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Could it be Lymphoma - Our Diagnostic Algorithm?

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ABSTRACT

Background: Diagnosing lymphoma of the central nervous system (CNS) could be challenging. A diagnostic algorithm was proposed by the presented clinical cases.

Methods: neurological exam, laboratory tests, magnetic resonance tomography (MRI), biopsy, electromyography (EMG).

Results: We present different clinical cases of patients with lymphoma of nervous system. We implemented a protocol that could be useful in the process of diagnosing. The algorithm include: neurological exam, brain imaging examination (magnetic resonance imaging- MRI, computed tomography- CT), cerebrospinal fluid (CSF) testing with flow cytometry examination (FCM) and additionally biopsy. In the article we present more precisely five patients with different neurological symptoms. First case is of a 44-year-old male admitted to the hospital with meningeal irritation syndrome, with MRI data for tumour in the left cavernous sinus area. Biopsy was performed 3 months earlier negative histology for tumour cells. It was discussed CNS infection an examination of cerebrospinal fluid (CSF) showed lymphocytic pleocytosis with atypical lymphocytes. FCM of CSF showed T-lymphoblastic lymphoma. The second case is of 50-year-old female with complaints of weakness in the lower limbs, dysphagia and facial nerve palsy. MRI of the brain showed no pathology. The patient was with suspicion for Guillain-Barre syndrome due to symptoms and performed EMG. CSF examination showed lymphocytic pleocytosis. The patient was diagnosed with B-lymphoblastic lymphoma due to result from FCM of CSF. The third case is of a 63-year-old male with right hemiparesis. It was discussed ischemic stroke, tumour, CNS infectious disease and progressive cognitive impairment.

MRI of the brain was performed with diffuse lesions in both hemispheres and left cerebellar peduncle. CSF examination showed no pathological changes. After brain tissue biopsy of one of the lesions the patient was diagnosed with diffuse large B-cell lymphoma. The fourth case is of a 71-year-old male with meningeal irritation syndrome, fever, diarrhea. CSF was with lymphocytic pleocytosis. CT of the abdomen was performed because of abdominal pain and weight reduction for several months. A tumour formation was found and biopsy of it showed B- cell lymphoma. The fifth case is of a 51- year-old male with headache and fever (38.5 degree Celsius). All test were negative, except FCM examination of CSF showing T- lymphoblastic lymphoma.

Conclusion: CNS lymphoma is a rare disease with complicated differential diagnose. An algorithm of exams could be a useful tool helping not to misdiagnosed it.

Keywords: Lymphoma; Nervous Systeml; Diagnostic Algorithm

Abbreviations: CNS: Central Nervous System; PCNSL: Primary Central Nervous System Lymphoma; CS: Corticosteroids; EMG: Electromyography; FCM: Flow Cytometric; DLBCL: Diffused Cellular B-Cell Lymphoma

Introduction

Lymphoma of the central nervous system (CNS)is a rare subset of non-Hodgkin lymphoma. According to the World Health Organization, primary central nervous system lymphoma refers to the CNS parenchyma, dura, leptomeninges, cranial nerves, and spinal cord or the intraocular compartment in immunocompetent patients [1]. The affected parts of the CNS could be different with variable clinical presentation. The diagnosis requires a novel approach of group of tests not to be missed. The prognosis of primary central nervous system lymphoma depends when the patient is diagnosed, with overall survival of 1.5 months when untreated, and a five-year survival rate of 30 % [2]. Primary central nervous system lymphoma (PCNSL) occurs at an incidence of 0.47 per 100,000 person-years [3]. Differential diagnose include brain tumours, neuro infection diseases, peripheral nerve disease, sarcoidosis, vascular disease, autoimmune disease. Definitive diagnose of central nervous system lymphoma (CNSL) relies on a positive CSF and biopsy examination [4]. Many studies have demonstrated the usefulness of FCM for detecting CNS disease in B-cell lymphoma [5,6]. More recent analyses of larger series of CSF-stabilized samples have confirmed the sensitivity of FCM [7]. The current gold standard method for diagnosis of CNS lymphoma is the stereotactic biopsy, since the lesions are usually deep seated and their resections were shown to be associated with worse prognosis [8,9]. However histopathological examination of stereotactic biopsies also has some limitations, not only because of small sample sizes, but also due to large spectrum of differential diagnoses, including inflammatory conditions such as vasculitis, multiple sclerosis and infection diseases.

