VOLUME - 12, ISSUE - 08, AUGUST - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Oncology

REFRACTORY IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE: A CASE REPORT

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ABSTRACT Castleman disease (CD) is a rare disease which includes a heterogeneous group of disorders that share morphological features, such as HHV-8-negative idiopathic multicentric CD (iMCD). We describe the case of a man affected by iMCD who develops ascites during anti-IL-6 treatment with siltuximab. The etiology of ascites was not related to any other conditions, such as hepatic disease or venous thrombosis. We modified therapy adding a short course of steroid and reducing the time intervals of siltuximab, obtaining a sustained improvement of the clinical picture. This case is of particular interest because it suggests that a second line therapy might be postponed in iMCD, a disease in which it is difficult to recommend a preferred second line for patients who relapse after anti-IL-6-based therapies.

KEYWORDS :

INTRODUCTION

Castleman disease (CD) is a rare disease which includes a heterogeneous group of disorders that share morphological features but have a wide range of etiologies, presentations, and treatments. The most common type of the disorder, unicentric CD (UCD), affects a single lymph node, while multicentric CD (MCD) affects multiple lymph node stations and has been associated with human herpes virus type 8 (HHV-8) and human immunodeficiency virus, whereas HHV-8-negative MCD cases remain idiopathic (iMCD). The heterogeneous clinical picture in many patients with iMCD is due to a cytokine storm that often includes interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) [1].

UCD involves one or more enlarged lymph nodes in a single region of the body which demonstrates CD histopathologic features ranging along a spectrum from the hyaline vascular histopathologic subtype on one side to the plasmacytic histopathologic subtype on the other, with a "mixed" subtype in the middle [2].

The iMCD generally affects male patients around 60 years. Diagnostic criteria include the following: multicentric lymphadenopathy with defined histopathology, 2 clinical/laboratory changes, and exclusion of iMCD mimics [2, 3]. Clinical hallmarks include fever, night sweats, lymphadenopathy, ascites, hepatosplenomegaly, elevated C-reactive protein (CRP), hypoalbuminemia, and anemia.

Among iMCD patients, two different variants have been described: the TAFRO syndrome characterized by thrombocytopenia, anasarca/ascites, bone marrow fibrosis, renal dysfunction, organomegaly, and typically normal immunoglobulin levels [4], and the idiopathic plasmacytic lymphadenopathy (IPL-like) that typically displays thrombocytosis, polyclonal hyperimmunoglobulinemia, and less severe fluid accumulation [2]. Moreover, iMCD can be occasionally associated with the paraneoplastic syndrome POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin lesions) [5].

Siltuximab, an anti-IL-6 antibody, is the only drug tested in a randomized trial and the only treatment approved in Europe for iMCD [6]. Other therapeutic options tested in different case reports and series include the anti-IL-6 receptor antibody tocilizumab, rituximab, steroids, sirolimus, and cytotoxic chemotherapy. For patients who fail to respond to anti-IL-6 antibodies there is no clear approach and additional therapeutic solutions are still required for refractory cases [1].

Case Presentation

A 66-years-old man was diagnosed with a plasmacytic variant iMCD in April 2013. Past medical history was unremarkable. HIV and HHV-8 status was negative. POEMS syndrome, other malignancies, autoimmune or infective diseases were ruled out. The clinical picture was characterized by multiple confluent axillary lymphadenopathies (maximum diameter 6 cm), splenomegaly (interpolar diameter 16 cm) and polyclonal hypergammaglobulinemia. At the time of diagnosis, no systemic symptoms were referred, and the patient was followed up without interventions until 2017. At the end of 2017, an increase in number and size of the lymphadenopathies, worsening of splenomegaly (interpolar diameter 20 cm) and weight loss were observed. Bone marrow and lymph node biopsy confirmed the diagnosis of iMCD. Diffuse bone thickening was observed without clear osteosclerotic areas on CT scan. Complete blood counts showed only mild neutropenia (grade 1 CTC-AEv5.0), while hepatic and renal functions were normal. No serum and urine monoclonal protein were detected, and serum electrophoresis, IgA, IgG, and IgM levels were normal, as well as ferritin, CRP, albumin, and erythrocyte sedimentation rate (ESR). No neurological symptoms were reported. Therapy with siltuximab at a dose of 11 mg/Kg every 3 weeks was started, obtaining a durable partial response (PR).

Starting from June 2019 siltuximab therapy was administered every 4 weeks maintaining a good PR, until June 2020 when a total body CT scan revealed the development of conspicuous abdominal effusion coupled with an increase in the size and number of lymphadenopathies; on the contrary, splenomegaly and diffuse bone thickening were stable. Blood tests showed thrombocytopenia (grade 2 CTC-AEv5.0), normal hepatic function, increased creatinine (1.5 mg/dL) and

blood urea nitrogen (49 mg/dL), no urine or serum monoclonal protein, normal IgG and IgA levels with low IgM (15 mg/dL), normal ESR, fibrinogen, ferritin, CRP, albumin, slightly elevated D-dimer with normal coagulation times, normal TSH and free light chains; no dyslipidemia was observed. Echocardiography and spirometry with diffusion lung CO did not reveal any abnormality. Neurological exam was unremarkable. VEGF levels were not elevated. TAFRO syndrome criteria were not met. The thrombocytopenia observed may have been due to splenomegaly or as an adverse effect of siltuximab treatment.

A trial with rituximab and steroids was offered, however the patient refused anti-CD20 therapy. Therefore, the previous therapy scheme was restored with siltuximab administered every 3 weeks with the addition of a short course of steroid (prednisone 1 mg/Kg/die over 2 weeks, followed by a rapid taper in other 2 weeks). An abdomen ultrasound scan performed after one month showed complete resolution of the ascites and the patient continued to be treated with siltuximab every 3 weeks, maintaining a partial response to date.

DISCUSSION

This case is of particular interest because it suggests that waiting before the start of another line of therapy can sometimes be beneficial in iMCD, a disease with very limited therapeutic options and without a preferred second line for patients unresponsive to IL-6 blocking strategies. Interestingly, our patient developed ascites, a complication mostly seen in TAFRO or POEMS-associated MCD, as the only sign of late iMCD relapse during siltuximab therapy. The etiology of the ascites could not be related to any other conditions, such as liver disease or venous thrombosis, hence we speculated about extravascular volume overload, but VEGF levels were normal, and no other signs of fluid overload were present. Among second line therapies, sirolimus was excluded due to low levels of VEGF, rituximab was rejected by the patient, and cytotoxic chemotherapy was deemed too dangerous. Although improvement with corticosteroids is well described in iMCD, it tends to be only temporary and associated with discrete morbidity; we did not expect a maintained response to a second trial with siltuximab, considering the absence of a significant inflammatory response (low levels of ESR, CRP, and ferritin), but the clinical picture improved durably even after prednisone discontinuation and our patient is still responding almost three years after this relapse.

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