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Brief communication

Schnitzler syndrome co-occurring with idiopathic multicentric Castleman disease that responds to anti-IL-1 therapy: A case report and clue to pathophysiology

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ABSTRACT

Patients with HHV-8-negative/idiopathic multicentric Castleman disease (iMCD) experience systemic inflammatory symptoms and polyclonal lymphoproliferation due to an unknown etiology. Schnitzler's syndrome (SS) is characterized by recurrent urticarial rash, monoclonal IgM gammopathy, and other clinical signs of inflammation. To our knowledge, we report the first case of iMCD associated with SS and the fourth case of anakinra inducing a complete response for an iMCD patient.

A forty-four year old woman with a history of a recurrent urticarial rash, presented to our hospital complaining of 6 months of night sweats, fever, chronic urticaria, iliac bone pain, and generalized lymphadenopathy. An IgM Kappa monoclonal component was measured at 7.8 g/L. A lymph node biopsy revealed histopathological features consistent with the plasma cell variant of iMCD. She was diagnosed with SS and iMCD. Anti-IL-1 treatment with anakinra (100 mg/day) was introduced. Within 48 h, we observed improvement in the fever and the urticarial rash. By one month, we considered the patient in complete remission. Two years later, the remission is persistent while the patient is still under therapy. Though this is only the fourth reported case of anakinra in iMCD, this is yet another case demonstrating the effectiveness of anti-IL-1 blockade in SS. We hypothesize that uncontrolled cytokine production is responsible for both the SS and the iMCD. The etiologies of SS and iMCD are unknown, and future research is necessary.

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1. Introduction

Castleman's disease (CD) describes a group of rare disorders involving characteristic histopathology and heterogeneous clinical features. CD is divided into unicentric CD (UCD), which involves enlarged lymph nodes localized to one region and an indolent course [1], and multicentric CD (MCD), which involves a proinflammatory cytokine storm, polyclonal lymphoproliferation, and multiple organ system dysfunction. Human Herpes Virus-8 (HHV-8) causes approximately 50% of MCD cases by signaling for uncontrolled cytokine secretion, and these individuals are often immunocom-

promised [2]. There is also a large group of HHV-8-negative MCD patients with unknown etiology that are referred to as idiopathic MCD (iMCD) [3]. These patients have a poor prognosis and require systemic treatment. Schnitzler's syndrome (SS) is characterized by recurrent urticarial rash, monoclonal IgM gammopathy, clinical and biological signs of inflammation, and a long-term risk of AA amyloidosis and overt lymphoproliferation [4]. We report the first association described between iMCD and SS and the fourth case of a dramatic response with anakinra for an iMCD patient.

2. The case

A forty-four years old woman with a history of a recurrent urticarial rash in 2006, while she was living in Algeria, presented to

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our hospital in May 2014 complaining of 6 months of night sweats, fever, chronic urticaria, iliac bone pain, and generalized lymphadenopathy. In 2006, she was treated with anti-histaminic medication for the recurrent urticarial rash without improvement. During a follow up visit in 2012, we found a white blood cell count of 12,400 neutrophils G/L and a C-reactive protein level at 100 mg/L (normal range: 0–10 mg/L). Serum protein electrophoresis (SPEP) showed an IgM Kappa monoclonal gammopathy at 8 g/L (normal range: 0.4–2.4 g/L). She had no lymphadenopathy on physical exam and no other systemic symptoms. She was not diagnosed with any disease at that time.

Clinical examination at presentation in May 2014 revealed inguinal, axillary, and maxillary lymphadenopathy without hepatomegaly or splenomegaly. An urticarial rash was present. There were no signs of peripheral neuropathy or fluid accumulation. We observed anemia with hemoglobin level at 8.4 g/dL, neutrophil count of 20.9 G/L (normal range: 4–8 G/L), albumin level of 26 g/L (normal range: 35–50) and a C-reactive protein level at 150 mg/L. The IgM Kappa monoclonal component was measured at 7.8 g/L. HIV serology and HHV-8 PCR in the blood were both negative as were the other viruses tested (i.e. CMV, EBV, parvovirus B19 and HSV). Antinuclear antibodies and ANCA were also negative. A myelogram showed 50% of cells were lymphocytes without lympho-plasmacytic proliferation. A lymph node biopsy revealed polytypic plasmacytosis consistent with the plasma cell variant of iMCD (Fig. 1). The lymph node was also negative for HHV-8 by LANA-1 immunohistochemistry. A bone marrow biopsy had a cellularity of 10% associated with medullar fibrosis (WHO stage 2 or 3) (Fig. 2). The plasma cells were mostly kappa light chain (Fig. 2). A pelvic CT scan revealed bilateral osteocondensation of wing ilium and lytic lesions. A pelvic MRI showed a diffuse infiltration signaling medullary replacement.