The dense cellularity of the tumour accounts for its isodense or hyperdense appearance on nonenhanced CT scan and hypointense appearance on long TR-weighted MRI imaging. Primary lymphoma of the central nervous system usually is diffusely infiltrative at the time of presentation and considered a "whole brain" disease. The areas of lymphoma are not visible on neuroimaging studies because they are behind a relatively intact blood–brain barrier [10,11] Prior exposure to corticosteroids (CS) presents the major diagnostic challenge. Because of the high sensitivity of lymphoma cells to corticosteroid-induced apoptosis, previous treating with CS can mask the morphology of lymphoma and even causing tumor vanishing [12]. Five different cases of central nervous system lymphoma are presented.

Methods

The described patients were admitted in clinic of neurology with different clinical presentation. Somatic and neurological exam were performed, laboratory tests including flow cytometric (FCM) immunophenotyping of cerebrospinal fluid, magnetic resonance tomography, computed tomography scan, trepan biopsy of bone marrow and tumor tissue, electromyography (EMG), X-ray on thorax, coronary angiogram. CNS lymphoma could manifest with atypical symptoms, which are either misdiagnosed or difficult to distinguish from other disease. It is necessary to perform further CNS imaging and/or CSF analysis, depending on the symptoms of the patient and the results of the other diagnostic tests.

Results

The described clinical cases are analyzed to construct a diagnostic algorithm for central nervous system lymphoma. The first case is of a 44-year-old patient admitted to the emergency department with complaints of progressively increased headache, stiffness of the neck, impaired coordination, nausea, vomiting. Neurological examination revealed a meningeal irritation syndrome and right limbs hypoesthesia. MRI of the head was done prior to the admission in neurological clinic with a data for tumor in the left cavernous sinus area. Patient has history for peripheral facial nerve palsy and MRI with showing extra-axial tumor formation in the left cavernous sinus area (Figure 1). Biopsy was performed 3 months earlier but without tumor cells. Performed laboratory tests show slightly increased troponin I - 1761.4 pg/ml and C- reactive protein 25.4mg/l. Systemic infection and autoimmune disease were excluded by additional tests. The results showed negative QuantiFERON TB-Gold test, negative hepatitis B and C tests, antiphospholipid antibody, negative rapid plasma reagin (RPR) and HIV. The X-ray on thorax was without pathological changes. Lumbar puncture was done to exclude infection of the central nervous system. Examination of cerebrospinal fluid showed lymphocytic pleocytosis, atypical ones in different phase of mitosis. CSF was negative for lymphocytic choriomeningitis, HSV, VZV, Epstain-Barr virus. Trepan biopsy of bone marrow showed no pathological changes. The patient was diagnosed with T-lymphoblastic leukemia / lymphoma after FCM of cerebrospinal fluid.

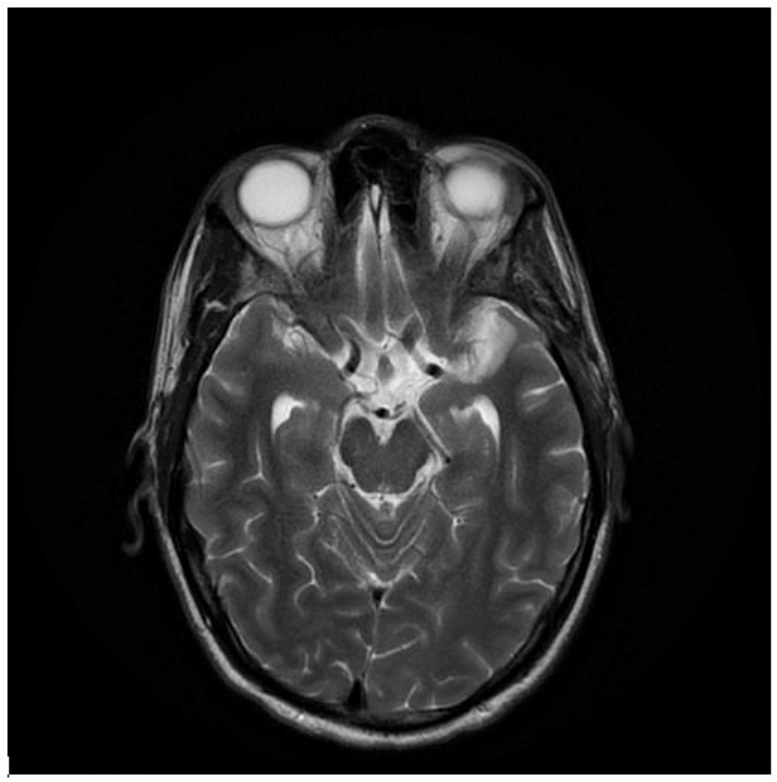

Figure 1.

