INTRAVASCULAR LARGE B-CELL LYMPHOMA: A RARE CAUSE OF STROKE-LIKE EPISODES, COMBINED WITH COGNITIVE DECLINE AND MYELOPATHY

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Abstract

Intravascular large B-cell lymphoma (IVBCL) is an extremely rare, frequently fatal, extranodal, non-Hodgkin lymphoma. Diagnostic delay is common, mainly due to the variety of atypical clinical symptoms and signs. Early intervention improves outcome, although response to chemotherapeutic agents remains poor. We present a case of IVBCL with rapidly progressive dementia, myelopathy and stroke-like episodes. MRI showed typical findings of subcortical white matter lesions with restricted diffusion and gadolinium enhancement and a thoracic spine lesion. Awareness should be raised among clinicians for this extremely rare, life-threatening clinical entity, because of the potentially treatable clinical outcome in the grounds of timely diagnosis.

Key words: stroke-like episodes, intravascular lymphoma, brain biopsy, immunohistochemistry

ΕΝΔΑΓΓΕΙΑΚΟ ΛΕΜΦΩΜΑ ΑΠΟ ΜΕΓΑΛΑ Β-ΚΥΤΤΑΡΑ: ΜΙΑ ΣΠΑΝΙΑ ΝΟΣΟΣ, ΜΙΜΟΥΜΕΝΗ ΕΓΚΕΦΑΛΙΚΑ ΕΠΕΙΣΟΔΙΑ, ΤΑΧΕΩΣ ΕΞΕΛΙΣΣΟΜΕΝΗ ΑΝΟΙΑ ΚΑΙ ΜΥΕΛΟΠΑΘΕΙΑ

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Περίληψη

Το ενδαγγειακό λέμφωμα από μεγάλα Β-κύτταρα είναι ένα εξαιρετικά σπάνιο και συχνά θανατηφόρο, εξωλεμφαδενικό, non-Hodgin λέμφωμα. Χαρακτηρίζεται από την ανεύρεση λεμφωματωδών κυττάρων στον τριχοειδικό αυλό, χωρίς την παρουσία λεμφαδενοπάθειας ή συμπαγούς όγκου. Η μέση ηλικία εμφάνισης είναι τα 67 έτη. Η προσβολή είναι πολυσυστηματική, με άτυπα συμπτώματα όπως εμπύρετο, κακουχία, ανορεξία, απώλεια βάρους, ενώ η διήθηση του Κεντρικού Νευρικού Συστήματος (ΚΝΣ) είναι συχνά η πρώτη εκδήλωση της νόσου. Εμφανίζεται με σύγχυση, διαταραχές μνήμης και βάδισης, επιληπτικές κρίσεις, και εγκεφαλικά

επεισόδια. Τα απεικονιστικά ευρήματα είναι μη ειδικά, ενδεικτικά νόσου μικρών αγγείων, εμβολικών ΑΕΕ, αγγειίτιδας ΚΝΣ, μηνιγγίτιδας ή μυελοπάθειας. Το παρόν άρθρο αφορά σε περιστατικό ενδαγγειακής λεμφωμάτωσης, με ταχέως εξελισσόμενη άνοια, μυελοπάθεια και εγκεφαλικά επεισόδια, με εκτενή αναφορά στα κύρια χαρακτηριστικά της νόσου, στη διαφορική διάγνωση και στα ευρήματα της ιστολογικής εξέτασης του εγκεφάλου. Σκοπός αυτού είναι η ευαισθητοποίηση σχετικά με αυτή τη σπάνια, αλλά δυνητικά θεραπεύσιμη, πολυσυστηματική κακοήθεια.

Λέξεις ευρετηρίου: ενδαγγειακό λέμφωμα, εγκεφαλικά επεισόδια, βιοψία εγκεφάλου, ανοσοϊστοχημεία

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare, usually fatal, high-grade, extranodal non-Hodgkin lymphoma. It is characterized by the selective growth of neoplastic lymphoid B-cells within the lumen of small vessels [1]. Clinical presentation is characterized by atypical signs and symptoms, making diagnostic approach challenging. Not uncommonly, diagnosis is only made postmortem. Here, we present a case of IVBCL in which stroke-like episodes, rapidly progressive dementia and myelopathy prevailed throughout the disease course.

