicated presence of a monoclonal population of cells with a phenotype CD19+/CD5+/CD23+ (apart from the patient with PLL), there was no presence of erythrocytes and the results of microbiological tests were negative. In three patients a histopathological study of the infiltrated tissue was conducted. It was a base of diagnosis for patient nos. 3 and 5. Radiological changes in case CNSi in patients with CLL are described as diffused infiltration of the meninges by a thin layer of leukemic cells or intracerebral infiltrates. At the same time, it is indicated that there are no visible changes in the imaging studies [3]. All that results in many difficulties in diagnosing CNSi. Above all, the doctor is required to have an awareness of the possible (although rarely considered) location of the disease, to conduct all possible tests and appropriate interpret them.

In the course of CLL a transformation into Richter's syndrome and prolymphocytic leukaemia is particularly significant. RS is a rare complication of CLL involving an evolution into more aggressive form of lymphoma [17]. In case of ''classic'' form of RS, it is a diffuse B-cell large lymphoma (DLBCL) [18], and a lot less often, into a Hodgkin lymphoma (HL) [19]. RS is typically present in the lymph nodes and bone marrow. Location outside of nodes concerns about 41% of cases. RS in CNS was described in very few cases, in the area of

meninges and the brain [20–22]. In the patient from our group, the leukemic infiltration was detected in the cavernous sinus. RS was developed after 71 months of the course of the disease and many types of treatments (COP, CHOP, FC, F, ofatumumab + idelalisib), which may constitute a voice in the discussion regarding the influence of the previous treatments in the development of RS. The patient died soon after finding the changes in CT (the final diagnosis of DLBCL was determined during the autopsy), which suggests especially poor prognosis of RS in CNS [21]. B-cell prolymphocytic leukaemia (B-PLL) is a rare proliferation, characterised by a very aggressive clinical course, resistance to the applied chemotherapy and a poor prognosis. It may both appear de novo and be a transformation of CLL diagnosed earlier [23]. Affection of the CNS in the course B-PLL and CLL/PLL is known only from descriptions of individual cases [24]. In our work we presented a patient, in whom after two months from the diagnosis of classic form of CLL, there was a transformation into B-PLL (CLL/PLL). Along with the appearance of the neurological symptoms, hyperleukocytosis with 70% rate of prolymphocytes in peripheral blood and increasing splenomegaly was found. Tatarczuch et al. suggest that cancerous prolymphocytes may demonstrate a specific tropism to the CNS, the mechanism of which is not yet sufficiently understood [25]. At the same time, according to some scholars a significant number of the leukemic cells in the peripheral blood predisposes to infiltration of the CNS as a result of a normal perfusion or extravasation [24]. Hyperleukocytosis is a known risk factor of the CNS infiltration in the course of acute myelogenous leukaemia and acute lymphocytic leukaemia. It is pointed out that the expression of neuronal adhesion molecule is also significant in this process [26]. The case of the patient, who was diagnosed with orbit involvement in CLL is also very interesting. In the available literature there are only several cases regarding that subject [27]. The patient presented by us was observed with the gradual growth of the eyeball exophthalmos and swelling of the upper eyelid. After three years of observation, due to intensifying of the aforementioned symptoms, after MRI evaluation orbital tumour was diagnosed and the patient was qualified for neurosurgery. Tumour resection was performed, and histopathological examination of the tissue revealed the presence of infiltration of small cell with phenotype CD19+/CD5+/CD23+. Based on the simultaneous changes in blood morphology and after the clinical evaluation CLL stage 0 according to Rai et al. was diagnosed. Orbital lymphomas are the only approx. 1% of all NHLs [28] and they are most often diagnosed primary orbital tumours (this applies to patients above 60 years of age) [29]. The most frequently observed histopathological types are extra-nodal marginal-zone B-cell lymphomas of mucosa-associated lymphoid tissue-MALT (57%) and follicular lymphomas (19%), while less frequently, diffuse large B-cell lymphomas and mantle cell lymphomas (MCL). Orbital lymphomas may be either isolated or form part of a systemic disease (30–35% of cases) [30]. The differential diagnosis should also take into account chronic dacryoadenitis, Wegener granulomatosis, idiopathic inflammatory pseudotumour, orbital lymphoid hyperplasia, orbital sarcoidosis. Diagnostic tests include ultrasound scan, CT and MRI. Lumbar puncture to evaluate the CNS should also be considered. The treatment usually involves the radiotherapy and/or complex chemotherapy. According to some authors orbital lymphomas in the course of a systemic disease have a better prognosis than those with a local location [31].