In the studied material were identified: 1.5% of CD45 + mature lymphocytes; 93% of CD45 + cells - T-lymphoblasts CD45 (+) low sCD3 (J +) partial, CD2 (+), CD5 (+), CD7 (+), CD4 (+), CD8 (+), CD34 (-), CD56 (-), CD10 (-), CD19 (-), CD20 (-). Intrathecal chemotherapy was started with high-dose methylprednisolone, vincristine, methotrexate and ara-C. It was combined with hyper-CVAD (cyclophosphamide, vincristine sulfate, adriamycin, and dexamethasone. The second case is of 50-year-old female with acute complaints of weakness in the legs, she was unable to walk alone. She reported for worsening of the condition with difficulty in swallowing, fatigue and chills. Neurological examination showed peripheral lesion for facial nerve on the right, weakened muscle strength for both legs MMT 4/5, diminished deep tendon reflexes. Romberg test was positive. She had decreased sensation for touch and pain for lower extremities. Brain tumor was excluded by performed MRI of the brain (Figure 2). The patient was with suspicion for Guillain-Barre syndrome because of the clinical presentation. EMG data showed sensory-motor axonal polyneuropathy. CSF examination showed lymphocytic pleocytosis (403x10 ^6/l), 47% atypical ones, high protein level-1.98 g/l (0/0.45) and lactate level 3.7 mmol/l (1.1/2.2). Laboratory tests did not reveal an infectious agent (EBV, CMV, VZV, HIV, COVID-19). It was performed FCM of cerebrospinal fluid. 122 546 cells were identified in CSF: 95.9% of all cells are CD45 (+); CD19 (+); CD10 (+); CD20 (+); CD3 (-); CD34 (-) cells with B-lymphocyte phenotype. Because of this exam the patient was diagnosed with B-lymphoblastic lymphoma.

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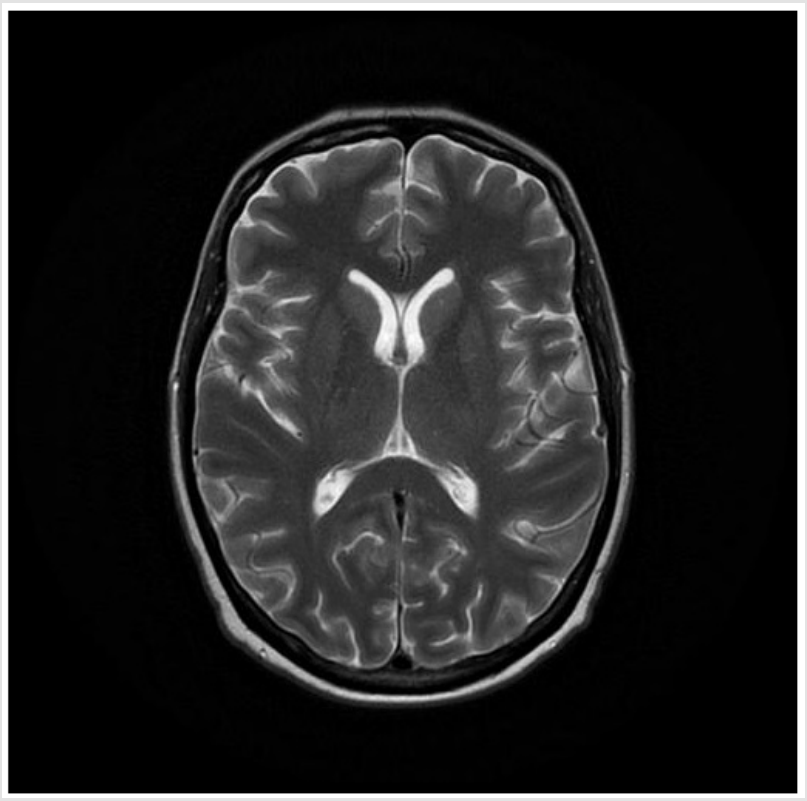

Figure 2.

