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Intravascular Large B-Cell Lymphoma Mimicking Central Nervous System Vasculitis

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Abstract

Intravascular large B-cell lymphoma (IVBCL) represents a rare subtype of extranodal diffuse large B-cell lymphoma characterized by selective growth of neoplastic cells within the lumen of small and medium-sized vessels. The clinical spectrum is heterogeneous dominated by neurological and skin manifestations. Intra-vitam diagnosis still remains challenging and usually requires brain biopsy since no pathognomonic neuroradiological findings do exist for IVBCL. We report on the case of a 65-year old male patient presenting with multifocal neurological signs and symptoms including cognitive deficits, aphasia and paraparesis as leading features. Imaging findings were suggestive for cerebral vasculitis prompting initiation of steroid treatment. After initial stabilization the patient deteriorated in spite of systemic steroid treatment, developed severe sepsis and finally died from multi-organ failure. Histopathological findings revealed CD20 positive lymphoma cells in small- and middle-sized vessels of the cerebrum, the lungs and the skin diagnostic for IVBCL. This case should raise the alertness for consideration of IVBCL as a differential diagnosis resulting in early brain biopsy, if no etiology for CNS vasculitis is evident.

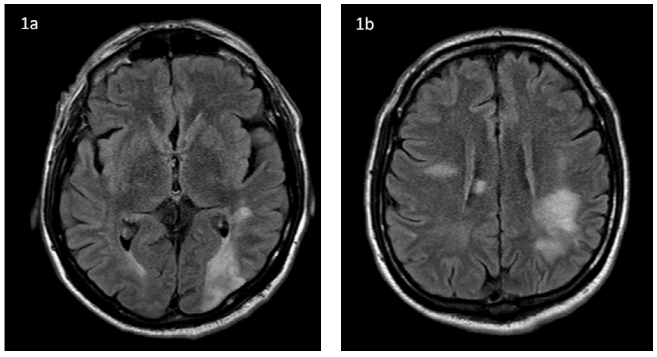
Keywords: Intravascular large B-cell lymphoma; CNS vasculitis; Brain biopsy; Cerebral ischemia

Introduction

Intravascular large B-cell lymphoma (IVBCL) is defined as a rare subtype of extranodal diffuse large B-cell lymphoma characterized by selective growth of neoplastic cells within the lumina of small and medium-sized blood vessels of several organs preferentially affecting the central nervous system (CNS) and skin [1-4]. Generally, patients present with non-specific clinical signs and symptoms such as fatigue, loss of appetite, fever of unknown origin accompanied by neurological symptoms and signs. The absence of nodular tumor formations usually characterizing CNS lymphomas diminishes clinical suspicion. Due to non-specific laboratory and neuroimaging findings, diagnosis is often obtained only at autopsy [2]. Hence, identifying IVBCL as the cause of neurologic disease still remains challenging. This case report of a histologically proven IVBCL mimicking CNS vasculitis aims to draw the attention to the difficulty of IVBCL diagnosis.

Case Report

A 65-year old male was admitted with acute paraparesis of the lower extremities, urinary and sphincter dysfunction. Upon clinical presentation the patient showed weakness of both legs and motor aphasia. The patient's medical history revealed one single episode of double vision and vertigo two weeks prior to admission, which had been classified as transient ischemic attack (TIA) seemingly underlined by the patient's history of coronary heart disease. The patient's wife had observed behavioral changes, anxiety and mild cognitive deficits over a period of six months. Cerebral and spinal MRI showed multifocal ischemic lesions (Figures 1a and 1b). CT-angiography was indicative for CNS vasculitis resulting in treatment with methylprednisolone. Subsequently, the patient was transferred to a tertiary care hospital and admitted to a stroke unit. Laboratory work-up showed slightly elevated levels of lactate dehydrogenase up to 270 U/l (normal range 100-250 U/l). Red and white blood cell count, platelets and erythrocyte sedimentation rate were unremarkable at this time point. CSF examination showed a slight increase in protein level (53 mg/dl, normal range <50 mg/dl) with normal glucose and cell count. On cytology no malignant cells were found, and microbiological and serological examination of CSF were also negative. MR-angiography and digital subtraction angiography (DSA) showed arterial narrowing in subsegments (M3 and M4) of the left middle cerebral artery suggestive for CNS vasculitis (Figures 2a and 2b). Under oral treatment with methylprednisolone a clinical stabilization with slight improvement of neurological symptoms was temporarily observed. Eight weeks after hospital admission and further neurological deterioration the patient developed severe pneumonia followed by respiratory insufficiency. As a consequence, the patient was transferred to the neurological intensive care unit. After stabilization of the respiratory status the patient presented with progressive aphasia, encephalopathy and cognitive impairment. In addition, weakness of the lower limbs increased. Cerebral and spinal imaging were repeated and showed further progression of cerebral MRI lesions resembling



