

CLINICAL STUDY

Dominant neurologic symptomatology in intravascular large B-cell lymphoma

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ABSTRACT

Intravascular large B-cell lymphoma (IVLBCL) is a rare variant of extranodal large B-cell lymphoma and it is characterized by selective intravascular proliferation of malignant cells. Typical features of the disease include aggressive behavior, rapid and frequently fatal course. Clinical picture is non-specific and heterogeneous, depending on the affected organ. It is not uncommon that this unique type of lymphoma is diagnosed post mortem. Herein, we report two cases of IVLBCL with neurologic symptomatology. In our clinical study patient 1 was an 80-year-old male with mixed paraparesis of lower extremities and difficulties with sphincter control. Patient 2 (56-year-old male) had vision malfunction, mental status changes and defect in phatic and motor functions. In both cases definite diagnosis was established by histological examination of necrotic material. We propose to include IVLBCL in differential diagnostic considerations in patients presenting with gradually impairing neurological status and spinal cord damage of unknown etiology (Fig. 2, Ref. 9). Text in PDF www.elis.sk.

Key words: intravascular large B-cell lymphoma, CNS vessels, neurologic symptoms.

Introduction

Intravascular large B-cell lymphoma is a rare type of lymphoma characterized by selective proliferation of lymphoma cells in the lumens of small vessels, especially capillaries, typically without affecting large arteries and veins (1). It usually affects middle-aged and elderly adults, with median age at diagnosis of 67 years and basically with no sex predominance (1, 2). Two types of this disease have been described: western type, presenting mainly with skin and central nervous system involvement and Asian type, with the presence of systemic symptoms, hemophagocytic syndrome and multiorgan failure but usually without dermatologic and neurologic symptomatology (2, 6). Clinical manifestation of IVLBCL results from occlusion of the vessel lumen by lymphoma cells with consecutive ischemic damage of the organs and is rather heterogeneous depending on the site of ischemia. Fever can be present. Lymphadenopathy is usually not seen. Many organs can be affected, commonly brain and spinal cord, skin, lungs and kidneys, although several cases with selective damage of only one organ

have been described (3, 4, 7). Since the symptomatology is non-specific and the course is rapid, the correct diagnosis is frequently established post-mortem. In the presented work we analyze 2 cases of IVLBCL, an 80-year-old male with mixed paraparesis of the lower extremities and a 56-year-old male with vision impairment, personality disorder and defects in phatic and motor functions.

Materials and methods

This study included 2 patients with neurologic symptomatology. Clinical data and hospital records were available in both cases. Autopsy was performed in a standard way at the Institute of Pathology, Healthcare Surveillance Authority, Antolska 11, Bratislava and the Institute of Pathology, Comenius University, Faculty of Medicine, Sasinkova 4, Bratislava. Formalin-fixed and paraffin-embedded tissue samples were evaluated in light microscope with the use of standard hematoxylin and eosin staining and immunohistochemical analysis.

Clinical study

An 80-year-old male with a history of arterial hypertension and ischemic heart disease was hospitalized for 15 days at the Department of Neurology for mixed paraparesis of the lower extremities and difficulties with sphincter control. Due to this clinical picture myelitis was considered and the patient was administered with a pulse dose of methylprednisone. Subsequently, macrocytic anemia and moderate thrombocytopenia were diagnosed. Consultant hematologist considered myelodysplastic syndrome, therefore bone marrow aspiration was performed. However, the result was not available during the patient's lifetime. Urine flow obstruction

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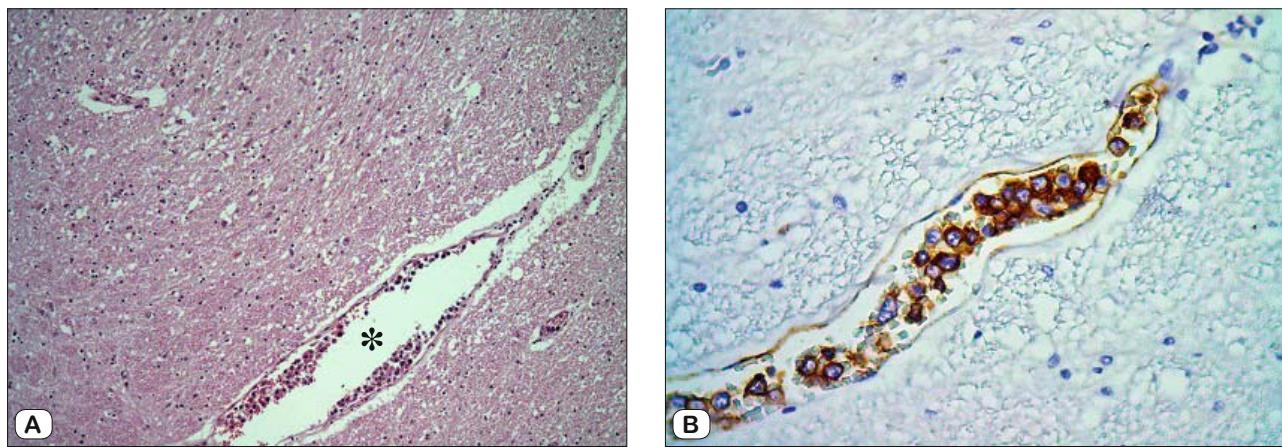