We decided that lower motor neuron symptoms (missing reflexes and weakness in four limbs) could be caused by a peripheral neuropathy mainly as a result of direct lymphoma infiltration. Treatment was continued with intrathecal chemotherapy (Cytosar and Methotrexate). The third case is of a 63-year-old male with right hemiparesis and progressive cognitive impairment. Neurological examination revealed dysarthria, mild right central hemiparesis, spasticity for the left limbs, exaggerated reflexes in four limbs, mild cognitive impairment. Several CT and MRI of the brain was performed with diffuse lesions in both hemispheres (Figure 3, 4). It was discussed ischemic stroke, tumor, CNS infectious disease. Laboratory tests did not reveal an infection disease-EBV, CMV, VZV, HIV, COVID-19. Examination of cerebrospinal fluid showed no pathological changes. Treatment with steroids was started. The condition of patient improved. Due to suspicion for lymphoma, trepan biopsy of bone marrow was performed. It was negative for lymphoma. Patient was diagnosed after brain tissue biopsy of one of the lesions. In order to determine the histogenesis and possible primary focus, an immunohistochemical study was performed. The result showed CD45 and CD20 - positive reaction in tumor cells, CD10 - a negative reaction in tumor cells, Ki67 - a positive reaction in about 80% of tumor cells, Cytokerarin AE1 / AE3 - adverse reaction, GFAP, S100 and Synaptophysin - a negative reaction in tumor cells with positive internal control in astrocytes, CD3 and CD5 - a positive reaction in a small number of mature T lymphocytes. The constellation was for diffused cellular B-cell lymphoma (DLBCL).

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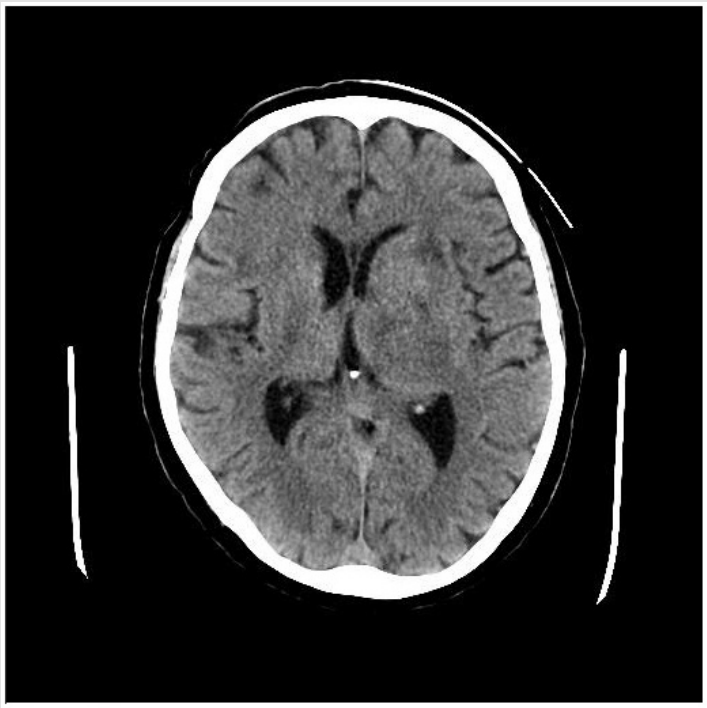

Figure 3.

