EJCRIM
European Journal
of Case Reports
in Internal Medicine

AN UNUSUAL CASE OF HHV-8 NEGATIVE, IDIOPATHIC, MULTICENTRIC CASTLEMAN DISEASE FOLLOWING CHRONIC LYMPHOCYTIC LEUKAEMIA

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Received: 05/06/2024
Accepted: 10/06/2024
Published: 05/08/2024

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent from patients has been obtained and is available if needed.
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How to cite this article: Sansen PY, Vellemans H, Fervaille, Krug B, Sonet A, Collinge E. An unusual case of HHV-8 negative, idiopathic, multicentric Castleman disease following chronic lymphocytic leukaemia. *EJCRIM* 2024;**11**:doi:10.12890/2024_004688

ABSTRACT

Background: Castleman disease is a rare condition characterised by polytypic lymphocytes proliferation and lymphadenopathy generally with a benign course. Whereas high grade lymphoma (Richter syndrome) is a classical complication seen in chronic lymphocytic leukaemia with a poor outcome, benign conditions mimicking this entity are infrequent.

Case description: We describe the case of an 81-year-old Caucasian male who developed a human herpesvirus-8 (HHV-8)–negative, idiopathic multicentric Castleman disease (iMCD) following a treated Binet C chronic lymphocytic leukaemia (CLL). The clinical and radiological pattern raised initially the suspicion of a classical Richter transformation. Blood analysis showed auto-immune haemolytic anaemia and thrombocytopenia. He had normal immunoglobulin levels. The anatomopathological analysis of a cervical adenomegaly showed hypervascularisation and a polytypic plasmocytic proliferation compatible with a plasmocytic iMCD type. Interestingly, bone marrow examination showed reticuline fibrosis but, in the absence of anasarca or generalised oedema, we were not allowed to conclude to the diagnosis of a TAFRO syndrome. We excluded all other mimicking conditions, comprising haematological malignancies, infections, and auto-immune diseases He was first treated with corticosteroids with poor results but dramatically responded to tocilizumab (anti-Il6).

Conclusion: To our knowledge, this the first case described of a Castleman disease following CLL and surprisingly mimicking Richter syndrome. Clinicians should be aware of this rare misleading condition.

KEYWORDS

Castleman disease, CLL, anaemia, thrombopenia

LEARNING POINTS

- Castleman disease can mimic a Richter transformation in a CLL patient.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

INTRODUCTION

Castleman disease is a rare condition characterised by polytypic lymphocytes proliferation and lymphadenopathy. It can be unicentric or multicentric in case of multiple lymphadenopathies. Multicentric types can be divided in two different entities: human herpesvirus-8 (HHV-8) positive and HHV-8 negative, which remain the idiopathic type (iMCD). The aetiologies are multiple and involve inflammatory dysregulation, paraneoplastic condition, and infections[1]. Recently, diagnosis criteria based on histopathological findings, laboratory and exclusion criteria have been proposed[2]. The exclusion of conditions mimicking Castleman histology, such as auto-immune disorders, infections and lymphoproliferative disorders (LPDs) is then mandatory. We describe an unusual case of iMCD mimicking a Richter transformation in a patient previously treated for Binet C chronic lymphocytic leukaemia (CLL). The CARE Checklist has been completed by the authors for this case report, attached as supplementary material.

CASE DESCRIPTION

We describe the case of an 81-year-old Caucasian male who developed an HHV-8 negative, iMCD following a history of CLL Binet C. The patient was treated four years ago for a CLL Binet C with severe thrombopenia. He received a treatment consisting of obinutuzumab-chlorambucil and achieved a complete remission following six cycles. He presented to the haematology department with fever, night sweat and loss of weight of about 10% of his body mass. At the blood analysis level, there was anaemia of 7.7 g/dl (normal 12–15 g/dl) associated with a thrombocytopenia of 39,000/µl (normal range 150,000–450,000). Albuminemia was low (2.6 g/dl, normal 3.5–5.5 g/dl) and C-reactive protein was 70 mg/l (normal < 10 mg/l). He had normal renal and liver function. Blood immunophenotyping showed no circulating CLL clone nor abnormal lymphocyte phenotype. The direct antiglobulin test was positive for IgG and C3 (complement) with low haptoglobin level, consistent with an autoimmune haemolytic anaemia. A positron emission tomography-computed tomography scan (PET-CT) scan was performed and showed disseminated lymphadenopathy at the supra- and infra-diaphragmatic compartment *(Fig. 1)*, which strongly suggests a Richter transformation (SUVmax 5.8). We performed a bone marrow biopsy and aspiration, which was normocellular without any neoplastic infiltration but showed reticulin fibrosis. A cervical adenomegaly was surgically removed and surprisingly showed a polytypic plasmocytic infiltration with germinal centre atrophy and hypervascularisation *(Fig. 2)*. HHV-8 was negative on the sample analysis and in the blood. We conducted an extensive aetiological work-up and excluded other causes. Infections analysis comprising blood polymerase chain reaction for Epstein-Barr virus, cytomegalovirus and toxoplasmosis, along with human immunodeficiency virus (HIV) serology and BK immunological assay were negative. Lupic serologies as well as other auto-immune serologies (antinuclear factor and antineutrophilic antibodies assay) remained negative. Bone marrow examination excluded multiple myeloma or other haematological malignancies. We used the international, evidence-based consensus diagnostic criteria