Fig. 1. Patient 1. Cervical spine, tumor cells (*) are present in the vessel lumen. (A, Haematoxylin and Eosin staining, x100). The neoplastic cells express antigen CD20 visualized by brown color. (B, immunoperoxidase technique, x200).

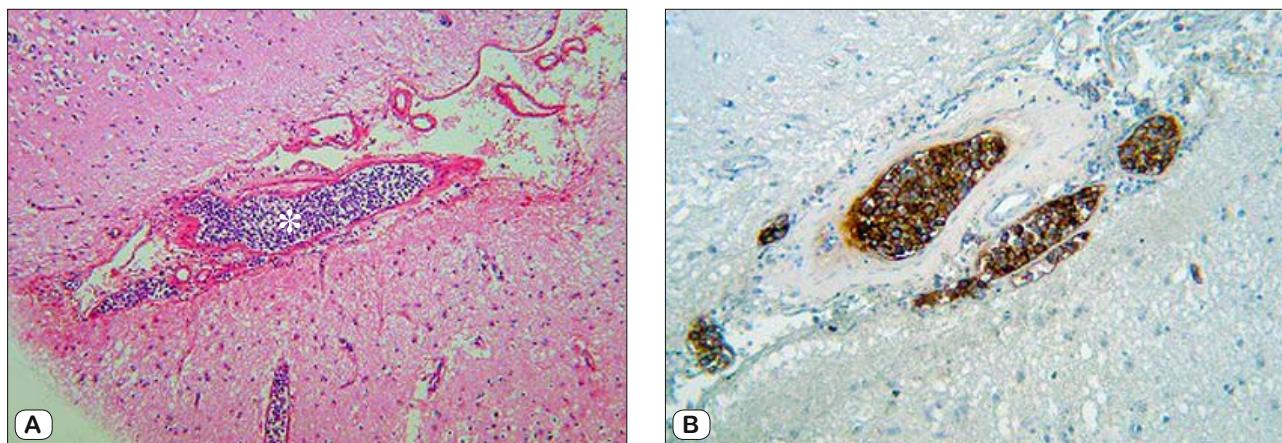


Fig. 2. Patient 2. Brain tissue, tumor cells (*) are filling the vessel lumen (A, Haematoxylin and Eosin staining, x100). The cells express antigen CD20 visualized by brown color (B, immunoperoxidase technique, x100).

caused by benign hyperplasia of the prostate required insertion of urinary catheter and due to possible infection of the urinary bladder the patient was treated with ciprofloxacin. Because the patient deteriorated rapidly, he was transferred to the Department of Anesthesiology and Resuscitation and later to the metabolic intensive care unit of the Department of Internal Medicine. Laboratory test results showed mild leukocytosis, acidosis of combined etiology, hypoxemia and urea and creatinine elevation pointing to renal insufficiency, possibly of prerenal type. Despite intensive care the patient suddenly died on the second day of hospitalization.

The autopsy revealed several pathologic findings. Two small foci of petechial haemorrhage were found in the frontoparietal and parietooccipital area of the right brain hemisphere. Apart from that no gross pathological findings in the brain and spinal cord were observed. Other findings included bilateral hydrothorax (250 ml), lung edema (predominantly of the lower left lobe), chronic bronchitis, emphysema and anthracosis of the lungs. Myocardium of the left ventricle was hypertrophic suggesting hypertensive heart disease. On the cut section, multiple small streaky scars and a large scar after myocardial infarction of the posterior wall of the left

ventricle (due to atherosclerosis of coronary arteries) were observed. Other findings included arteriolosclerotic nephrosclerosis, 3 scars after kidney infarctions, diverticulosis of descending colon, hemorrhagic infarction of the colon, passive hyperemia of the abdominal organs, chronic cholecystitis with cholezystolithiasis, benign nodular hyperplasia of the prostate with hypertrophy of the muscle layer of the urinary bladder and hyaline perisplenitis (sugar icing spleen). Lymphadenopathy was not present.