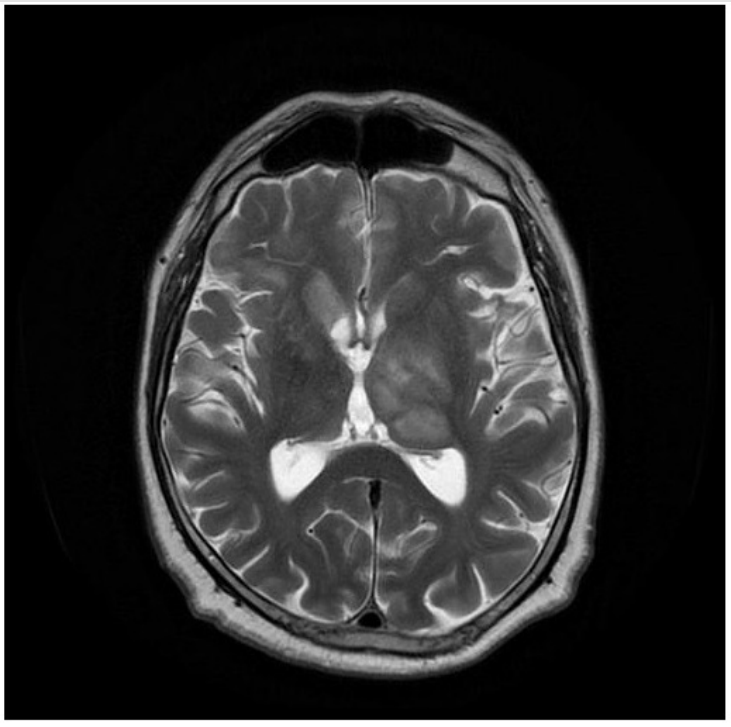

Figure 4.

The fourth case is of a 71-year-old patient with acute complaint of fever, diarrhea, confusion, headache. He was admitted with meningeal irritation syndrome. CT and MRI of the brain showed small vessel disease. Laboratory tests were negative for autoimmune and infection disease. The patient had fatigue and weight reduction. Due to these symptoms and abdominal ones a CT of the abdomen was performed. CT showed soft tissue formation - a conglomerate of enlarged lymph nodules in the abdomen (mesenteric and retroperitoneal). CSF and FCM were negative, a biopsy of lymph nodules showed B-cell non-Hodgkin's lymphoma, Grade 1-2 CD20+, CD10+, BCL2+ and focally positive BCL6, CD3-, CD5-, CD23-, Cyclin D1-, with proliferative activity - 12-15 %. The fifth case is of 51-year-old man with fever for two weeks, severe headache and periods of confusion. He was admitted with suspicion for meningitis. The CSF was negative for viral and bacterial infection (including HIV, HSV1, HSV2, EBV, CMV) despite lymphocytosis (14x10^6/L). CT of the brain and x-ray of the chest were without pathological changes. A patient was diagnosed with T-lymphoma after performed FCM of CSF. A biopsy of axillar enlarged lymph nodule confirmed the result.

Conclusion

We try to compose a diagnostic algorithm on the base of clinical cases in our experience. A table was presented with group of tests that could be used in the tricky diagnose of CNS lymphoma (Table 1). A special attention should be dedicated to FCM of cerebrospinal. Flow cytometry is a highly sensitive method for detecting malignant cells [13-15]. FCM can detect CNS disease before the manifestation of systemic disease symptoms. If we start to use routinely flow cytometry and cytology it will be possible to detect early neoplasm of CNS. A lot of studies have demonstrated the utility of FCM for detecting CNS disease [16-19]. CSF examination should be done in presence of neurological symptoms, in addition to imaging techniques (MRI, CT) [20]. It is challenging to diagnose a patient with CNS lymphoma due to broad differential diagnoses. High-grade gliomas, meningioma, granulomatous and demyelinating diseases, vasculitis, could be take in consideration. Metastatic disease from systemic malignancies as well must be ruled out with a careful package of diagnostic tests. Of course every case is individual but if we performed the proposed algorithm it could ease the process. The main role on this group of tests is on cerebrospinal fluid cytology. It could ensure a definitive diagnostic information in CNS lymphoma and with the help of immunohistochemical studies, it could identify atypical lymphoid cells or neoplastic. Sensitivity improves when a larger volume (≥10.5 mL) is analyzed and when serial CSF samples are examined [21]. Sensitivity is reduced when there are slowdown in processing or after exposition to corticosteroids, causing cytolysis [22]. Abnormalities of the peripheral nervous system occur in 5% of patients with lymphoma. Some of the therapies used in lymphoma could also cause neuropathy. The incidence of Guillain-Barré (GBS) syndrome appears to be raised in association with lymphoma [23-27].

Table 1.

Diagnostic algorithm	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
1-Neurological exam- pathological changes	+	+	+	+	+
2-Blood test including PCR for viral infection	-	-	-	-	-
3-CSF test including PCR for viral nfection and culture test for bacterial infection	-	--	-	-	-
4-Brain imaging pathological finding	+	-	+	-	-
5- Imaging test of the chest and abdomen	-	-	-	+	-
6- FCM of CSF	+	+	-	+	+
7-Performe biopsy if it is possible	+	-	+	-	+

Disclosures

No Disclosures.

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