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THE VALUE OF A PET SCAN IN SELECTING THE BEST LYMPH NODE TO BIOPSY, AND CONFIRMING THE DIAGNOSIS OF IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE WITH HLH AND EBV VIREMIA IN A PREVIOUSLY HEALTHY ADULT

Erica Bitektine[1], Hamila Hagh-Daoust[1], René P. Michel[2], Stephane Isnard[3], Jean-Pierre Routy[3,4]

[1] Department of Internal Medicine, McGill University, Montreal, Canada
[2] Department of Pathology, McGill University, Montreal, Canada
[3] Research Institute of the McGill University Health Centre, Montreal, Canada
[4] Division of Hematology, McGill University Health Centre, Montreal, Canada

Corresponding author's e-mail: jean-pierre.routy@mcgill.ca

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ABSTRACT

Introduction: Castleman disease (CD) is a rare lymphoproliferative disorder having a variegated clinical presentation. Diagnosis of the idiopathic HIV- and HHV8-negative multicentric CD (iMCD) subtype poses a challenge given its non-specific clinical manifestations. iMCD presents as diffuse lymphadenopathy with inflammatory manifestations, primarily driven by interleukin-6 (IL-6). Treatment includes suppressing the inflammation by targeting IL-6 with monoclonal antibodies such as siltuximab and, in severe cases, immuno-chemotherapy to control B- and plasma-cell activation.

Case description: A previously healthy 43-year-old male presented to the emergency department with fever, night sweats, anasarca, anaemia, thrombocytopenia and acute renal insufficiency. Extensive blood and imaging workup was initiated. Several diagnoses were entertained including viral infections (comprising COVID-19), haemophagocytic lymphohistiocytosis, lymphoma and autoimmune conditions. Initial axillary lymph node biopsy was not diagnostics. A positron emission tomography (PET) scan showed diffuse and symmetrical cervical and hilar/mediastinal lymphadenopathies. A mediastinal lymph node biopsy was then performed and indicated iMCD. The patient was treated with high-dose steroids and siltuximab. An Epstein-Barr virus (EBV) PCR was positive, and rituximab was added to the treatment. The patient recovered and felt well after two months.

Conclusions: Non-specific symptoms, non-diagnostic first biopsy and iMCD resemblance to haemophagocytic lymphohistiocytosis further complicated the diagnosis. A PET scan allowed the best selection of a lymph node to be biopsied. Anti-IL6 is the recommended treatment; however, we are lacking information on the duration of siltuximab, and the long-term toxicity and immunosuppressive effect of this treatment. The contribution of EBV reactivation in the development and treatment of iMCD needs further investigation.

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KEYWORDS

Lymphoproliferative disorders, multicentric Castleman disease, Epstein-Barr virus, siltuximab, interleukin-6

LEARNING POINTS

- A positron emission tomography (PET) scan is important to identify the optimal lymph node biopsy site for diagnostics.
- Epstein-Barr virus reactivation has a role in the pathogenesis and treatment choice of idiopathic multicentric Castleman disease.

INTRODUCTION

Castleman disease (CD) is a lymphoproliferative disorder with variable anatomic presentations: unicentric CD and multicentric CD. Multicentric CD is further divided into HHV-8-associated CD and a HHV-8 negative form called idiopathic multicentric CD (iMCD)[1]. Given its varied and non-specific clinical presentations, iMCD remains difficult to diagnose, as presentation can range from constitutional symptoms to a life-threatening cytokine storm, organ failure or death.

Diagnostic criteria for iMCD were established in 2017 by an international working group (the Castleman Disease Collaborative Network)[2]. These must include two major criteria: 1) enlarged lymph nodes seen in more than two lymph nodes, and 2) histopathologic features consistent with the iMCD spectrum meeting at least 2 of 11 minor criteria (based on laboratory and clinical findings). Additionally, infection with HHV-8, inflammatory conditions and malignancies need to be excluded[2]. Histopathologically, it is divided into the hypervascular, the plasmacytic and the mixed subtypes[2]. The hypervascular subtype is characterised by the presence of regressed germinal centres and follicular dendritic cell prominence, whereas the plasmacytic subtype is characterised by hyperplastic germinal centres and prominent plasmacytosis[2]. Then iMCD is further divided into two clinical subtypes: iMCD-TAFRO (thrombocytopenia, anasarca, fever, reticulin - fibrosis of the bone marrow, and organomegaly), as well as the less aggressive type iMCD-NOS (not otherwise specified) that presents with lymphadenopathy and hypergammaglobulinaemia[1,2]. First-line management of iMCD is by anti-interleukin-6 (IL-6) siltuximab or tocilizumab with or without corticosteroids, depending on the severity[1,3].