Microscopic evaluation of cervical and lumbar spinal cord revealed intravascular proliferation of large round cells and large blasts with round nucleus and scant cytoplasm. These lymphoid cells were occasionally seen also in the interstitial tissue of the spinal cord (Fig. 1A) and were also present in the vessels of other organs including the lungs, right and left ventricle of the heart, kidneys, prostate and bone marrow. The cells were CD45 and CD20 positive (Fig. 1B) and showed negative reaction for CD3, CD5, CD10, CD30, CD45RO, Bcl2 and chloroacetate esterase (CHAE) activity.

A 56-year-old male with history of arterial hypertension, type 2 diabetes mellitus and ischemic heart disease was admitted to

the Department of Internal medicine and later to the Department of Neurology for sudden onset of speech impairment, change in behavior, smudged and double vision. The symptoms emerged three weeks prior to the hospitalization. The patient also experienced weakness of the thigh muscles. Physical examination revealed defects in both components of phatic functions. Fever was not present. Laboratory tests showed elevated blood glucose and alanine transaminase (ALT), anemia and leukocytosis. A computed tomography (CT) and magnetic resonance imaging (MRI) of the brain disclosed infiltrative mass in the deep portion of the temporal lobe. Based on the result of subsequent magnetic resonance spectroscopy (MRS) a glial tumor was considered. Due to location and infiltrative growth of the mass radical resection of the tumor was not possible and the patient was transferred to the Department of Neurosurgery for biopsy of the tumor. Despite repeated brain biopsies navigated by MRI and combined MRI and positron emission tomography (PET) the microscopic evaluations failed to confirm presence of tumor cells in the biopsy specimens. During hospitalization, the patient's clinical status deteriorated gradually. Repeated brain MRI showed progression of the mass with involvement of the left temporal, frontal and occipital lobe, the brain stem and the cerebellum, consistent with encephalitis, therefore the patient was administered with ceftriaxone and glucocorticoids. Cerebrospinal fluid analysis was pursued to exclude intracranial infection, however, with negative result. Consecutive brain PET scan demonstrated a pathologic mass in the left temporal lobe, which showed decreased metabolism of 18 fluorodeoxyglucose (18 FDG) in both phases and in the second phase a viable mass with the diameter of 1 cm at the dorsomedial margin of the left temporal lobe was visualized. Microscopic evaluation of the biopsy specimen from this region showed non-specific reactive changes that can be seen basically in any kind of brain damage. Repeated imaging tests of the brain indicated alternating progression and regression of the pathologic process, non-specific changes of uncertain etiology and brain edema. During following weeks, the patient gradually developed right-sided hemiparesis, disorientation and aggressiveness. A transient improvement of the clinical status was observed after craniotomy. Despite intensive care and repeated tests the patient died 5 and a half months after the onset of first neurological symptoms.

The autopsy revealed bilateral brain edema and multiple foci of petechial hemorrhage in both grey and white matter of both hemispheres, predominantly on the left side. These foci were largest in the left frontal, parietal and temporal lobe, with a diameter up to 15 mm. A dark purple focus with a diameter of 8 mm was observed in the cerebellum. Petechiae were also seen in the brain stem. Other autopsy findings included generalized atherosclerosis, bilateral, semi-turbid pleural effusion, bilateral lung edema, non-specific chronic colitis and splenomegaly.

Microscopic evaluation of the brain tissue revealed foci of perivascular hemorrhage and brain edema. In some vessels we observed moderately large blastic lymphoid cells (Fig. 2A) with high mitotic activity and typical immunophenotype: CD45 and CD20 positivity (Fig. 2B) and negative reaction for CD3, CD5, CD10, CD30, CD45RO, Bcl2 and chloroacetate esterase (CHAE)

activity. We did not identify lymphoid cells in the vessels of other organs. Other microscopic findings included lung edema, passive hyperemia of the lungs and spleen, disseminated myocardial fibrosis, mild arteriolosclerotic and arteriosclerotic nephrosclerosis and non-specific chronic colitis.