Figures 1a and 1b: Cerebral MRI (1a=axial diffusion weighted; 1b=FLAIR) upon onset of neurological symptoms showing multiple bihemispheric ischemic lesions.

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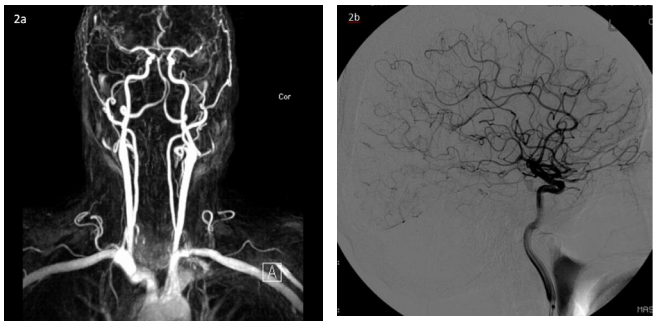
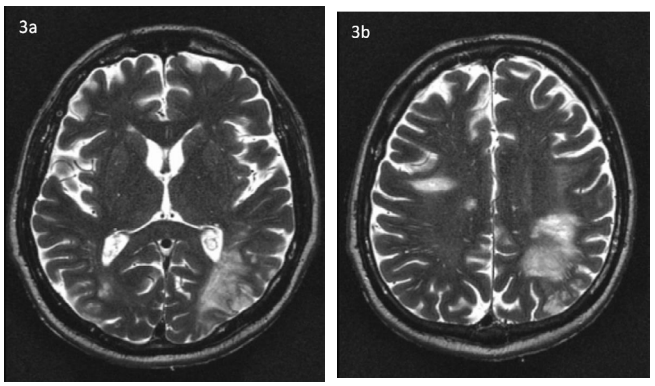


Figures 2a and 2b: MR-angiography, (Figure 2a) shows a widening followed by narrowing a left M3 segment. Digital subtraction angiography reveals this lesion and an additional narrowing of a parietal M4 branch (Figure 2b).



Figures 3a and 3b: Cerebral MRT (3a=axial diffusion, 3b=T2 weighted) 8 weeks after hospital admission. Corresponding to clinical symptoms cerebral imaging showed a progression of bihemispheric ischemic lesions under ongoing treatment with methylprednisolone.

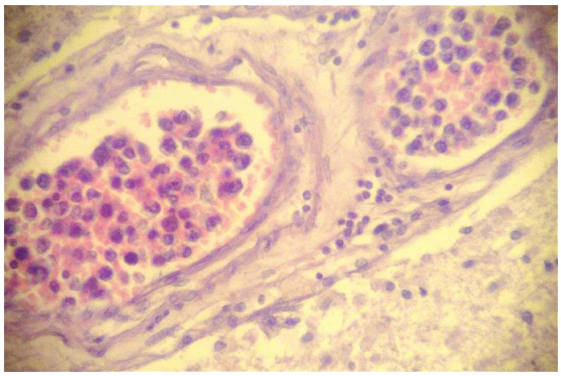


Figure 4: Brain autopsy showing small blood vessels filled with lymphoma cells and perivascular reactive lymphocytes (3 HE, x400).

multifocal ischemia under ongoing treatment with steroids (Figures 3a and 3b). Lactate dehydrogenase levels were consistently slightly above the normal range up to 400 U/l. Laboratory findings revealed progressive pancytopenia. Due to progressive clinical deterioration a brain biopsy was indicated and steroids were tapered off. Over the following days inflammatory parameters increased and elevated levels of serum lactate up to 402 mg/dl were measured repeatedly. Abdominal CT scan showed intestinal perforation confirmed by subsequent surgical intervention showing occult perforation of the small intestine. Post-surgery the patient developed a sepsis syndrome with multi-organ failure. The patient died 10 weeks after onset of neurological symptoms before brain biopsy was performed. Autopsy showed intestinal perforation leading to Pseudomonas aeruginosa sepsis as the primary cause of death. Histopathological findings revealed CD20 positive lymphoma cells in small- and middle-sized vessels of the cerebrum (Figure 4), the lungs and the skin diagnostic for IVBCL.