CASE DESCRIPTION

A 43-year-old previously healthy male, originally from Colombia and living in Canada for 15 years, presented to another hospital in March 2024 with fever, diffuse lymphadenopathy, night sweats and a cough. He worked in an office for the Canadian army and had no relevant family history. He presented with symmetrical small cervical and axillary lymph node swelling with anaemia, thrombocytopaenia and acute kidney failure *(Table 1)*. Initial treatment with antibiotics did not provide any improvement. Infectious disease and respirology specialists conducted extensive infectious laboratory workup and bronchoscopy, in the context of the patient's tropical region in Colombia and clinical presentation resembling an acute viral illness. Four weeks after initial presentation, he developed anasarca with hyperkalaemia, hyperphosphataemia and hyperuricaemia, suggesting a lymphoma with tumour lysis syndrome. A positron emission tomography (PET) scan showed diffuse and symmetrical lymphadenopathies with cervical standardised uptake value (SUV) at 4.1 and hilar/mediastinal at 4.6 with smaller axillary lymph nodes. In addition, splenomegaly, mild hypermetabolic bone marrow and ascites were observed. An excisional lymph node axillary biopsy showed lymphoid proliferation, suggesting a reactive process. Interfollicular expansion with vascular proliferation and a few histiocytes with haemophagocytosis were also noted. A bone marrow biopsy showed a hypercellular marrow, without evidence of myelodysplasia or lymphoproliferation, suggestive of reactive process. The number of megakaryocytes without atypia was high. Haemophagocytosis was noted, leading to the hypothesis of haemophagocytic lymphohistiocytosis (HLH). The patient was treated with intravenous immunoglobulin (1 g per kg) and high-dose pulse steroids (1,000 mg intravenously daily every three days).

Given the absence of improvement, the patient was transferred in late April 2024 to the McGill University Health Centre (Montreal, Canada – a tertiary care centre) for further investigations and management. Serology assessment of HIV and viral hepatitis were negative and the HHV-8 polymerase chain reaction (PCR) measure in plasma was below the level of detection. Neuropathy, monoclonal peak or skin lesion were not observed, indicating an absence of polyneuropathy, organomegaly, endocrinopathy, myeloma protein or skin changes (POEMS) syndrome. His levels of C-reactive protein (CRP) were elevated to 325 mg/l and his albumin was at 23 g/l. The PCR for EBV was positive in the blood with a viral load of 12,023 copies/ml. Extensive auto-antibody assessments were negative for systemic lupus erythematosus and other rheumatological causes. The steroid treatment (50 mg daily) post pulse steroid therapy was then stopped due to negative autoimmune testing. A second excisional lymph node biopsy was performed on a large right mediastinal lymph node, which previously showed high SUV in the initial PET scan. Histology showed regressive transformation of germinal centres with the characteristic "twinning", a few "lollipop" vessels and onion-

skinning of follicular dendritic and mantle cells, suggestive of early partial hyaline-vascular type CD, illustrated in *Fig. 1*. Immunohistochemistry also showed rare, scattered cells positive for EBV-encoded ribonucleic acid (EBER). Kappa and lambda light chains by in situ hybridisation was polytypic in the plasma cells. The combination of clinical and pathological findings in the context of HLH led to the diagnosis of the hyaline-vascular subtype of iMCD-TAFRO.

