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Idiopathic multicentric Castleman disease: case report and literature review

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Abstract
Castleman disease is a rare disease characterized by lymphoproliferative disorders. We report the case of a 60-year-old man with diffuse lymphadenopathy, hepatosplenomegaly, and chylous ascites of unknown origin. A diagnosis of idiopathic multicentric Castleman disease (MCD) was performed, and the patient underwent treatment with cycles of rituximab, cyclophosphamide, and dexamethasone. Six months of treatment resulted in marked clinical and radiological improvement; maintenance therapy with rituximab alone was continued every 2 months. A review of the scientific literature shows that at least a third of all published cases of MCD are idiopathic. Corticosteroids, immunomodulatory or immunosuppressive agents, cytotoxic chemotherapy, and anti-interleukin-6 therapy have been used for patients with MCD. Timely diagnosis and appropriate treatment can significantly impact patient survival. Data on idiopathic MCD are limited, so MCD represents a clinical challenge because of the rarity of the disease and the lack of knowledge about it.

Introduction

Castleman disease represents a spectrum of lymphoproliferative disorders characterized by common histopathologic patterns. It was in 1954 that Castleman *et al*. presented, as a new syndrome, the case of a mediastinal mass whose histological examination was characterized by a hyperplasia of the nodal lymphatic structures.[1] Two years later the same author describes the salient characteristics and proposes the criteria to perform a differential diagnosis with thymoma with which the injury had been confused in the past due to the frequent mediastinal localization and the similarity, in the histological examination, of hyalino-vascular structures, own of Castleman's disease, with the corpuscles of Hassall in the thyme.[2]

From a clinical perspective, Castleman's disease is subdivided into unicentric (UCD) and multicentric (MCD) forms; histopathologically, it is distinguished into hyaline vascular and plasma cell subtypes.[3-5] UCD is characterized by involvement of one or more lymph nodes within a single anatomical region and demonstrates a histopathologic spectrum ranging from hyaline vascular at one extreme to plasmacytic at the other, with a mixed subtype occupying an intermediate position.[3,6] MCD presents with lymphadenopathy across multiple anatomical regions and exhibits a corresponding histopathologic continuum from hypervascular to plasmacytic, with mixed features in between.[3,6] MCD is further subclassified into HHV-8–associated MCD and HHV-8–negative/idiopathic MCD (MCDi).[3,6] Various viral, autoimmune, and neoplastic mechanisms have been suggested as potential underlying causes of UCD; most patients remain asymptomatic and are typically identified when an enlarged lymph node is detected during physical examination or imaging studies.[3,7,8] Laboratory tests are usually normal.[3] Definitive diagnosis requires histopathologic evaluation of a fully excised lymph node, which should reveal features consistent with hyaline vascular, plasmacytic, or mixed subtypes. HHV-8 negativity is required for MCDi diagnosis.[3] Complete surgical excision of the affected lymph node(s) is generally curative and remains the established gold standard for management.[3,8-12] The pathogenesis of MCDi remains largely unclear: hypothesized contributing mechanisms include autoimmune processes, autoinflammatory pathways mediated by interleukin (IL)-6 and other cytokines, neoplastic transformation, and infectious triggers.[13] Patients typically present with systemic manifestations, including fever, night sweats, weight loss, hepatosplenomegaly, edema, ascites; laboratory evaluation may reveal elevated C-reactive protein, anemia, thrombocytopenia, hypoalbuminemia, elevated IL-6 levels, increased vascular endothelial growth factor (VEGF), and hypergammaglobulinemia.[13-15] Whole-body computed tomography combined with fluorodeoxyglucose positron emission tomography typically reveals lymphadenopathy in multiple anatomical regions.[13] Definitive diagnosis requires histopathologic assessment of a fully excised lymph node.[13] Following identification of Castleman disease-like histopathologic features, immunohistochemical staining for LANA-1 should be performed to differentiate HHV-8-associated MCD from MCDi.[13] In cases where the initial biopsy is non-diagnostic but clinical suspicion remains high, repeat lymph node biopsies may be warranted to establish the diagnosis.[13] Management of MCDi remains a therapeutic challenge, as evidenced by the diversity of available protocols. While the current international consensus guidelines recommend IL-6 directed therapy, specifically siltuximab, as the first-line gold standard for non-severe cases, clinicians must often adapt strategies based on disease severity and local availability. Based on the literature data, the current first-line treatment for systemic Castleman's disease involves the use of siltuximab, an IL-6 inhibitor.[16] Alternatively, treatment regimens containing anti-inflammatory or immunomodulatory drugs or well-defined immunochemotherapeutic regimens, such as the combination of anti-CD20, steroids, and cyclophosphamide (R-CD regimen), can be used.[13,17] Persistent HHV-8 infection is recognized as the definitive underlying cause of HHV-8-associated MCD.[18,19] In patients exhibiting characteristic clinical features, diagnosis typically relies on the presence of plasmablastic histopathology in lymph node biopsy specimens, detection of HHV-8 either through LANA-1 staining in the lymph node or by polymerase chain reaction in peripheral blood during active disease, and involvement of multiple lymph node regions.[18] Evidence on the management of HHV-