Discussion

This case report highlights the challenges of an ante-mortem diagnosis of IVBCL, an aggressive and rare form of extranodal non-Hodgkin´s lymphoma, mostly of B-cell lineage. The pathological hallmark of the disease is the proliferation of tumor cells in the lumen of small and medium-sized vessels without involvement of lymph nodes, bone marrow, or peripheral blood [1,2]. The exclusive intravascular localization of malignant cells is supposed to result from loss of function of adhesion molecules, which are required for tissue homing [5]. Vascular occlusion may affect any organ, including the CNS, skin, kidney, lungs or liver resulting in ischemic, hemorrhagic or necrotic lesions [3,6,7]. Noteworthy, the reason for the occlusion of the affected vessels remains still unclear. Injury of the endothelial surface may trigger thrombotic microangiopathy leading to platelet activation, thrombocytopenia and red blood cell fragmentation followed by the formation of microthrombi. In case of microangiopathy endothelial damage might be induced either by a direct interaction of neoplastic cells with endothelial cells or tumor-derived factors [8].

According to previous case reports, CNS and skin involvement are commonly observed in Western countries, whereas a hemophagocytic syndrome including fever, hepatosplenomegaly, thrombocytopenia and bone marrow involvement has been described in Asian countries [2,7]. In the Western variant neurological symptoms are reported at initial presentation in over 30% of all patients diagnosed with IVBCL; two-thirds of all cases may develop neurologic alterations during the course of the disease [9,10]. Neurological symptoms are manifold including stroke-like episodes, (sub-acute) encephalopathy, cognitive impairment, seizures, motor and sensory deficits, paresis, cranial neuropathy and myelopathy [3,4,11-14]. IVBCL is difficult to diagnose, especially when neurologic alterations are the only manifestation. However, prior to the occurrence of focal neurological deficits patients may develop a global impairment of higher brain functions or psychiatric disorders as described in our patient [15]. Additionally, nonspecific symptoms such as fever, malaise, weight loss, and asthenia have been reported in up to 50% of all cases [12,13]. Skin involvement is rare in patients with neurological alterations. However, even without obvious cutaneous involvement, random skin biopsies should be performed, if IVBCL is considered as underlying disease [16,17]. In 6 patients IVBCL was diagnosed by random skin biopsy at sites of healthy appearing skin [16]. Being a systemic disease bone marrow biopsy has been reported as an appropriate diagnostic tool in a small group of antemortem diagnosed patients, especially in Asian disease's variant [18,19]. However, its significance may be reduced within an intensive care setting because of treatment induced bone marrow toxicity (i.e. anticonvulsive and antimicrobial drugs). Our patient presented with multifocal neurological signs indicating CNS vasculitis supported by neuro-imaging findings (MRI, CT-, MRT-angiography, DSA). According to Song et al. IVBCL imaging findings may mimic CNS vasculitis [20,21]. Typical features for this disease are inflammatory damage of vessel walls and vascular thrombosis. Progressive neurological deficits observed in CNS vasculitis are frequently associated with cerebral (and spinal) ischemic lesions on MRI and CT scans. In patients with IVBCL, cerebral MR images may be normal or display hyperintense nonspecific lesions on T2- or FLAIR-weighted images located in the white matter indicating small vessel ischemic disease or demyelination [20]. Likewise, obliteration of the affected blood vessels can lead to multifocal cerebral infarcts reflected by a subacute infarction pattern in the MRI [22]. In

our case, cerebral CT-angiography revealed short segment stenoses as well as changes in the vessel diameter indicative for a cerebral inflammatory vascular disease. Furthermore, MR-angiography (MRA) and digital subtraction angiography (DSA) showed arterial narrowing in subsegments of the left middle cerebral artery suggesting CNS vasculitis. Findings mimicking CNS vasculitis in cerebral angiography appear in nearly half of all cases of IVBCL with CNS manifestation [23]. Nevertheless, in view of its lower spatial resolution, MRA should not be considered as being equivalent to conventional angiography for the detection of CNS vasculitis [24] and shows no pathognomonic findings for establishing the diagnosis of IVBCL. Though neuro-imaging characteristics in IVBCL and CNS vasculitis may be similar, radiologic findings are nonspecific for both disorders.