At the moment there is no single therapeutic treatment algorithm for patients with CLL and CNSi. Many drugs used in the standard systemic treatment do not cross the blood–brain barrier. In the case of leukemic infiltration of the meninges, the most commonly used are corticosteroids, intrathecal methotrexate in monotherapy and/or in combination with cytarabine and dexamethasone and radiotherapy. Well-known are the opinions confirming, as well as questioning the effectiveness of such treatment [24]. Methotrexate is a drug with poor capacity of passing through the blood-brain barrier. Achieving the therapeutic concentration in CSF is possible with high intravenous (iv) doses or intrathecal injection (then it achieves a particularly beneficial, uniform concentration in the subarachnoid space) [32]. There are known reports of beneficial effects of intrathecal injection therapy, which were, unfortunately, not continued and confirmed in further studies [33]. While the intrathecal administration of drugs is often effective for treating leukemic infiltration of the meninges, it does not seem to be sufficient for intracerebral infiltration, having a particularly high sensitivity to radiotherapy [3]. Knop et al. decided to give iv fludarabine to two patients with CLL and CNSi, while sacrificing the intrathecal treatment and radiotherapy. Each patient achieved complete eradication of leukemic cells with CSF and remission of neurological symptoms, and in the patient with symptoms of systemic disease, regression of nodal changes and normalisation of peripheral blood. Importantly, there were no signs indicating neurotoxicity of fludarabine. According to the authors, these results may indicate the possibility of application of the fludarabine iv in CLL patients with CNS involvement, who at the same time have an advanced systemic disease [34]. Questions about the role of rituximab in the treatment of CNS leukemic changes in the course of CLL are still to be answered. Pharmacokinetic studies, when administered iv, showed its significantly lower concentration in CSF compared to the serum (approx. 1% of the value of the serum concentration). It is caused by a large molecular weight of the rituximab (146 kDa) limiting its penetration to the CNS, even at damaged blood–brain barrier [35]. The alternative would be to provide rituximab intrathecally, but at the moment we do not have any information on tests to be taken of such treatment in patients with CLL and CNSi. We know, however, instances of application of this monoclonal antibody with other drugs. Faivre et al. described three patients with neurological disorders and leukemic cells present in the CSF. Patients received 5–6 courses of bendamustine and rituximab (BR) as a result of which all patients achieved complete regression of the lesions [36]. Benjamini et al. presented the case of a 44-year-old patient with CLL and leukemic infiltrates in the eye socket and CSF. Initially, it was decided to administer methylprednisolone with rituximab and then, with complete success, 3 courses of fludarabine with cyclophosphamide and rituximab (FCR). The authors suggest that there is a potential ability to use systemic chemioimmunotherapy in this highly selected group of patients [37]. Hanse et al. described five CLL patients with clinical signs of CNS involvement in the course of leukaemia. The withdrawal of

neurological disorders was achieved as a result of systemic and intrathecal therapy. However, no complete eradication of leukemic cells with CSF was determined. Nevertheless, three patients were tested at follow-up without symptoms for two and three, and one for the next seven years. According to the authors, asymptomatically extending presence of leukemic cells in the CSF is not necessarily an automatic indication for further treatment [14]. Perhaps one should, at least in some cases, wait for the possible re-emergence of neurological disorders. These findings call into question the suggestion of some authors that the location of leukemic changes in the CNS in the course of CLL is in any case unfavourable prognostic factor. Three patients presented in our work have been treated with intrathecal treatment and one with radiotherapy (preceded by a neurosurgical procedure). Unfortunately, the other three died before treatment. Recently, there were reports about the possibility of penetration of the blood-brain barrier by the kinase inhibitors. Russwurm et al. described a patient with relapsed form of CLL in the CNS, after failure of systemic therapy with cytarabine and mitoxantrone and intrathecal methotrexate. Dasatinib was used at a dose of 70 mg 2 times a day, giving a total regression of numerous lesions in the CNS. This spectacular effect is particularly worth noticing as the pharmacokinetic studies indicate relatively small, compared to the plasma, concentration of the drug in the CSF (5–28%) [38]. Wanquet et al. in his publication presented a very interesting proposition of possibly effective treatment of CNSi using ibrutinib. In four patients the disappearance of neurological symptoms and changes in CSF as well as a normalisation to the radiological image were obtained after applying standard dose of medicine (420 mg/d) [39]. The effectiveness of ibrutinib in this extremely difficult clinical situation is also confirmed by Tam et al. [40].