Steroid treatment was then reinitiated. After four days, the patient's renal function and global presentation improved, together with decreased anaemia and thrombocytaemia. EBV viremia decreased to 3,890 copies/ml on 10 May; however, anasarca required significant diuresis and paracenteses. Ascites drainage was performed as an outpatient in the patient's initial local hospital. He was readmitted to the McGill University Health Centre on 11 June 2024 to start the anti-IL-6 siltuximab at 11 mg/kg every three weeks. After initiating siltuximab, as EBV PCR was detectable and patient presentation was severe; rituximab was given at 375 mg/m^2 weekly for four doses as an adjuvant therapy.

Two months after initiating siltuximab and rituximab the anasarca was controlled, and kidney function return to normal as indicated by creatinine levels. His daily oral dose of steroids was tapered down; his muscular mass had increased. Both CRP and albumin levels normalised, indicating control of inflammation. Relevant clinical laboratory results are presented in *Table 1*.

DISCUSSION

As seldomly observed and with unspecific presentation, iMCD presents a diagnostic challenge. The acute manifestation of iMCD is suggestive of acute viral infections or autoimmune conditions, which could be associated with HLH as evidenced by this case. Three months of investigations, including two lymph node biopsies, were required to establish the iMCD diagnosis for this patient. The non-specific constellation of symptoms, along with HHV-8 negativity (idiopathicity) resulted in a more challenging path to diagnosis. This patient's geographical origin and work in the military further complicated the investigation process given the high suspicion of tropical infectious diseases.

The diagnosis of Castleman's disease principally lies on lymph node histopathological characterisation[2]. However, this case demonstrates that excisional lymph node biopsies do not always yield a diagnosis. Upon CD suspicion, in addition to haematological, serological and chemistry assessment in the blood, the recommended diagnostic workup begins with a lymph node biopsy followed by a PET/CT scan. Our case indicates that PET/CT should be performed before lymph node biopsy, as it would indicate the preferred region to biopsy. Our observations emphasise the importance of biopsy of larger and SUV-high lymph nodes for a better chance of a diagnosis. The final diagnosis in our case was the iMCD subtype TAFRO. It often presents similarly to HLH, as both iMCD and HLH present with haemophagocytosis, severe inflammation, pancytopenia and a severe course[1]. This resemblance initially complicated the diagnostic process prompting initial HLH-targeting treatment. However, given the presence of lymphadenopathy, a lack of hypertriglyceridemia and repeated lymph node biopsy allowed confirmation by pathology of the diagnosis of iMCD-TAFRO. Both EBV and HHV8 are part of the same gammaherpesvirus family, and HHV8 is a known cause of multicentric CD (MCD). However, the influence of EBV replication on MCD or iMCD was not demonstrated in the context of HHV8 positive or negative MCD. EBV may foster angiogenesis in hyaline-vascular MCD[4] through stimulation of IL-6 production[5]. In our case only scant EBER positivity was noted in the lymph node biopsy, which could be due in part to a reduction of EBV immune control by steroid treatment. Conversely, EBV could be reactivated due to the extreme immune response and cytokine storm, and as such positive EBV PCR would be a marker of non-specific immune activation during iMCD. This observation warrants more