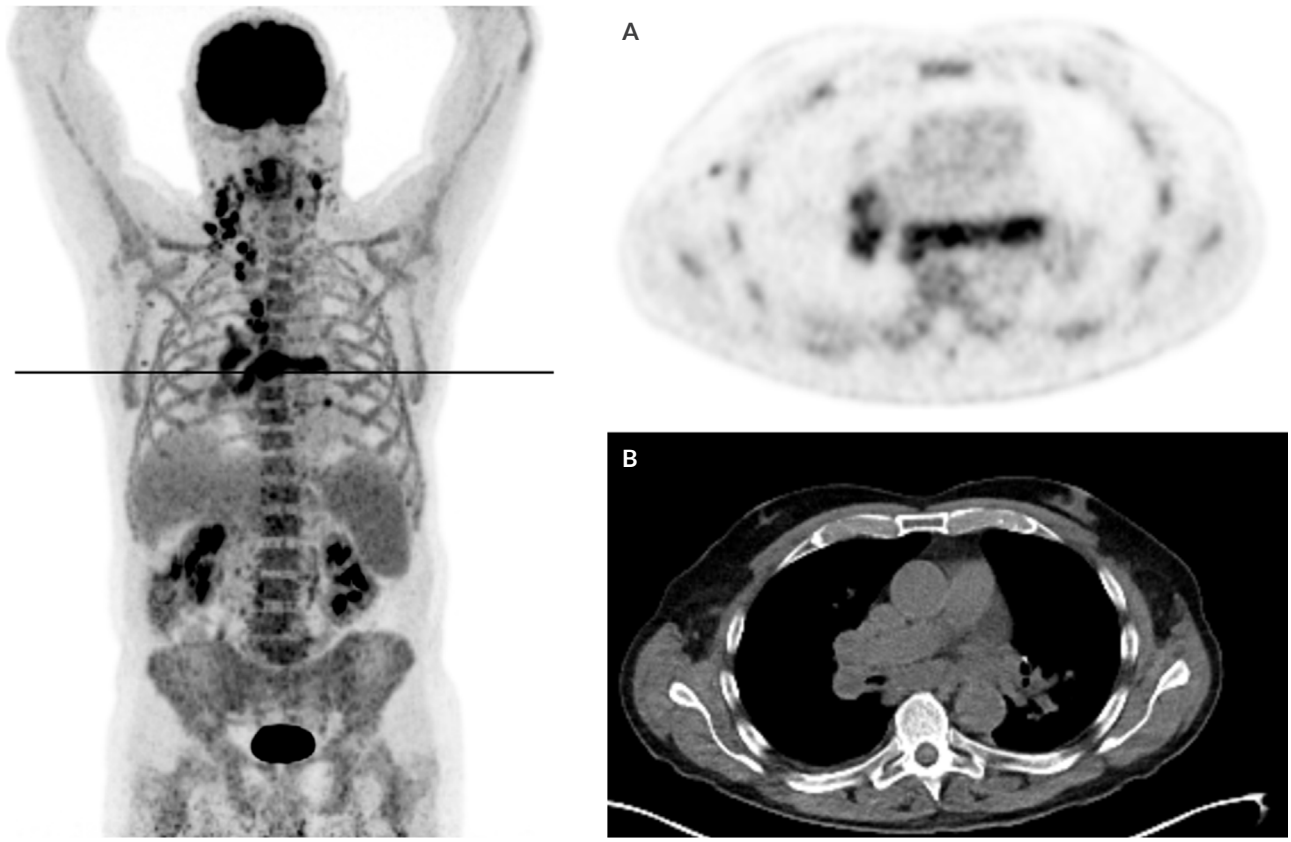

Figure 1. Axial view of ^{18}F-FDG-PET scan of the patient showing of ^{18}F-FDG uptake of adenopathy in right hilar area and station 7.

