

Intravascular lymphoma as an unusual cause of multifocal cerebral infarctions discovered on FDG-PET/CT

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ABSTRACT

Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive variant of diffuse large B-cell lymphoma with frequent involvement of the central nervous system. Its atypical presentation often delays the diagnosis and due to its aggressive behaviour, the diagnosis is made post-mortem in half of the cases. We report a case of a 67-year-old male patient presenting with speech difficulties and balance disturbances in whom a magnetic resonance imaging (MRI) scan showed multiple lesions of the white matter, denoted as embolic infarctions. He was treated for a suspected endocarditis with antibiotics, but deteriorated neurologically with persistent fever. A consecutive FDG-PET/CT revealed an increased uptake in the adrenals, of which a biopsy showed IVLBCL. The patient was successfully treated with systemic R-CHOP with intrathecal methotrexate and achieved complete remission after six cycles of chemotherapy. The potential role of FDG-PET/CT is illustrated by this case leading to an exceptional diagnosis of IVLBCL.

KEYWORDS

Intravascular diffuse large B-cell lymphoma, cerebral infarction, FDG-PET/CT

INTRODUCTION

Cerebrovascular accidents (CVA) are vascular events with a high prevalence, currently estimated to be the second cause of death in the Western world.¹ They are either ischaemic or haemorrhagic in origin, of which approximately 80% are due to ischaemia. Ischaemic CVA is usually caused by atherosclerosis, carotid artery stenosis or cardiac emboli.

However, in a small minority of patients cerebral infarction may be cryptogenic of origin.^{1,2} In the present report, we describe a patient with such cryptogenic multifocal cerebral infarctions and symptoms of systemic illness. A FDG-PET/CT guided towards a rare haematological disorder causing the unexplained neurological symptoms.

CASE REPORT

A 67-year-old man, with a history of hypertension and diabetes mellitus type 2, was referred to the department of neurology because of progressive speech difficulties and disturbances in balance. At physical examination he had a broad-based gait and he was remarkably slow of speech. CT scanning showed multiple small subcortical infarctions highly suspicious for ischaemic CVA. The patient was admitted to hospital and treated according to our stroke protocol. However, he slowly deteriorated and a consecutive magnetic resonance imaging (MRI) showed widespread lesions of the white matter, suspect for multiple emboli (*figure 1*). The combination of a continuous subfebrile temperature and a possible vegetation on a bicuspid aortic valve at transthoracic echocardiography raised the possibility of an endocarditis causing cerebral emboli. While blood cultures remained sterile, pragmatic treatment with intravenous antibiotics appeared to improve the condition of the patient with partial neurological recovery. However, several weeks later he was readmitted because of recurrence of neurological deficits and a relapse of the fever. The erythrocyte sedimentation rate (ESR) was 44 mm/hour (normal range (N) <15), the C-reactive protein (CRP) was 34 mg/l (N <10) and lactate dehydrogenase (LDH) was 728 IU/l (N <500). A repeated MRI disclosed new subcortical lesions. Blood cultures were negative

Figure 1. T2-weighted axial magnetic resonance image (MRI) showing widespread subcortical lesions of the white matter and diffuse cerebral atrophy

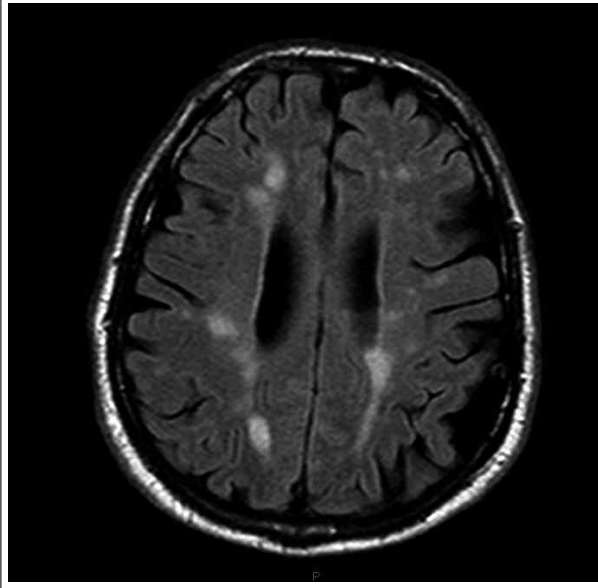
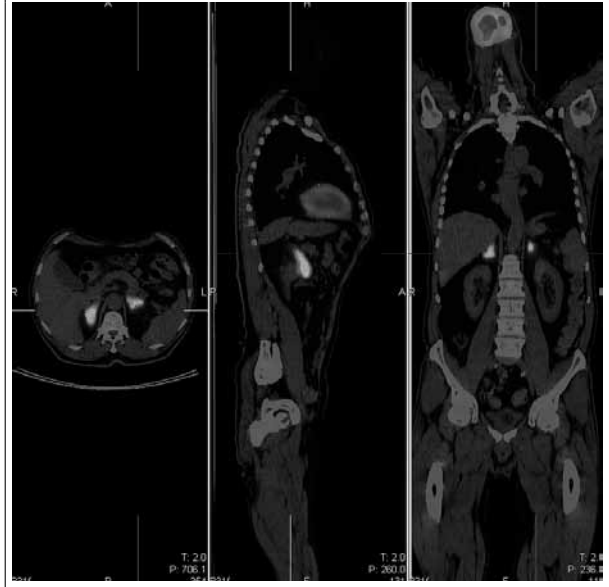