8–associated MCD is derived from systematic literature reviews, case series, and case reports: in patients without life-threatening organ dysfunction and in the absence of Kaposi sarcoma (KS), rituximab is recommended, whereas those with KS or with life-threatening organ failure in the absence of KS may benefit from a combination of rituximab and pegylated liposomal doxorubicin.[18] MCDi rapresents a clinical challenge because of the rarity of the disease and the lack of knowledge about it.

Case Report

A 60-year-old man presented to the Emergency Department due to the onset of exertional dyspnea, persistent anasarca, and worsening of swelling in the right inguinal region, the site of a recently excised inguinal lymph node; the patient has been treated with steroids until one week before hospitalization. He was subsequently admitted to the Internal Medicine Department for further evaluation and appropriate treatment. His medical history included the detection in 2024 of diffuse lymphadenopathy and chylous ascites of unknown origin. The patient previously underwent a TC-PET scan (negative for high glucose-metabolism pathologies, but showing multiple supra- and subdiaphragmatic lymphadenopathies showed a low uptake value typical of inflammatory nodes with SUV <5), a right inguinal lymph node biopsy (reactive changes), immunophenotypic analysis of ascitic fluid (negative for atypical cells), and lymphoscintigraphy (mild insufficiency of the superficial lymphatic circulation). At admission, clinical examinations revealed hepatosplenomegaly, generalized anasarca, and widespread superficial supra-and subdiaphragmatic lymphadenopathy. During hospitalization a pig-tail catheter was placed to drain a recurrent right inguinal lymphocele. A contrast-enhanced CT scan of the chest and abdomen revealed lymphadenopathy in the mediastinal, axillary, and bilateral inguinal regions and para-aortic and mesenteric root areas (Figure 1). It was decided to surgically remove a left inguinal lymph node. Histological analysis showed marked plasmacytosis suggestive of mixed-type Castleman disease with a notable plasma cell component. Laboratory tests revealed normocytic anemia (Hb 10 g/dL), hypoalbuminemia (3 g/dL) and hypergammaglobulinemia (gamma 28%). Quantiferon tests and serologies for Bartonella, Brucella, syphilis, and EBV were negative. HHV-8 DNA and HIV tests were also negative. However, IL-6 and VEGF levels were elevated [IL-6: 66 pg/mL (5-10 pg/mL), VEGF: 1256 pg/mL (<115 pg/mL)]. Given the diagnosis of MCDi (based on clinical and laboratory criteria, along with high histological suspicion) and in consideration of the clinical and social factors related to the patient and described below, a multidisciplinary team decided to start an immunochemotherapeutic treatment of proven manageability, such as the RCd protocol, consisting of 21-day 6 cycles of Rituximab, Cyclophosphamide, and Dexamethasone (rituximab 375 mg/m² on day 1, cyclophosphamide 600 mg/m² iv on day 1, and dexamethasone 20 mg iv on day 1-4). At the end of the 6 cycles, a follow-up contrast-enhanced chest and abdominal CT scan showed a volumetric decrease of the mesenteric and axillary lymph nodes. The patient was in fair general condition and continued maintenance therapy with rituximab approximately every 2 months.

Discussion

Liu *et al.* indicates that approximately one-third of reported MCD cases are idiopathic.[14] In this systematic review of studies published since 1995, a total of 1923 MCD patients were identified: 42% were HHV-8–positive, HIV-positive, or both; 25% were HIV-negative with unknown HHV-8 status; and 33% were HHV-8-negative.[14] A total of 128 patients with MCDi fulfilled all inclusion criteria (pathology-confirmed Castleman's disease in multiple nodes and minimum clinical and treatment information on individual patients).[14] The median age at diagnosis among the 128 individual cases was 50 years, and 58% were male (Table 1).[14] 72 patients were from Asia, 38 from Europe and the Middle East, 16 from North America, one from South America, and one from Australia.[14] The histopathological characteristics of these patients showed a predominance of the plasma cell and mixed pathology variants.[14] The main clinical features included multicentric lymphadenopathy, hepatomegaly, splenomegaly and fever; laboratory findings showed elevated C-