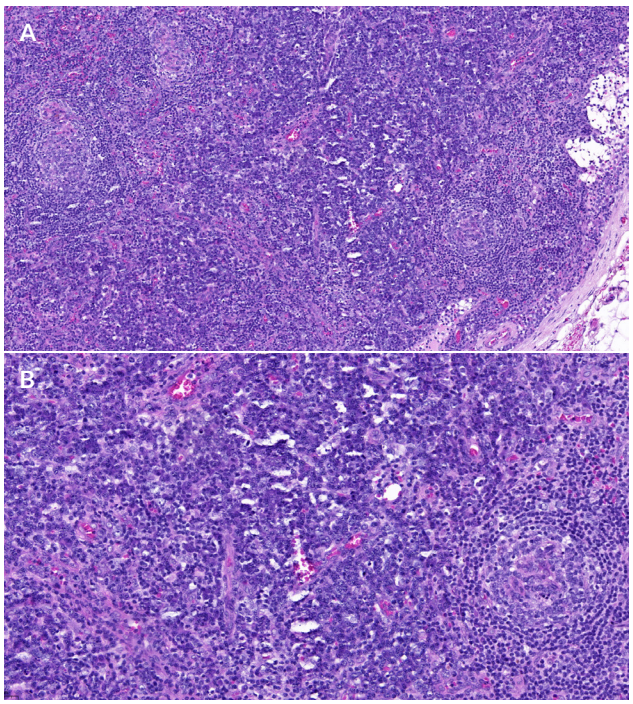

Figure 2. Histopathological features of cervical lymphadenopathy. (A) Hemalun-eosine 10× and (B) 20×.

for iMCD[2] and all the required findings were met *(Table 1)*. We then concluded the diagnosis as HHV-8 negative, idiopathic, multicentric Castleman disease.

We started initially a treatment with corticosteroids which achieved poor results. Given the diagnosis of Castleman disease, tocilizumab was proposed, which dramatically improved the clinical and biological parameters.

DISCUSSION

Castleman disease remains a rare and particularly difficult diagnosis to make. Our case is atypical in many ways. First, the history of a treated CLL followed by the appearance of disseminated lymphadenopathies with constitutional symptoms are strongly consistent with a Richter transformation diagnosis. This represents a first diagnostic trap. Second, iMCD usually precedes a lymphoproliferative disorder and the contrary is quite infrequent. This presupposed a link between immune dysregulation, induced either by immunotherapy agents used to treat CLL (i.e. obinutuzumab) or by neoplastic cells themselves, and the development of Castleman disease. We assume there are limited data to support such hypothesis and other cases

1. Major criteria met	**Characteristics of the met criteria**
Multicentric lymphadenopathy	Supra and infra-diaphragmatic
Typical histopathological pattern (grade) - A: Regressed Germinal Centers (GCs) - B: Follicular Dendritic Cell (FDC) Prominence - C: Vascularity - D: Hyperplastic Germinal Centers - E: Plasmacytosis	Histological grade 1 2 1 0 3
2. Minor criteria met	
Laboratory	
Elevated CRP (> 10 mg/l)	70 mg/l
Anemia (< 12.5 g/dl for male)	7 g/dl
Thrombocytopenia (< 150 k/µl)	35 k/µl
Hypoalbuminemia (< 3.5 g/dl)	2.6 g/l
Clinical	
Constitutional symptoms	Night sweats, fever, weight loss and fatigue
Lymphocytic interstitial pneumonitis	Ground glass changes
3. Exclusion criteria	
Exclusion of infection-related disorders, auto-immune/inflammatory diseases and malignant/lymphoproliferative disorders	Yes

Table 1. Diagnostic criteria for iMCD met in our patient following International Consensus Diagnosis Criteria for iMCD[2]. Diagnosis requires the two major criteria, at least two of the eleven minor criteria with at least one laboratory criterion and all the exclusion criteria.
Abbreviations: FDC, follicular dendritic cell; GCs, germinal centres

are needed. At the diagnosis level, we find it helpful to use the international evidence-based consensus diagnostic criteria 2017. It is emphasised that few cases of the new entity TAFRO syndrome have been described as specific subsets of iMCD. Our patient interestingly presented a reticuline fibrosis of the bone marrow which is one of the main diagnostic criteria of this entity. However, the absence of anasarca is less common so we cannot conclude it to be TAFRO syndrome. Another challenge is the presence of an auto-immune haemolytic anaemia IgG/C3 specific which raises the suspicion of an auto-immune condition. Nevertheless, association of Castleman disease and auto-immune haemolytic anaemia has already been described and it can account up to one third of the patients[3].

In conclusion, we describe a case of Castleman disease following CLL and surprisingly mimicking Richter syndrome. Clinicians should be aware of this rare misleading condition.

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