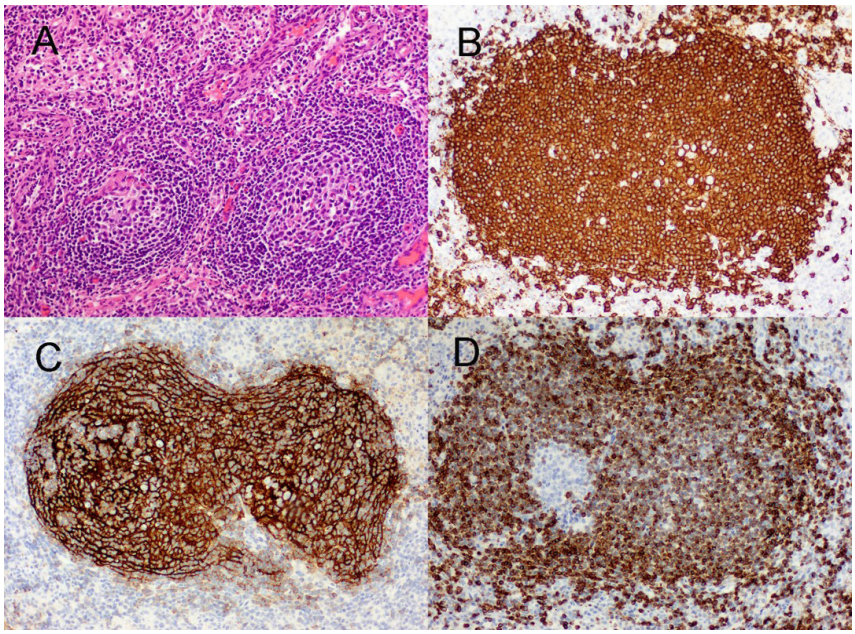


Figure 1. A) Light micrograph showing twin germinal centres with vessels in and around them; B) Immunohistochemical stain for the B-lymphocyte antigen CD20 in the twin germinal centres; C) Immunohistochemical stain for the CD23 (IgE) receptor in the twin germinal centres showing the "onion skin" layering; D) Immunohistochemical stain for the BCL2 gene in the twin germinal centres, showing positivity of the mantle cells, with the negative small germinal centre unstained.

	26/04/2024: Initial presentation	08/04/2024: Second presentation	20/04/2024: Prior to IVIG/ steroids	27/04/2024: Transfer to our hospital	02/05/2024: Prior to start of pulse steroids	21/05/2024: Prior to discharge	10/06/2024: Upon readmission, before siltuximab, rituximab	14/08/2024: Two months post-treatment initiation
Abs neutrophils count (10^9/l)	10.9			8.21	6.21	6.27	6.51	13.7
Platelet count (10^9/l)	164	125	13	72	25	142	85	236
Haemoglobin (g/l)	94 (BL around 140)	79	83	72	69	111	115	120
Creatinine (µmol/l)	135 (BL around 80 in 2021)	128	198	166	198	82	182	73
Albumin (g/l)		23	20	23	22		28	40
Uric acid (µmol/l)				481	450		605	323
Potassium (mmol/l)				4.7	4.9	4.3		3.9
LDH (U/l)	254			197				186
ALP (U/l)				169				64
Ig (g/l)				IgA: 1.08; IgM: 0.53; IgG: 9.79				
CRP (mg/l)	220			134, 30 April	67, 3 May			0.2
Serum IL-6 (ng/l)						13.8	22.7	
EBV PCR (copies/ml)				12,023		3,890	9,120	

Table 1. Clinical presentation and laboratory results.

research to better understand the pathogenesis and triggers of iMCD development, which should take into account EBV serostatus and PCR. Moreover, it remains unclear whether rituximab treatment benefits were directly due to decreased B-cell production of IL-6 or indirectly improved inflammation by decreasing the number of EBV infected cells.

Novel therapies against EBV such as allogenic T-cell therapy could be explored in the setting of MCD with positive EBV PCR.

A panel of experts recommended treating severe cases with high-dose steroids and siltuximab. In the absence of a response, second-line treatment such rituximab, cyclosporine, tacrolimus, lenalidomide or short-term combined chemotherapy should be included depending on disease severity and patient characteristics[1]. Our patient received steroids, siltuximab and four weekly doses of rituximab, which yielded positive effects on his clinical state. However, anti-IL6 therapy remains the mainstay of treatment of iMCD, recommended as a long-term therapy to avoid relapse[3]. However, there is no consensus on laboratory outcomes and targets to evaluate dosing interval and doses, which relies on clinical judgement. To be able to target the cause of iMCD, further research is warranted to identify the cause or the causal agent involved in iMCD pathogenesis, as therapies concentrate on downstream control of IL-6-induced inflammation.

CONCLUSION

Despite recent increased information and education about iMCD, its diagnosis and management remain a challenge, as illustrated by the case of this previously heathy middle-aged man and his convoluted road with HLH features and EBV reactivation finally leading to a diagnosis of iMCD-TAFRO. This case indicates that PET scans can guide the selection of the SUV-high lymph node to be biopsied for optimal chances at a diagnosis. Moreover, the contribution of EBV to the pathogenesis of CD with or without HHV-8 should be further studied.

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