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CASE REPORT
Rare diseases of the heart

Intravascular large cell lymphoma mimicking central nervous system vasculitis in a patient with rheumatoid arthritis (RCD code: VI-2C.2)

Joanna Sulicka-Grodzicka[1]*, Magdalena Strach[2], Krzysztof Okoń[3], Wadim Wojciechowski[4], Mariusz Korkosz[1]

[1] Department of Rheumatology, Jagiellonian University Medical College, Kraków, Poland; [2] Department of Internal Medicine and Gerontology, Jagiellonian University Medical College, Kraków, Poland; [3] Department of Pathomorphology, Jagiellonian University Medical College, Kraków, Poland; [4] Department of Radiology, Jagiellonian University Medical College, Kraków, Poland

Abstract

Increased incidence of lymphomas in patients with rheumatoid arthritis has been reported and may be associated with several factors, including genetic factors, chronic inflammation, and immunosuppressive treatment. Intravascular large cell lymphoma (ILCL) is a rare subtype of large cell lymphoma with undetectable lymphoma cells in peripheral blood and without any extravascular localisation. Diagnosis is often delayed because bone marrow, spleen, and cerebrovascular fluid may not be involved and there are no specific laboratory studies for intravascular large cell lymphoma. We report the case of a 63-year-old woman with a 10-year history of seropositive rheumatoid arthritis and intravascular large cell lymphoma recognised at autopsy. The patient presented with progressive central nervous system-related symptoms mimicking vasculitis without lymphadenopathy or bone marrow involvement. Malignant lymphoproliferative disorders should be considered in RA patients with varying clinical presentation, even in the absence of lymphadenopathy and bone marrow involvement. JRCD 2018; 4 (1): 15–17

Key words: rare disease, diffuse large B-cell lymphoma, intravascular large cell lymphoma, vasculitis, rheumatoid arthritis, multimodality imaging

Introduction

The prevalence of rheumatoid arthritis (RA) is estimated to be about 1 percent in the general population and incidence peaks between ages 50–75 years [1,2]. RA is associated with nonarticular manifestations and advanced age is a risk factor for extraarticular disease [3]. Clinical manifestations of central nervous system (CNS) involvement may include stroke, headaches, and cognitive impairment. Increased rates of cognitive dysfunction are reported in patients with RA compared to healthy controls [4]. Disease activity and aging may contribute to cognitive dysfunction in RA, and blood-brain barrier alterations associated with chronic inflammation may be involved in CNS manifestations, although the underlying mechanism is poorly understood. Furthermore, patients with RA have a twofold increased risk of lymphoproliferative disorders when compared with the general population and the strongest risk factors are exposure to methotrexate and disease activity. Symptoms of intravascular lymphoma may mimic vasculitis, especially when there is no peripheral blood, bone marrow, spleen, or cerebrovascular fluid involvement in the course of lymphoma. Furthermore, constitutional symptoms are present in the majority of patients with both malignancies and systemic vasculitis.

Case report

A 63-year-old female patient with a 10-year history of RA, diagnosed based on 1987 ACR (American College of Rheumatology) criteria [5], was admitted to the hospital due to cognitive problems and postural instability for the last 2 months resulting in

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* Corresponding author: Department of Rheumatology, Jagiellonian University Medical College, Kraków, ul. Śniadeckich 10, 31-531 Kraków, Poland; phone: +48 424 88 00; fax: +48 424 88 54; e-mail: jsulicka@su.krakow.pl

