Case report

Coexistence of Behcet's disease and chronic myelomonocyte leukemia with trisomy 8: a case report and review of the literature

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ABSTRACT

Behçet's disease (BD) is a multisystem inflammatory vasculitis of unknown etiology and pathogenesis. Coexistence of BD along with hematological malignancies is extremely rare. We describe a patient diagnosed with BD and chronic myelomonocytic leukaemia (CMML) with trisomy 8. This case suggests that trisomy 8 may be involved in the concurrent manifestation of myelodysplastic syndrome (MDS) and BD with gastrointestinal ulcers.

Introduction

Behçet's disease is a chronic relapsing multisystem inflammatory vasculitis of unknown etiology. In the pathogenesis of the disease genetic factors, environmental agents, microbial factors and immune aberrations are implicated (1). The prevalence varies from 3-17:10000 in Japan to 0.1~7.5:100000 in Europe and USA and 80-370:100000 in Turkey (2). Clinical diagnostic criteria include recurrent oral aphthae, genital ulceration, eye lesions and folliculitic skin lesions (3). Skin pathergy test, being positive in about 50% of patients with BD (4), is also positive in some CML patients treated with IFN-α without any BD symptoms (5). The association between BD and hematological disorders is extremely rare and only a limited number of cases have been reported (6). Until now 27 patients with BD and MDS have been reported in literature. Interestingly, it was found that the majority of MDS patients whom presented BD symptoms had trisomy 8 and moreover, most of them had gastrointestinal manifestations (7). In this article, a case of BD coexistent with chronic myelomonocyte leukaemia (CMML) and trisomy 8 is described for the first time.

Case report

A 68-year-old man was admitted to our Department because of fever, recurrent aphthous stomatitis, painless genital ulceration and pain in the left calf. He had two oral aphthous lesions, a groin ulcer and a painful edema in the left calf (triplex ultrasonography showed deep vein thrombosis of the left calf, popliteal and femoral veins). He had hemoglobulin 12.1g/dl, white blood cells (WBC) $16.260x10^9$/L (49% neutrophils, 16% lymphocytes, 22% monocytes, 3% metamyelocytes, 6% myelocytes and 2% promyelocytes) and platelets $184x10^9$/L. The initial laboratory tests were normal except for CRP: 131mg/L, ESR: 120 mm/h though blood, urine, sputum and bone marrow cultures for bacteria and fungi, as the search for IgM virus antibodies were negative. The bone marrow aspiration and biopsy indicated a MDS of CMML subtype with 10% blasts. The flow cytometric analysis of blood mononuclear cells and bone marrow confirmed the diagnosis of CMML. Cytogenetic analysis of bone marrow mononuclear cells with RHG-banded and M-FISH technique detected 47,XY,der(2)t(2;4;7),-3,der(4)t(3;4;7),del(5),der(7)t(7;15),+8,der(12)t(2;12),-5,+21,+22 (Fig. 1). The pathergy test was positive and B51 was absent in HLA typing.

Based on the patient's clinical history and positive result in pathergy testing, we diagnosed the patient with BD (according to the diagnostic criteria by the International Study Group, Lancet 1990) (8) coexisting with the CMML.

Total gastrointestinal endoscope revealed ulcers in the stomach, the ileocecal region, the ascending, the transversal and the sigmoid colon. The biopsies of gastrointestinal, oral and genital ulcera-

tive lesions showed active inflammation compatible with the diagnosis of BD. Initially wide-spectrum antibiotics were introduced to the patient without any signs of improvement but when corticosteroids were given (14th day of hospitalization) he became afebrile. The patient's hemogram (37th day) showed WBC 75x10^9/L and 5% blasts in blood smear. Due to disease progression the patient was treated with hydroxyurea. One month later he had a chest pain and dyspnea because of left-sided pleural effusion. The flow cytometry of the pleural fluid showed infiltration of 70% blast cells, compatible with acute myelomonocyte leukaemia. A few days later, the patient died due to acute leukemia.

Discussion

The association of BD with malignancies is rarely reported and even less with hematological malignancies. In the literature 112 cases of malignancies have been referred with BD. Sixty of these cases had hematological malignancies and 26 of them were classified as MDS (6). Trisomy 8, observed in 10-20% untreated MDS patients, is the most common chromosomal abnormality reported in MDS patients associated with BD (78%) like our patient (7). He had also multiple ulcerations in the gastrointestinal track, as well as deep vein thrombosis of left popliteal and femoral veins. The gastrointestinal involvement of BD is higher among Japanese patients (50-60%). Kimura *et al*. investigated that trisomy 8 involve in MDS as a risk factor for intestinal ulcers and thrombosis in BD (9). It has been reported that the presence of trisomy 8 facilitates cytokine production, which enhances neutrophil function in MDS patients and may have a role of a risk factor for intestinal ulcers and thrombosis in BD (10).

