Behçet’s disease, chronic myelomonocytic leukemia and trisomy 8

Behçet’s disease, is an inflammatory disease of unknown etiology with multisystem involvement and chronic course. In addition to the triad (recurrent oral and genital ulcers, and uveitis), it may exhibit involvement of other organs, but it is a rare hematologic commitment. Behçet’s disease association with myelodysplastic processes, although uncommon, has been previously described. We report the case of a patient with Behçet’s disease who developed thrombocytopenia and monocytosis. Trisomy 8 was found in karyotypic analysis and findings of myelodysplastic/myeloproliferative disease in the bone marrow. We discuss the relationship between trisomy 8, myelodysplastic syndrome and Behçet’s disease.

Keywords: Behçet’s disease • chronic myelomonocytic leukemia • myelodysplastic syndrome • trisomy 8

Case description

The case study is a 24-year-old woman with no past medical history of autoimmune or neoplastic disorder in the family. She had been symptomatic for the past 9 months (from August 2011) and had been admitted into another hospital; there she was presented with fatigue, subjective fever, and recurrent episodes of painful oral and genital ulceration, which healed over 10–14 days. The diagnosis of Behçet’s disease (BD) was made and the patient was treated with colchicine and corticosteroids.

As disease evolved, she developed pustular cutaneous lesions on the buttocks and anterior chest wall, as well as dysenteric diarrheal stools, thrombocytopenia and heavy vaginal bleeding. Thus, referral for rheumatologic consultation was necessary.

She first presented to our hospital in April 2012 to be assessed by the rheumatologist. In the initial evaluation, new oral and genital ulceration were recorded along with a positive result on pathergy testing (Figure 1), fever and abdominal pain.

A colonoscopy was performed due to gastrointestinal symptoms, which showed an ulcerated ileitis, as well as a colon biopsy, which ruled out inflammatory bowel disease. There were no ocular or neurologic manifestations.

Since admission to the hospital, the presence of severe and persistent thrombocytopenia and monocytosis was evident (Figure 2); bone marrow biopsy and cytogenetic analysis was necessary to rule out associated myelodysplastic syndromes (MDS).

B51 was absent in HLA typing. Cytogenetic analysis reported trisomy 8 and bone marrow biopsy demonstrated features of myelodysplastic/myeloproliferative malignancy compatible with chronic myelomonocytic leukemia (Figure 3). In addition to the presence of thrombocytopenia and karyotype of high risk, hemoglobin less than 10 g/dl (which remained between 7 and 8.9 g/dl throughout hospitalization) and peripheral blood blasts were noted as poor prognostic factors.

Further to this, during hospitalization, saphenous vein thrombosis and pulmonary thromboembolism was documented. Therapy to the patient began with decitabine, but she developed febrile
neutropenic colitis and bowel perforation with peritonitis. She died at 20 days of the initial chemotherapy cycle, secondary to septic shock and multiorgan system failure.

Discussion
BD, described in 1937 by Hulusi Behcet [1,2], is an inflammatory disease of unknown etiology with multisystem involvement and chronic course, included by some authors in the group of vasculitis, since it can affect vessels of different types and sizes [3,4], and among autoinflammatory syndromes by others [5].

Although more common in the countries of the eastern shore of the Mediterranean, the Middle East and East Asia, it has a worldwide distribution [1,4,6]. In addition to the triad (recurrent oral and genital ulcers, and uveitis), BD can exhibit characteristic

![Figure 1. Oral and genital ulceration. Pustular cutaneous lesions on buttocks. Positive pathergy testing.](image)

![Figure 2. Leukocyte/monocyte tendency and platelet count (persistent thrombocytopenia and monocytosis).](image)
skin lesions, as well as pulmonary, cardiovascular, musculoskeletal, gastrointestinal and neurologic involvement [1,6–9].

Even though hematologic involvement is not commonly seen, there are few case reports of neutropenia and thrombocytopenia according to the literature [10,11]. Thus, in patients with BD who present with leukopenia or thrombocytopenia, an underlying hematologic disorder should be suspected.

MDS are a heterogeneous group of stem cell disorders characterized by multilineage dysplasia and refractory chronic hemocytopenias due to ineffective hematopoiesis where there is risk of infection, hemorrhage and leukemic transformation [12,13]. In many cases, underlying cytogenetic abnormalities exist, including trisomy 8 (10–20%) [13–15].

BD, in association with myelodysplastic processes, although uncommon, has been previously described [16–19]. In our series, we had a case report of hypereosinophilic syndrome associated to inferior vena cava thrombosis and CNS hemorrhage, but no MDS cases were found [20].

In a study of 1769 patients with BD, 32 (1.8%) developed malignancy, with MDS being the most frequent (21%), followed by thyroid carcinoma [21]. Since 1988, there have been reported in the literature more than 65 cases of BD with MDS, most commonly from Japan, in relation to the geographical distribution of the disease [16,22]. A study comparing patients with BD and MDS in relation to BD alone, found that patients with both diseases had a lower frequency of ocular disease (11.1 vs 69.1%), cutaneous manifestations (75.55 vs 87.1%) and HLA-B51 (36.7 vs 54.9%). On the other hand, they had a higher prevalence of gastrointestinal disease (67.95 vs 15.5%), and a positive result on pathergy testing.