The patient's clinical and pathological findings were consistent with the recently published diagnostic criteria for iMCD. She met both required major criteria (histopathology consistent with iMCD, multiple regions of enlarged lymph nodes), at least two minor criteria (elevated CRP, anemia, hypoalbuminemia, and constitutional symptoms), and exclusion of disease mimics [5].

According to Strasbourg diagnostic criteria [4] SS was diagnosed. There were two major criteria (chronic urticarial rash and monoclonal IgM gammopathy) and three minor (recurrent fever, abnormal bone remodeling and elevated CRP).

Anti-IL1 treatment with anakinra (100 mg/day) was initiated in September 2014. Within 48 h, we noticed an improvement in the fever and the urticarial rash. Within 1 week, bone pain and lymphadenopathy began to improve. By one month, all signs and symptoms had disappeared, she had gained 3 kilograms, and the patient was in complete remission. Two years later, the remission is persistent while the patient is still under treatment.

3. Discussion

To our knowledge, we report the first case of SS associated with iMCD. CD was first described in 1954 as angiofollicular lymph node hyperplasia in a localized lymph node region [1]. In the 1970s, patients were reported to have these histological features in multiple regions of enlarged lymph nodes along with associated inflammatory symptoms [6]. These MCD cases are further subdivided into HHV-8-associated MCD and HHV-8-negative MCD or iMCD.

HHV-8-associated MCD involves excessive cytokine signaling in lymph node plasmablasts by HHV-8, which has evaded host immune control because of HIV infection or another cause of

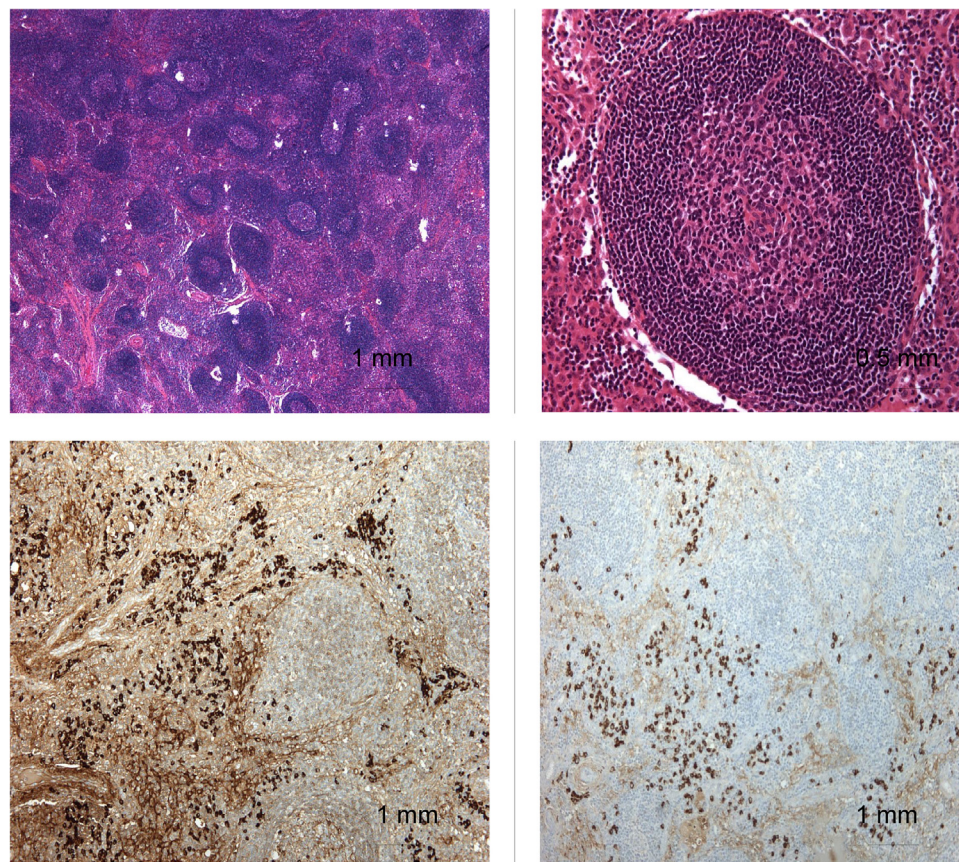


Fig. 1. Histologic examination of lymph node biopsy.

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