Figure 3. Coronal image of fused PET/CT with increased uptake in both adrenals



again and cardiological re-evaluation did not show any signs of aortic valve vegetations at this time. Virus and autoimmune serology were negative and lumbar aspiration was not diagnostic. Because of the persisting subfebrile temperature with elevated inflammation markers, a FDG-PET/CT was performed. This showed an increased FDG uptake in both adrenals (figures 2 and 3). A biopsy of the left adrenal gland demonstrated an intravascular, CD20-positive, diffuse large B-cell lymphoma (IVLBCL, figures 4 and 5). An additional bone marrow biopsy did not show lymphoma location. The patient further

Figure 4. Biopsy of left adrenal: extensive infiltration of malignant lymphoid cells, located in sinusoids (haematoxylin-eosin staining, original magnification x50)

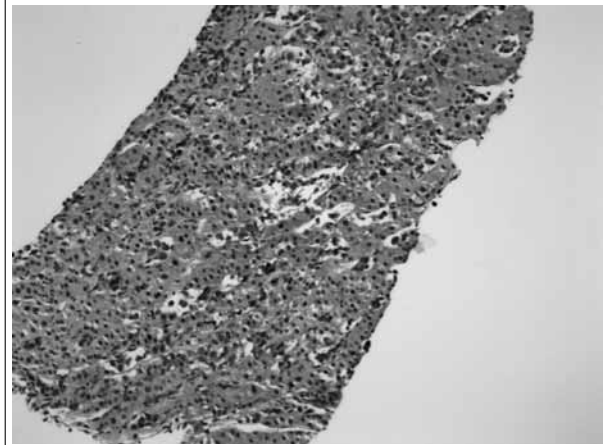


Figure 2. Coronal image of whole body FDG-PET with increased uptake in both adrenals

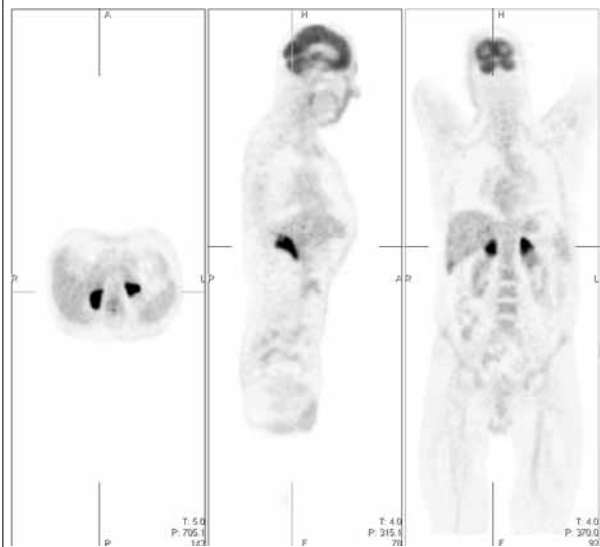
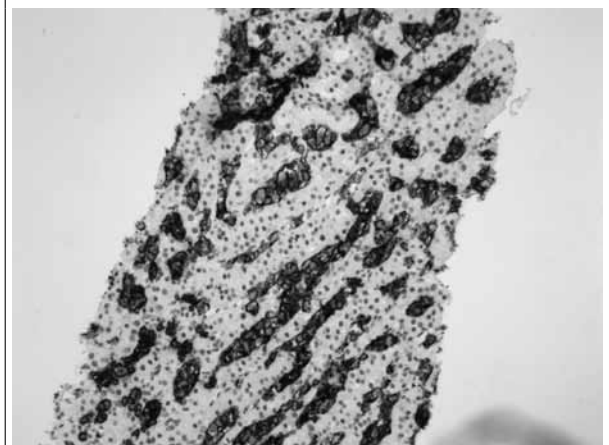


Figure 5. CD20 staining showing the intravascular location of lymphoid cells (original magnification x50)



deteriorated, being subconscious at the time of diagnosis with development of a right hemiparesis. Chemotherapy with systemic R-CHOP and intrathecal methotrexate was instituted. While his condition initially worsened, due to a cytokine release syndrome, he recovered well during treatment and the neurological symptoms faded. After six cycles of chemotherapy complete remission was established on a repeated FDG-PET/CT scan. Until now, seven months after finishing chemotherapy, the patient is still in remission and in good condition.