Case description

A 73-year-old man presented with a 3-month history of gait disturbance, numbness of lower limbs and trunk, incontinence and constipation. Family reported of anorexia, memory deficits and personality change over the last 8 months. No fever or skin alterations were reported. The medical history included hypertension and hypercholesterolemia, treated with amlodipine, valsartan, simvastatin and clopidogrel for stroke prevention. The patient was a former smoker (37 pack-years) and denied alcohol consumption.

The neurological examination revealed emotional lability, disinhibition and cognitive deficits (mMSE 14/30). Spastic right hemiparesis with spastic paresis of the left leg, T7 level of hypoesthesia, incontinence and constipation were present. During his hospitalization, the patient exhibited an acute left hemiparesis with complete paralysis of left lower limb, confusion, irritability and hallucinations. Brain MRI revealed lesions of high T2 signal with restricted diffusion and gadolinium enhancement in centra semiovale bilaterally and right temporal lobe (Figure 1). Thoracic spine MRI revealed a small, non-enhancing intramedullary lesion (<1cm in diameter) at T7 level, on the right of the midline, close to the dorsal column (Figure 1).

Differential diagnosis included embolic strokes, primary CNS angiitis, demyelinating and autoimmune diseases, infectious and neoplastic CNS invasion and paraneoplastic encephalomyelitis.

Complete autoantibody panel (ANA, anti- dsDNA, anti-Scl, ACA, ENA, anti-SM, anti-RNP, anti- SSA/Ro, anti-SSB/La, anti-cardiolipin IgM & IgG, anti-β2GP1, anti-MPO, anti-PR3, anti-M2 and lupus anticoagulants) were negative. Antibodies against HIV, RPR test for syphilis and IGRA for tuberculosis were also negative. Mild anemia and ESR elevation (32mm/hr) were the only abnormal blood values. LDH was within normal levels at presentation. CSF analysis showed mild pleocytosis (7 WBC/mm3) and elevated total protein (654mg/l). Nested Multiplex PCR in the CSF was negative for Escherichia Coli, Heamophilus Influenza, Listeria Monocytogenes, Neisseria Meningitidis, Streptococcus Agalactiae, Streptococcus Pneumoniae, Cytomegalovirus, Enterovirus, Herpes Simplex 1 and 2, Human Herpesvirus 6 (HHV-6) Human Parechovirus, Varicella Zoster virus and Cryptococcus Neoformans/gattii. CSF cultures for bacteria, fungi and mycobacteria were also sterile. A thorough search for cancer was performed, with no pathological findings; whole-body CT scan and PET-CT scan, scrotal ultrasound, GI endoscopy and serum antineuronal antibodies (anti- Ri, Yo, Hu, Ma2, CV2, amphiphysin) were negative. Digital substraction angiography of the brain, 24-hour cardiac rhythm monitoring, transthoracic, transesophageal echocardiography and transcranial doppler bubble study did not reveal any pathology. Considering the inconclusive work up and the patient's severe disability and rapid deterioration, a trial of pulse dose intravenous methylprednisolone (1gr/day x3 days) was administered, with no clinical response.

Further diagnostic approach included stereotactic brain biopsy. Sample tissue was obtained from the right temporal lobe lesion. Photomicroscopy revealed infiltration of the lumen of brain capillaries with large atypical lymphoid cells and CD 20. Pax5 immunohistochemistry demonstrated the B-cell immunophenotype of the intravascular lymphoid cells. The Ki-67 proliferation index was almost 100% (Figure 2). At this point, diagnosis of intravascular B cell lymphoma was made. The patient underwent 1 cycle of treatment with rituximab 375mg/m^2, high dose intravevous methotrexate 2500mg/m^2 and cytarabine 3gr/m^2/d. His poor medical condition did not allow him to receive any further cycles of chemotherapy, as he became septic from hospital acquired infections and died.

Figure 1. MRI lesions with typical findings of IVBCL

T2, FLAIR hyperintense lesions (A, B) with contrast enhancement (C) and restricted dif-fusion (D, E). Thoracic spine MRI with small, non-enhancing, lesion of less than 1cm, located right and posteriorly at T7 level (F)