A possible role of IFN-α or hydroxyurea treatment in patients with CML in the occurrence of BD has been reported (11-14). Our patient did not present any progression of the BD, although he was treated with hydroxyurea. However, it is difficult to suggest a possible relationship between BD and hydroxyurea, as it may be a coincidence, because both disorders act by changing the adhesion profile of neutrophils and monocytes. Increased serum level of INF-γ, IL-2, TNF-α, IL-6, and IL-8 by mononuclear cells were found in patients with BD and a few MDS patients with trisomy 8 (5, 12). CMML presents features of peripheral leukocytosis that have been attributed to abnormal adhesion. On the other hand, neutrophils and monocytes of patients with BD exhibit an increased adhesion to endothelial cells. Thus a patient with CMML and BD may present a neutrophil-rich inflammation that leads to thrombosis. Le Beau *et al*. reported a series of 63 patients with chemothe-rapy–related MDS, 97% of them carrying chromosomal abnormalities, 87% with abnormalities of chromosome 5 and/or 7 (15). Our patient, except for the trisomy 8 had also deletion of the long arm of chromosome 5[del (5) (q13q35)] and translocation of the long arm of chromosome 7 with the long arm of 15 [der(7)t(7;15)(q13;q?)], but he was never treated with immunosuppressive drugs. Therefore, the MDS in our patient is attributed to the multiple chromosomal abnormalities. The frequent appearance of trisomy 8 in patients affected by both BD and MDS could suggest that the chromosomal abnormalities predispose to the development of autoimmune disorders.

In the literature, there are 27 other cases of BD and MDS combined. The pre-sence of trisomy 8 has been reported in most of these cases (17/27), and one third of them (10/27) have presented gastrointestinal manifestations (7). The trisomy 8 and other complex chromosomal abnormalities detected in our patient could be due to CMLL but it is unclear if this implicates to manifestation of BD. In the literature, there is only one case with CMML and BD, that has already been reported, but

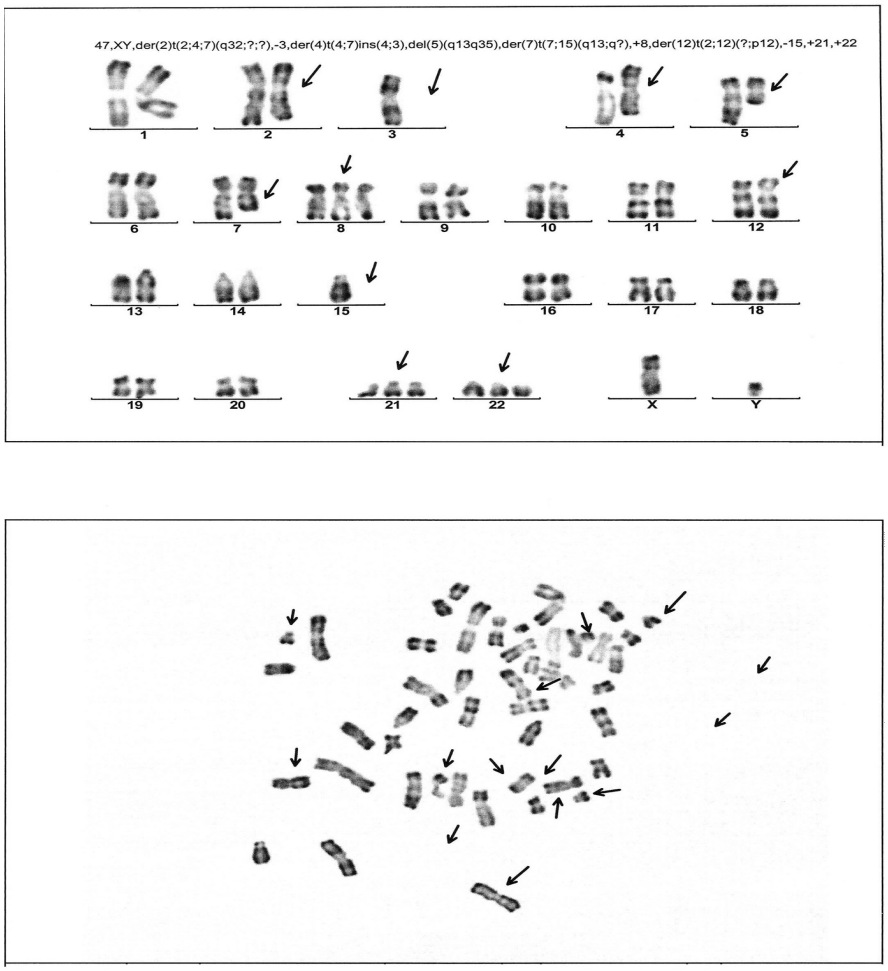

Fig. 1. RHG-banded Karyotype, which shows the trisomy 8 and the other chromosome abnormalities (arrows).

without trisomy 8 or gastrointestinal involvement (16).

In conclusion, the review of the literature shows that this is the first case of the coexistence of Behçet's disease with gastrointestinal involvement and CMML with trisomy 8, underlying the involvement of trisomy 8 in patients with combined BD and MDS.

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