reactive protein levels, anemia, hypergammaglobulinemia, and abnormalities in platelet counts.[14] IL-6 levels were reported in 63 patients and were elevated in 57; soluble IL-2 receptor levels were increased in 20 of 21 cases, and VEGF concentrations were elevated in 16 of 20 patients in whom this cytokine was reported.[14] Corticosteroid monotherapy (47/128) and chemotherapeutic regimens (47/128) were the most commonly reported first-line treatments (Table 1). Chemotherapeutic regimens most frequently included cyclophosphamide and rituximab; sometimes etoposide, vinblastine, vincristine, doxorubicin, bleomycin, and dacarbazine were used.[14] Anti-IL-6 agents were used as first-line therapy without cytotoxic agents in 11 patients and in combination with cytotoxic chemotherapy in 4.[14] Although based on a limited number of cases, anti-IL-6 therapy (tocilizumab and siltuximab) without cytotoxic chemotherapy appeared to be the most effective first-line regimen.[14] 49 of 116 patients did not respond to first-line therapy.[14] The two-year survival rate was 88% (Table 1), and 27 of 121 patients died by the end of the observed follow-up period (median 29 months); the most common causes of death were organ failure, sepsis, malignant disease, and disease progression.[14] Hoffman *et al*. analyzed 32 studies including 1023 cases of MCDi (377 females; 545 males; 101 not reported; mean age 47 years). The plasmacytic histopathological subtype was the most common. Laboratory tests frequently showed elevated PCR levels, anemia, and hypoalbuminemia.[20] Clinically, all patients presented lymphadenopathy; fever and hepatosplenomegaly were also common manifestations.[20]

The case described in this paper posed a particular challenge for the diagnosis. Some clinical features that characterized his long medical history are typical of Castleman's disease, such as multiple lymphadenopathies and hepatosplenomegaly. Less characteristic, however, is anasarca with chylous ascites, although cases with severe fluid retention have been reported. These findings may reflect the high degree of systemic inflammation with increased vascular and lymphatic permeability and a reduction in oncotic pressure induced by reduced protein synthesis related to liver dysfunction and are likely related, in this case, to the large number of lymph nodes involved. Finally, chylous ascites may be related to the involvement or compression of major lymphatic vessels, such as the supra- and subdiaphragmatic trunks and ducts. These clinical signs are considered, however, as minor diagnostic criteria. Finally, the negativity of the PET was due to a therapy with steroids before the scan.

The case described, based on the clinical and biological characteristics, was considered to correspond to a classic multicentric form, excluding those associated with more complex clinical pictures such as the TAFRO subtype, given the absence of thrombocytopenia and marrow fibrosis.[21]¶ The long clinical history of the reported case was due to the atypical and unclear findings on histological examination, as the pictures mimicked nonspecific lymph node inflammation.

Regarding treatment choices, there was evidence confirming that the standard first-line therapy for Castleman's disease involves the use of monoclonal antibodies against IL-6 work that are able to perform a blocking of the formation of the IL-6/IL-6 receptor complex, resulting in inhibition of the activation of the JAK/STAT pathway. Two anti-IL-6 drugs are currently available: tocilizumab and siltuximab. In the case described here, we preferred a treatment with less impact on the patient's immunological status, considering the patient's high risk of infection due to behavioral and social factors. The patient, in fact, had no caregiver, and his living conditions were characterized by poor personal care and attention, suboptimal compliance and adherence to therapies, as well as a lifestyle characterized by smoking and an unsuitable diet.

Conclusions

MCDi rapresents a clinical challenge because of the rarity of the disease and the lack of knowledge about it. The heterogeneous clinical presentation and variable prognosis of MCDi underscore the necessity for standardized diagnostic guidelines.[14] Timely diagnosis and appropriate treatment can significantly impact patient survival. Therefore, it is essential to continue investigating the pathogenic mechanisms underlying the disease and to promote the dissemination of information that may support prognosis, therapeutic decision-making, and overall disease management.

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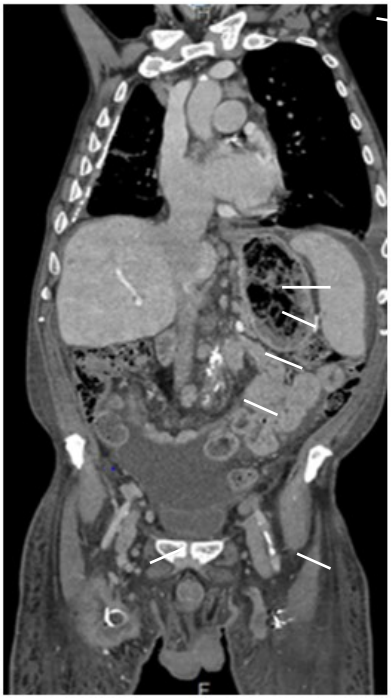

Figure 1. Supra- and sub-diaphragmatic lynphadenopathy (arrows).

Table 1. Characteristics, treatment and outcomes of patients with MCDi.

Patients with MCDi	128
Female	54
Male	74
Median age	50 years
Corticosteroid monotherapy	47/128
Chemotherapeutic regimens	47/128
Anti-interleukin-6 agents	11/128
Two-year survival rate	88%