The prognosis of CLL patients with CNS involvement is not easy to define. Based on available literature data, Moazzam et al. determined the average period of time since the appearance of neurological symptoms to death to approx. 12 months. The average time from diagnosis CLL with CNS involvement was 2.62 years. However, the authors failed to accurately determine the duration of the obtained remission and the number of patients with disease recurrence in the CNS [3]. In our material the CNSi prognosis can be described as extremely unfavourable. Five patients died within a very short period of time (1–3 months). Presumably, it was also influenced by the transformation in the RS and PLL. Nonetheless, two patients, after a complete remission due to the treatment, is still under the clinical observation.

5. Summary

CNS involvement in the course of CLL is rare and usually unexpected, as a result the knowledge that we have at the moment on this issue is certainly not sufficient. In each case with CLL with unexplained neurological disorders, CNS involvement should be considered in the course of the underlying disease and the basic diagnostic radiology (MRI) and CSF examination (cytological, immunophenotyping, cytogenetics) should be performed, with the knowledge of all the constraints and concerns they bring. CNSi may occur at any stage of the disease, either as the first manifestation or after several years of treatment, often in the phase of progression or transformation into more aggressive clinical form (prolymphocytic leukaemia, Richter's syndrome). This may suggest the existence of independent mechanisms affecting the development of this complication. Lack of uniform algorithms means that each patient requires an individual assessment, also in terms of comorbidities. The preferred therapeutic effect can be obtained after the intrathecal treatment (MTX, Ara-C) and radiation therapy. It is probably a bad prognosis for the complication of CLL, often leading to death. It seems, however, that at the moment there are no indications for the use of routine CSF or MRI in all patients with CLL.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

REFERENCES

[1] Chiorazzi N, Rai KR, Ferrarini M. Chronic lymphocytic leukemia. N Engl J Med 2005;352:804–15.
[2] Ratterman M, Kruczek K, Sulo S, et al. Extramedullary chronic lymphocytic leukemia: systematic analysis of cases reported between 1975 and 2012. Leuk Res 2015;38:299–303.
[3] Moazzam AA, Drappatz J, Kim RY, et al. Chronic lymphocytic leukemia with central nervous system involvement: report of two cases with a comprehensive literature review. J Neurooncol 2012;106:185–200.
[4] Cramer SC, Glapsy JA, Efird JT, et al. Chronic lymphocytic leukemia and the central nervous system: a clinical and pathological study. Neurology 1996;46:19–25.
[5] Barcos M, Lane W, Gomez GA, et al. An autopsy study of 1206 acute and chronic leukemias (1958 to 1982). Cancer 1987;60:827–37.
[6] Tomita N, Kodama F, Sakai R, et al. Predictive factors for central nervous system involvement in non-Hodgkin's lymphoma: significance of very high serum LDH concentrations. Leuk Lymphoma 2000;38:335–43.
[7] Wolf MM, Olver IN, Ding JC, et al. Non-Hodgkin's lymphoma involving the central nervous system. Aust N Z Med 1985;15:16–21.
[8] Mackintosh FR, Colby TV, Podolski WJ, et al. Central nervous system involvement in Hodgkin lymphoma: an analysis of 105 cases. Cancer 1982;49:586–95.
[9] Liang R, Chiu E, Loke SL. Secondary central nervous system involvement by non-Hodgkin's lymphoma: the risk factors. Hematol Oncol 1990;8:141–5.
[10] Hamblin AD, Hamblin TJ. The immunodeficiency of chronic lymphocytic leukaemia. Br Med Bull 2008;87:49–62.
[11] Dearden C. Disease-specific complications of chronic lymphocytic leukemia. Hematol Am Soc Hematol Educ Program 2008;450–6.
[12] De Vito N, Mui K, Jassam Y, et al. Small lymphocytic lymphoma presenting as a paraneoplastic syndrome with