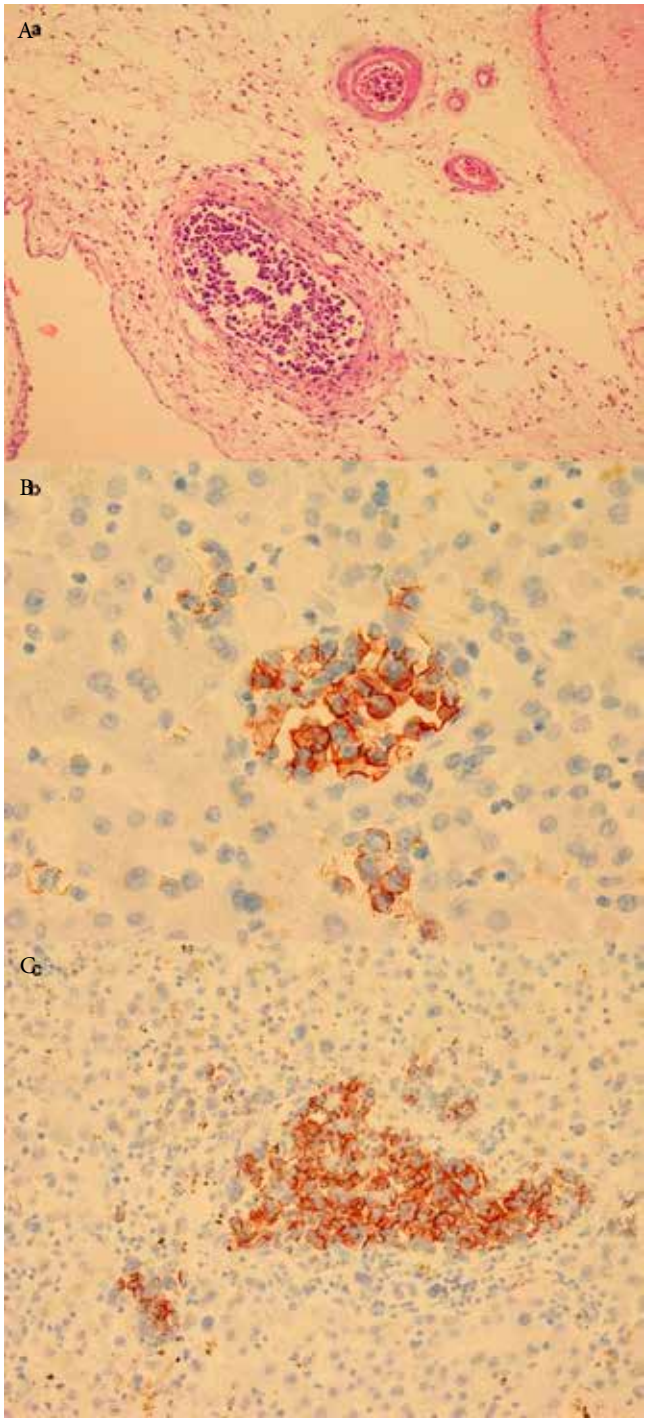

Figure 1. A. Brain autopsy. Large cells with hyperchromatic, irregular nuclei in small brain vessels (hematoxylin and eosin stain) (**B**) and (**C**) large cells in small brain blood vessels expressing CD20 (immunohistochemistry)

falls and accompanied by exacerbation of RA, fever, and weight loss. The patient had a history of diabetes mellitus type 2. Current medication included methotrexate, folic acid, methylprednisolone, diclofenac, alendronate, sulphonylurea, menopausal hormone therapy and acetylsalicylic acid. On admission, the patient was alert and oriented, presented with symmetrically swollen and painful hand joints, and had marked ataxia and left sided hemiparesis. She reported difficulties in concentration, sporadic confusion, and memory impairment. The results of routine work-up including laboratory monitoring, chest X-ray, ultrasound of carotid arteries and abdomen, and echocardiography were normal except for elevated erythrocyte sedimentation rate and C-reactive protein, pancytopaenia, elevated ferritin and lactate dehydrogenase, and decreased serum protein and albumin. Magnetic resonance imaging (MRI) of the brain indicated an ischaemic left cerebellar hemisphere infarction and several hyperintense white matter lesions in the right cerebral hemisphere. On the second day after admission, the patient's neurological status deteriorated. She became incoherent, disoriented to place, time or situation, and symptoms progressed with new, diffuse ischaemic brain lesions. The cerebrospinal fluid examination was normal. Bone marrow examination indicated unspecific alterations with normal myeloid and erythroid maturation. Blood and urine cultures were negative. Test results for antibodies to human immunodeficiency virus, hepatitis B, and hepatitis C were negative. Standard coagulation tests were normal. Testing for hypercoagulable disorders was negative, as were tests for antinuclear antibodies and antineutrophil cytoplasmic antibodies. There was a deficiency in complement protein C4. Therapy using methylprednisolone and cyclophosphamide for central nervous system vasculitis was introduced, and initially symptoms slowly resolved, but the patient deteriorated subsequently. The course of the disease was fatal.

Autopsy findings were unspecific, with signs of pulmonary oedema, foci of bronchopneumonia, cardiac hypertrophy, and atherosclerosis. No peripheral lymphadenopathy was present and the spleen was mildly enlarged with inflammatory features. Brain autopsy showed no macroscopic abnormalities, however, on histological examination small areas of liquefactive necrosis were present and large cells with hyperchromatic, irregular nuclei were found in the small brain vessels. Similar cells were found in vessels of other organs, especially in the meninges, kidneys, and liver. On immunohistochemistry, these cells expressed CD20 (Figures 1a, 1b, 1c). An autopsy diagnosis of ILCL was made.

Discussion

RA may be associated with nonarticular manifestations in about 40 percent of patients, and advanced age is a risk factor for extraarticular disease [3]. Clinical manifestations of CNS vasculitis are nonspecific, with cognitive dysfunction being a possible feature. Symptoms usually evolve over the course of weeks and months. The diagnosis is challenging and includes exclusion of other disorders (infection, atherosclerosis, systemic vasculitis involving the brain, intravascular lymphoma, autoimmune encephalitis). Hyperintense white matter lesions on MRI suggesting vasculitis are also nonspecific. Brain biopsy is the definitive diagnostic test. In RA, the risk of developing another nonarticular manifestation, lymphoma, is increased by twofold when compared to the general population [6]. In this case, intravascular lymphoma could have mimicked vasculitis, considering the presence of constitutional symptoms, anaemia, elevated sedimentation rate, the 3-fold elevation of lactate dehydrogenase, and low C4 levels [7]. However, there was no lymph node, peripheral blood, cerebrospinal fluid,

or bone marrow involvement in this case and the diagnosis was recognised only upon autopsy. ILCL is a rare type of large cell lymphoma with symptoms associated with occlusion of the small blood vessels by proliferating lymphoma cells. Median age at diagnosis is 60 to 70 years. The bone marrow, lymph nodes, peripheral blood, and cerebrospinal fluid are seldom involved. Immunophenotyping identifies the cells to be mature B cells in about 90% of cases. Constitutional symptoms are seen in the majority of patients. In Europe, patients most commonly present with symptoms related to involvement of the CNS and skin, and rarely with bone marrow, spleen, and liver involvement [8]. There are no specific laboratory studies for ILCL. The diagnosis is made by identifying large lymphoma cells within small to medium blood vessels. The treatment of patients with ILCL involves a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (R-CHOP). Overall survival rate at 2 years in is 66% [9]. This case is noteworthy for the clinical presentation of ILCL mimicking CNS vasculitis.

Conclusion

Elderly patients with RA have an increased risk of haematologic malignancies and elevated risk for extraarticular manifestations, however, clinical presentation may vary.

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