Putting the pieces together: Castleman disease in a patient with HIV

Margarida R. Fonseca[1]
Miguel Oliva Teles[1]
Ana Rita Barradas[1]
João Domingos[1]
Ana Pãosinho[1]
Isabel Madruga[1]

1. Egas Moniz Hospital, Western Lisbon Hospital Center, Lisbon, Portugal.

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INTRODUCTION

Castleman disease (CD) is a nonclonal lymphoproliferative disorder that can present as localized lymphadenopathy or disseminated disease. The simultaneous occurrence of Kaposi Sarcoma (KS) and multicentric CD was first described by *Lachant* in 1985[1,2]. Human herpesvirus 8 (HHV-8) infection plays a central role in the pathogenesis of its disseminated form and in Human immunodeficiency virus (HIV) associated CD[3].

We present the case of a 43-year-old man with HIV stage C3 infection with mucocutaneous Kaposi Sarcoma and multicentric Castleman Disease.

CASE DESCRIPTION

A 43-year-old man with HIV stage C3 infection (poor compliance with anti-retroviral therapy) and mucocutaneous Kaposi Sarcoma (undergoing treatment with liposomal B Doxorubicin every other week) was admitted to the infectious diseases ward with a six-day history of asthenia, high fever (39.5ºC), diarrhea, dyspnea, and cough. Amoxicillin/clavulanate and Ciprofloxacin was prescribed four days earlier without clinical improvement. On admission, he was hypotensive and febrile, with no remarkable finds on physical examination other than the cutaneous lesions related to his Kaposi Sarcoma. The blood work showed Hb 12.1g/dL (normal range (NR) 13-16g/dL), platelets 42000/mcL (NR 150-450000/mcL), leukocytes 5000/mcL (NR 10-15000/mcL), C-reactive protein 30.8mg/dL (NR < 0.5mg/dL), creatinine 1.98mg/dL (NR 0,7 - 1.2mg/dL), urea 79mg/dL (NR 13 – 43 mg/dL), AST 69U/L (NR < 74U/L), ALT 101U/L (NR < 30U/L), FA 177U/L (NR 35 – 105U/L), GGT 95U/L (NR 6 – 42U/L). Cytomegalovirus viral load was negative, as was Cryptococcus neoformans antigen and fecal examination (including Clostridium difficile antigen). The urine culture grew Enterococcus faecalis, and he was started on

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CORRESPONDING AUTHOR: Margarida R. Fonseca
Egas Moniz Hospital - Rua da Junqueira, 126, Lisboa, Portugal - 1349-019
E-mail: margarida.rfonseca@gmail.com

Piperacillin/tazobactam admitting urinary sepsis. After one week, the patient was transferred to the Intermediate-Care Unit due to clinical degradation: asthenia, dyspnea, and blood loss through the rectum were noticed. On examination, the patient was jaundiced and with peripheral saturation of 88% on 5L/min oxygen mask, with no pain, and mobile axillary and inguinal adenopathies were noticed as well as tender hepatosplenomegaly. The blood work was redone and it showed anemia (Hb 7.1g/dL), thrombocytopenia (Platelets 33000/mcL), hyperbilirubinemia (total bilirubin 21.5mg/dL, conjugated bilirubin 16.3mg/dL) with cytocholestasis (AST 112U/L, ALT 50U/L, FA 1145U/L, GGT 493U/L) and C-reactive protein 31.5mg/dL. The arterial blood gas showed hypoxemia, and chest CT revealed bilateral pleural effusion and abdominal CT ascites and intraabdominal adenopathies. Abdominal ultrasonography showed no biliary duct dilatation. Pulmonary sepsis was admitted, and the patient was started on Meropenem and Atovaquone, which he maintained for fourteen days. A colonoscopy was done, which excluded involvement by Kaposi Sarcoma. Pneumocystis jiroveccii infection was confirmed by a positive polymerase chain reaction in the bronchoalveolar lavage product. After four days of therapy, there was significant clinical and analytical improvement. Inguinal adenopathy was biopsied, and the histology confirmed hyaline vascular Castleman disease. The patient was discharged and chemotherapy with Doxorubicin and Rituximab was planned.

DISCUSSION

First described by Benjamin Castleman in 1954, Castleman Disease describes a rare heterogeneous group of disorders that share lymph node enlargement and similar pathologic findings (abnormal vascularization, plasmacytosis, or both)[4]. Regarding the latter, three distinct subtypes can be distinguished: hyaline vascular, plasmacytic, and mixed[1].

Unicentric CD (UCD) affects one lymph node station, and patients are rather asymptomatic, with the diagnosis being incidental, or with symptoms due to compression of neurovascular or other vital structures[1,4,5]. On the other hand, *Multicentric CD* (MCD) is characterized by the involvement of more than one lymph node station, presence of systemic symptoms (fever, night sweats, asthenia, anasarca, and pleural effusion), hepatosplenomegaly and an increase of inflammation markers and acute phase proteins (elevated C-reactive protein, hypergammaglobulinemia, hypoalbuminemia). Multicentric CD comprises two subgroups: HHV-8-related MCD and idiopathic MCD (HIV and HHV-8 negative and with autoimmune associated phenomena)[4].

HHV-8 and HIV positive MCD is the most frequent form of MCD. Its incidence has increased over time since antiretroviral therapy does not prevent disease development[1,4]. Kaposi Sarcoma (another clinical entity HHV-8 and HIV related) can coexist with CD in up to 40% of the cases[4].

Interleukin-6 (IL-6) plays a central role in CD pathophysiology. Excess IL-6 in these patients induces a pro-inflammatory syndrome with severe systemic symptoms and elevation of acute phase reactants[1,5]. Anemia, typically present in MCD patients, is related to IL-6 mediated hepcidin overproduction[5].

Given its heterogeneity and nonspecific clinical presentation, diagnosis depends on a high suspicion[1]. Excisional lymph node biopsy and examination by an experienced pathologist are essential[4].

The authors report the case of an HIV patient with known KS in whom disease progression was first suspected with pulmonary and gastrointestinal involvement. After the exclusion of pulmonary and gastrointestinal involvement, and given the clinical presentation with systemic symptoms, hepatosplenomegaly, and an inflammatory syndrome, the hypothesis of MCD was considered and later confirmed by lymph node biopsy. The *Pneumocystis jiroveccii* infection was related to the patient's immunosuppression status.

CD disease treatment differs upon presentation and association with KS. The preferred management of UCD is surgical excision or local radiotherapy. MCD is treated with single or combination chemotherapy with Rituximab being used mainly in HIV patients and idiopathic forms[5].

MCD in HIV patients behaves aggressively, with poor prognosis. The median survival does not exceed 25 months and it has a high mortality rate[1]. With this case, the authors aim to raise awareness of this rare but severe entity, especially in patients with HIV.

PALAVRAS-CHAVE: *Hiperplasia do linfonodo gigante. HIV. Sarcoma de Kaposi.*

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