Most patients with IVBCL show various, unspecific abnormalities on blood examination. Increased serum lactate dehydrogenase (LDH) as seen in our patient and elevated β2-microglobuline levels are observed in over 80% of all cases [25,26]. Anemia is the most frequent cytopenia (63%), usually accompanying leucopenia or thrombocytopenia that do not occur without anemia. Interestingly, the appearance of cytopenias, especially thrombocytopenia, bone marrow and hepatosplenic involvement is also common. The erythrocyte sedimentation rate is increased in over 40% and a monoclonal serum component is seen in 14% of the cases [7]. Abnormal results after performing hepatic [27-29], renal and thyroid [30] functional tests are common features in IVBCL. Hence, these function tests are useful in staging IVBCL. Indeed, altered findings are always associated with organ involvement by neoplastic lymphatic cells [7].

Despite the intravascular localization of the neoplastic cells, circulating tumor cells in the peripheral blood and CSF are very rare. Analysis of CSF may show increased protein level and mild leukocytosis, but cytologic findings are non-specific. In comparison with other malignancies affecting the hematological system, the involvement of lymph nodes is minimal or absent [20]. Due to the disseminated character of IVBCL, gastrointestinal involvement has been described in few case reports [7]. In our case, histological analysis of the resected tissue ante- and post-mortem revealed no evidence of tumor infiltration. Therefore, occult perforation of the small intestine was most likely not caused by underlying tumor disease. Following treatment with methylprednisolone a clinical stabilization with slight improvement of neurological symptoms was temporarily observed in our patient, followed by a rapid neurological deterioration despite steroid treatment. Generally both, IVBCL and CNS vasculitis, may respond to corticosteroid therapy, although the treatment effect is almost exclusively transient in IVBCL [31]. Most patients diagnosed with IVBCL are treated with regimens used for the treatment of diffuse large B-cell lymphoma. The most common chemotherapy combination includes cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab, a recombinant anti-CD20 antibody (R-CHOP). Rationale for the use of rituximab combined with anthracycline-based chemotherapy comes from retrospective analyses and case reports [7, 32-34]. Shimada et al. revealed in a retrospective study of 106 patients with newly diagnosed IVBCL that patients treated with CHOP or CHOP-like chemotherapy plus rituximab had significantly higher overall survival and progression free survival rates. Initially, CNS involvement is seen in up to 30% of all patients and occurs in 25% during disease progression [26]. Therefore treatment directed towards CNS is required, either as prophylaxis or treatment of CNS involvement, since systemically given R-CHOP chemotherapy does not sufficiently penetrate into the brain or spinal cord. Such treatment varies depending on the exact disease site, but can include intrathecal chemotherapy and systemic high dose methotrexate [35-37]. Additionally, several reports have demonstrated efficacy for treatment with autologous stem-cell support (ASCT) [29,38,39].

The clinical presentation in our patient was dominated by ischemic stroke-like episodes. Unspecific angiographic findings indicative for CNS vasculitis and a temporary response to steroid treatment masked the underlying disease. Unfortunately, brain biopsy was delayed by repetitive infectious complications ultimately resulting in a lethal sepsis syndrome. The disease course and duration in our patient is similar to previously reported cases. If untreated, IVBCL leads to death within several weeks to months. Infectious complications are common causes of death, since an immunosuppressive state is present in most patients with progressive IVBCL.

Conclusion

Although being a rare disease our case should raise the alertness for consideration of IVBCL as a differential diagnosis, if no etiology is evident for CNS vasculitis. Early brain biopsy should be accomplished in cases of progressive neurological deterioration concomitant with unspecific findings in cerebral MR imaging. Random skin biopsies, even without clinically apparent cutaneous involvement, may also lead to an early diagnosis of IVBCL.

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