Discussion

Intravascular large B-cell lymphoma, also known as intravascular lymphomatosis and angiotropic lymphoma, is a rare subtype of extranodal diffuse large B-cell lymphoma (2). Since the typical feature of this disease is selective proliferation of malignant cells in the vessel lumen, malignant transformation of the endothelium was previously considered, thus the obsolete term "malignant angioendotheliomatosis" (8). This unique variant of lymphoma, unlike other lymphomas, does not primarily affect lymphatic tissue but vessels of essentially any organ. Therefore, the disease frequently presents with a set of non-specific symptoms and signs resulting from involvement of one or several systems (2, 3, 5). IVLBCL should be taken into differential diagnostic consideration in the cases of ischemic damage of the organs combined with non-specific symptoms, signs and laboratory test results including mainly fever and cytopenia, in middle-aged and elderly patients. Symptoms connected with ischemic damage of only one organ can be seen in the cases of its involvement by IVLBCL (3, 5, 7). Neurologic symptomatology involves progressive dementia, generalized muscle weakness, deterioration of sensory and motor functions, paraparesis (in spinal cord involvement) and sphincter dysfunction. Affection of kidneys may result in nephrotic syndrome, skin lesions are heterogeneous. Systemic symptoms and signs, particularly fever, night sweats, fatigue and weakness are quite common. Involvement of the central nervous system may present with non-specific MRI changes – cortical and subcortical lesions suggesting ischemia or demyelination. The most frequent laboratory test results are anemia, elevated level of lactate dehydrogenase (LDH) and high erythrocyte sedimentation rate. Thrombocytopenia and leukopenia are less commonly observed and occasionally, malignant lymphoid cells can be identified in the peripheral blood smear. Nevertheless, definite premortal diagnosis of IVLBCL can be established only by microscopic evaluation of a biopsy specimen (3, 4, 5, 6). It has been reported that a random skin biopsy can be helpful in identifying the presence of lymphoid cells in the vessels of the dermis and subcutaneous tissue, even in the absence of dermatologic lesions (5). Currently there is no specific clinical, imaging or laboratory technique for diagnosis of IVLBCL. Because of heterogeneous clinical manifestation, rapid course and poor prognosis, the disease remains a major challenge for clinicians and is often diagnosed post mortally (3, 9).

IVLBCL is characterized by proliferation of lymphoma cells in the lumen of small and medium-sized vessels. It is typically confined to intravascular spaces, although extravascular involvement has also been reported. Neoplastic cells are large, with prominent nucleoli and multiple mitotic figures. They express B-cell-associated antigens (CD19, CD20, CD22 and CD79a), CD5 and CD10 expression or co-expression can be seen in some cases. The selec-

tive intravascular growth of the tumor cells has been thought to be secondary to a defect in homing receptors on the cells (1, 2).

Neurological status of the first patient was remarkable for mixed paraparesis of the lower extremities. Laboratory test results showed several abnormalities, including anemia, thrombocytopenia, slight elevation of markers of inflammation and elevation of urea and creatinine. During his hospitalization, he deteriorated several times with signs of circulatory failure. Some of the frequent signs of IVLBCL (such as skin involvement and fever) were not present in the first patient, yet dominant features in the clinical picture were paraparesis of unknown etiology, recurrent episodes of reduced vigilance and signs of circulatory failure. These were considered a result of heart failure due to presence of risk factors for atherosclerosis. Despite used diagnostic methods and several clinical consultations, the diagnosis of IVLBCL was not established premortally. The result of histological evaluation of bone marrow biopsy was not available during the patient's lifetime. Symptoms and signs caused solely by involvement of the spinal cord without those caused by affection of the central nervous systems represent a rare presentation of IVLBCL. In addition, biopsy in this area is quite limited and imaging methods reveal non-specific findings (3, 6). For these reasons, IVLBCL was not considered in differential diagnosis.

Neurologic symptomatology of the second patient suggested damage of the central nervous system. Considering severe diseases of the cardiovascular system and type 2 diabetes mellitus, ischemic damage of the brain resulting from atherosclerosis was taken into account in differential diagnosis. Other common signs of IVLBCL were not present. The results of imaging tests were non-specific, variable and demonstrated alternating progression and regression of the pathologic mass in the brain. Repeated brain biopsies and their microscopic analysis did not uncover the presence of tumor cells of IVLBCL.

Conclusion

IVLBCL is a unique type of lymphoma characterized by extremely heterogeneous clinical manifestation, rapid course and poor prognosis. Histological evaluation of a biopsy specimen remains the only method capable of confirming the diagnosis of IVLBCL premortally. The presented cases demonstrate that signs and symptoms of IVLBCL are variable, non-specific and may often imitate other diseases. In addition, one of our cases is unique in uncommon dominant clinical presentation caused by involvement of the spinal cord. In conclusion, we propose to include IVLBCL into differential diagnostic considerations in patients presenting with gradually impairing neurological status and spinal cord damage of unknown etiology.

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