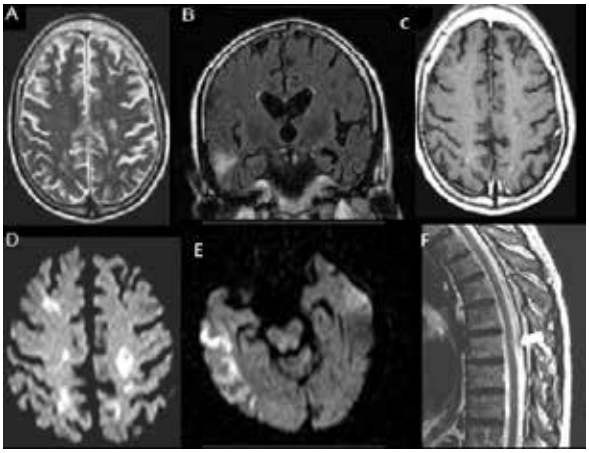
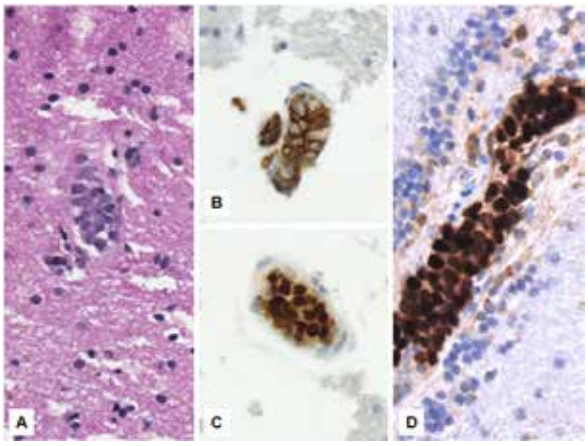


Figure 2. Brain biopsy with typical histopathology findings of IVBCL

Photomicrography of brain biopsy (x40), stain H&E, shows the presence of large atypical lymphoid cells in the lumen of a brain capillary (A). CD20 and Pax5 immunohistochemistry, demonstrates the B-cell immunophenotype of the intravascular atypical lymphoid cells, (B, C respectively). The Ki67 proliferation index is almost 100% (D)



Discussion

Intravascular large B-cell lymphoma is a rare subtype of non-Hodgkin lymphoma, characterized by intracapillary proliferation, without capillary infiltration, of malignant B-cells. Mean age of onset is 67 years old (41-85 years). IVLBCL is a multisystemic disease, mainly involving the skin and the CNS. Random skin and muscle biopsy, from unaffected regions are diagnostically valuable, with sensitivity ranging from 67% to 100% in different studies [3, 4].

Systemic symptoms, such as low-grade fever, general malaise, anorexia, weight loss and respiratory symptoms may be present. Characteristically, there is absence of lymphadenopathy and extranodal mass lesions, although infiltration of bone marrow may occur. Involvement of the CNS is evident in 60% of patients, presenting as encephalopathy, rapidly progressive dementia, gait disturbance, seizures and stroke-like episodes. Myelitis of conus medullaris and infiltration of cauda equina are typical, but spinal cord lesions may also present as a longitudinally extensive spinal lesion. Brain MRI findings are non-specific, resembling small vessel disease, embolic strokes or CNS angiitis. Multifocal T2/FLAIR hyperintense lesions with restricted diffusion in subcortical white matter and cortex are mainly encountered. Gadolinium enhancement lacks typical pattern and is both parenchymal and meningeal. Enhancement may reverse with treatment initiation, although it is not considered as a prognostic marker of treatment response [5].

In most cases, CSF shows pleocytosis with elevated protein. An elevated β2- microglobulin[6] in the CSF is a marker of intrathecal invasion. In our case, diagnosis could only be made with brain biopsy. Differential diagnosis of IVBCL includes other types of lymphomas (lymphomatoid granulomatosis, CD5+ diffuse large B-cell lymphoma, primary CNS lymphoma, reactive lymphoid hyperplasia), and leukemias. Therapeutic strategies are rituximab-combined chemotherapeutic agents and autologous stem cell transplantation [2].

Conclusion

The absence of typical features and the rarity of the disease leads to diagnostic and therapeutic delay. However, early intervention improves morbidity and mortality rates. Thus, intravascular large B-cell lymphoma, although rare, should be suspected in cases with watershed strokes in MRI, especially when associated with other, unexplained, neurological and systemic symptoms.

Declarations

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Abbreviations

IVBCL	intravascular B-cell lymphoma
mMSE	mini-mental state examination
MRI	magnetic resonance imaging
CNS	central nervous system
ESR	estimated sedimentation rate
CSF	cerebrospinal fluid
PCR	polymerase chain reaction
FLAIR	fluid attenuated inversion recovery

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