acute central nervous system demyelination. Clin Lymphoma Myeloma Leuk 2014;14:131–5.
[13] da Silva RL. Spectrum of neurologic complications in chronic lymphocytic leukemia. Clin Lymphoma Myeloma Leuk 2012;3:164–79.
[14] Hanse MC, Van't Veer MB, van Lom K, et al. Incidence of central nervous system involvement in chronic lymphocytic leukemia and outcome to treatment. J Neurol 2008;255:828–30.
[15] Garicochea B, Cliquet MG, Melo N, et al. Leptomeningeal involvement in chronic lymphocytic leukemia identified by polymerase chain reaction in stored slides: a case report. Mod Pathol 1997;10:500–3.
[16] Nowakowski GS, Call TG, Morice WG, et al. Clinical significance of monoclonal B cells in cerebrospinal fluid. Cytometry B Clin Cytom 2005;63:23–7.
[17] Richter MN. Generalized reticular cell sarcoma of lymph nodes associated with lymphatic leukemia. Am J Pathol 1928;4:285–92.
[18] Rossi D, Spina V, Deambrogi C, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. Blood 2011;117:3391–401.
[19] Tsimberidou AM, O'Brien S, Kantarjian HM, et al. Hodgkin transformation of chronic lymphocytic leukemia: the M. D. Anderson Cancer Center experience. Cancer 2006;107:1294–302.
[20] Robertson LE, Pugh W, O'Brien S, et al. Richter's syndrome: a report on 39 patients. J Clin Oncol 1993;11:1985–9.
[21] Resende LS, Bacchi CE, Resende. et al. Isolated Richter's syndrome in central nervous system: case report. Arq Neuropsiquiatr 2005;63:530–1.
[22] Lane PK, Townsend RM, Beckstead JH, et al. Central nervous system involvement in a patient with chronic lymphocytic leukemia and non-Hodgkin's lymphoma (Richter's syndrome), with concordant cell surface immunoglobulin isotypic and immunophenotypic markers. Am J Clin Pathol 1988;89:254–9.
[23] Melo JV, Catovsky D, Galton DA. The relationship between chronic lymphocytic leukemia and prolymphocytic leukemia. I. Clinical and laboratory features of 300 patients and characterization o fan intermediate group. Br J Haematol 1986;63:377–87.
[24] Hoffman MA, Valderrama E, Fuchs A, et al. Leukemic meningitis in B-cell prolymphocytic leukemia. A clinical, pathologic, and ultrastructural case study and a review of the literature. Cancer 1995;75:1100–3.
[25] Tatarczuch M, Blombery P, Seymour JF. De novo B-cell prolymphocytic leukemia with central nervous system involvement. Leuk Lymphoma 2014;55:1665–7.
[26] Lazarus HM, Richards SM, Chora R, et al. Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis: result from the international ALL trial MRC UKALL XII/ECOG E2993. Blood 2006;108:465–72.
[27] Bonavolontà G, Strianese D, Grassi P, et al. An analysis of 2480 space-occupying lesions of the orbit from 1976 to 2011. Ophthal Plast Reconstr Surg 2013;29:79–86.
[28] Ahmed S, Shahid RK, Sison CP, et al. Orbital lymphomas: a clinicopathologic study of a rare disease. Am J Med Sci 2006;331:79–83.
[29] Demirci H, Shields CL, Shields JA, et al. Orbital tumors in the older adult population. Ophthalmology 2002;109:243–8.
[30] Isaacson PG, Wright DH. Malignant lymphoma of mucosal associated lymphoid tissue: a distinctive type of B cell lymphoma. Cancer 1983;52:1410–6.
[31] Agrawal AH, Khobragade VD, Patil AA, et al. Orbital lymphoma – a diagnostic challenge. Int J Recent Trends Sci Technol 2016;18:391–3.
[32] Kroin JS, Schaefer RB, Penn RD. Chronic intrathecal administration of dexamethasone sodium phosphate: pharmacokinetics and neurotoxicity in an animal model. Neurosurgery 2000;46:178–82.
[33] Diwan RV, Diwan VG, Bellon EM. Brain involvement in chronic lymphocytic leukemia. J Comput Assist Tomogr 1982;6:812–4.
[34] Knop S, Herrlinger U, Ernemann U, et al. Fludarabine may induce durable remission in patients with leptomeningeal involvement of chronic lymphocytic leukemia. Leuk Lymphoma 2005;46:1593–8.
[35] Miller K, Budke H, Orazi A. Leukemic meningitis complicating early stage chronic lymphocytic leukemia. Arch Pathol Lab Med 1997;5:524–7.
[36] Faivre G, Songer S, DeAngelis L, et al. Rituximab and bendamustine for CNS involvement by chronic lymphocytic leukemia. Neurology 2014;82. Supp. P7.261.
[37] Benjamini O, Jain P, Schlette E, et al. Chronic lymphocytic leukemia with central nervous system involvement: a high-risk disease? Clin Lymphoma Myeloma Leuk 2013;13:338–41.
[38] Russwurm G, Heinsch M, Radkowski R, et al. Dasatinib induces complete remission in a patient with primary cerebral involvement of B-cell chronic lymphocytic leukemia failing chemotherapy. Blood 2010;116:2617–8.
[39] Wanquet A, Birsen R, Lemal R, et al. Ibrutinib responsive central nervous system involvement in chronic lymphocytic leukemia. Blood 2016;127:2356–8.
[40] Tam CS, Bimber T, Seymour J. Ibrutinib monotherapy as effective treatment of central nervous system involvement by chronic lymphocytic leukaemia. Br J Hematol 2016;176:829–31.