DISCUSSION

Intravascular diffuse large B-cell lymphoma

Intravascular diffuse large B-cell lymphoma (IVLBCL) is a rare and aggressive form of non-Hodgkin's lymphoma. This lymphoma variant was first reported by Pleger and Tappeiner in 1959 and is considered to be endothelial in origin.³ The current World Health Organisation classification defines IVLBCL as an extranodal diffuse large B-cell lymphoma characterised by the presence of neoplastic lymphocytes only in the lumina of small vessels,⁴ leading to occlusion of the vessel and consequently tissue infarction.⁵

Clinical manifestations

Clinically two distinct forms are recognised. The 'classical' or Western variant frequently involves the central nerve system (CNS) and skin, while in Asian countries the disease predominately presents with a haemophagocytic syndrome.⁶

The Western variant, as in our patient, has a median age of presentation of 60 to 70 years with a slight male preponderance.⁶ Its clinical manifestations are highly variable and non-specific. Systemic symptoms such as fever, weight loss and fatigue are present in half of the cases,⁶ however, lymphadenopathy is mostly absent. The majority of patients have neurological symptoms at the time of presentation,⁷ including focal or diffuse cerebral signs, dementia and other confusional states and less often spinal cord syndrome, seizures, mono- and polyneuropathy or myopathy.^{3,7} Besides the CNS, the skin is frequently involved (22 to 26%) but infiltration can take place in virtually any organ of the body, such as lung, liver, prostate, bone marrow and spleen.⁶ IVLBCL of the adrenals is peculiar but has been reported and may be complicated by adrenal insufficiency.⁸

DIAGNOSIS

Due to its atypical and heterogeneous presentation and aggressive behaviour, the diagnosis of an IVLBCL is

unfortunately made post-mortem in almost half of the cases.⁹ Non-specific findings on blood examination and negative imaging studies complicate a prompt and accurate diagnosis. Laboratory findings that can be encountered include anaemia (63 to 65%), an increased LDH (80 to 90%) and an elevated ESR (43%).⁴ Computed tomography (CT) is frequently not supportive because lymphadenopathy and hepato-splenomegaly are usually absent. Only in half of the patients is CNS involvement of an IVLBCL seen on MRI as non-specific white matter lesions.¹⁰ Cerebrospinal fluid examination can show a pleiocytosis and increased protein concentration, but no malignant lymphoma cells.^{5,11} Despite these diagnostic difficulties, a representative biopsy of an organ involved is essential in diagnosing IVLBCL. In our patient a FDG-PET/CT scan was of enormous value in detecting the adrenals as one of the organs involved, which were accessible for biopsy and consequently led to the diagnosis of IVLBCL. In most types of lymphoma the combination of FDG-PET with CT is highly accurate in detecting nodal and extranodal involvement.¹² A few articles report the successful use of FDG-PET in diagnosing IVLBCL in cases of fever of unknown origin.^{13,14} However, its diagnostic accuracy in IVLBCL remains unclear, as false-negative results have also been noted.¹⁵

TREATMENT AND PROGNOSIS

Patients with IVLBCL need to be treated with systemic chemotherapy as any disseminated malignant disease. Anthracycline-based chemotherapy is considered first-choice therapy, as results of other chemotherapeutic regimes have been disappointing.¹⁶ In case of CNS involvement, CNS-oriented chemotherapeutic agents, such as methotrexate or cytarabine, should be added. However, despite intensive chemotherapy, recurrence of disease is seen in more than half of the cases with an ultimately poor prognosis.⁴ A recent retrospective study showed promising results from the addition of rituximab, the standard therapy for CD20-positive lymphomas,¹⁷ improving disease-free and overall survival.¹⁸ Nevertheless, the optimal treatment of this rare distinct variant of non-Hodgkin's lymphoma, with a largely unknown biological behaviour, remains unclear.⁶

CONCLUSION

The presented case demonstrates a patient with an IVLBCL as a rare cause of initially denoted cryptogenic multifocal cerebral infarction. IVLBCL is not an obvious consideration in patients presenting with unexplained neurological symptoms. However, its aggressive behaviour

and devastating clinical course challenge the need for an early diagnosis that is crucial for the survival chances of patients. This case report illustrates the potential value of a FDG-PET/CT in unexplained neurological illness, fever and low-grade inflammation, with a small but evident chance of finding a clue to the unique diagnosis of IVLBCL.

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