The simultaneous presentation of BD and MDS occurs in 49% of cases, and 31.4% before MDS diagnosis [22,23]. Overall, there is a slight predominance of the disease in women (ratio: 0.8) [22]. Regarding the age of presentation, BD with MDS appears to have two peaks of incidence: one in the third decade of life, predominantly affecting women, and the other in the sixth decade with male preponderance [22]. In patients over 50 years, MDS can precede or present simultaneously with BD, indicating a para-neoplastic behavior. By contrast, young people have the tendency to manifest BD before MDS, suggesting that, in these cases, the MDS is associated with the course of BD [22].

Mortality is significantly higher in patients who develop the disease in the sixth decade of life compared with patients with onset in the third decade (40 vs 6.3%) [22].

The MDS subtypes, in most cases, correspond to refractory anemia (65%), followed by refractory anemia with excess blasts, and refractory anemia with ringed sideroblasts (14 and 7%, respectively), with refractory anemia with excess blasts in transformation and chronic myelomonocytic leukemia being less frequent [22–27].

Together with the present case, there have been only three case reports of BD with chronic myelomonocytic leukemia reported in the literature [28,29]. There was one case without trisomy 8: a 67-year-old man who presented with fever, penile and groin painless ulcers, as well as oral and esophageal ulcerations [29]. As in our case, he had no uveitis or CNS abnormalities. The other case, a 68-year-old man with fever, recurrent aphthous stomatitis, painless genital ulceration, vein thrombosis of the left calf, ulcers in the stomach, the ileocecal region, the ascending, the transversal and the sigmoid colon and trisomy 8, was most similar to our patient, except for the presence of deletion of the long arm of chromosome 5 and translocation of the long arm of chromosome 7 with the long arm of 15. Unlike other cases, our patient was female and younger.

Eder et al. analyzed the cases reported in the literature until 2005 [30]. The majority of the patients had oral and genital ulcers, gastrointestinal symptoms, fever and skin lesions, as was the case in our patient. They observe that the percentage of patients...
with trisomy 8 in MDS patients with BD is markedly higher than in patients with MDS alone \[30\].

The trisomy 8 chromosome abnormality is the most frequently seen in patients with BD and MDS (78–87%) \[22\]; trisomies 9 (13%) and 15 (8.8%) \[22\] have also been described. Kimura and colleagues found that trisomy 8 in BD represents a risk factor for intestinal ulcers and thrombosis \[28\]. They also noted that MDS patients from Japan who were younger, with less blast count and trisomy 8 were at increased risk of associated intestinal BD \[31\]. It has also been described in children the relationship between the presence of trisomy 8 and BD, but the strong relationship with gastrointestinal involvement and development of myelodysplastic syndrome as found in adults is apparently not observed \[32\].

The high frequency of trisomy 8 in these patients has led some authors to suggest a role of this chromosomal abnormality in the pathogenesis of the disease. According to them, trisomy 8 found on granulocytes, lymphocytes and monocytes may induce cytokine production in different tissues \[18\]. Some inflammatory cytokines are increased in the serum of BD patients. Cytokines, such as TNF-\(\alpha\), have also been observed in bone marrow findings of some patients with myelodysplasia, therefore suggesting a common pathway between the two diseases, involving Th-1 cytokines (TNF-\(\alpha\) and interferon). Reactive oxygen species (expressed in neutrophils from patients with BD and in bone marrow findings of some patients with MDS), have been linked to the pathogenesis of both diseases, without this relationship being completely defined \[16,22,23\]. We did not measure cytokines and reactive oxygen species in our patient; this could be a limitation because the increase has been described in BD-like symptoms in MDS cases.

Treatment of patients with BD and MDS consists of corticosteroids and oral colchicine for BD, less often cyclosporin A, and bone marrow transplantation for MDS. Nonetheless, control of symptoms with corticosteroids and immunosuppressive agents is difficult in the treatment of BD in the context of MDS, and many patients die due to infection, hemorrhage or severe recurrent gastrointestinal ulcers before definite management of MDS. Some authors consider cell transplantation promptly in severe disease \[22,23,33–35\] since immunoablation may be insufficient, requiring the elimination of abnormal myelodysplastic clones.

**Conclusion**

The case we report illustrates the clinical features described in the literature: patients with BD and MDS with trisomy 8 (ileocecal ulcers, elevated acute-phase reactants and thrombosis). Trisomy 8 found in BD, makes it different or special regarding the possibility of a MDS or for the severity of clinical manifestation. This is one of the few cases reported in the literature of myelomonocytic leukemia, BD and trisomy 8.

**Future perspective**

Trisomy 8 found in BD makes it different. In the future, it may be useful to determine the karyotype in this patient group to foresee the development of complications.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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**Informed consent disclosure**

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

**Executive summary**

- Behçet’s disease (BD) is included by some authors in the group of vasculitis since it can affect vessels of different types and sizes, as well as among autoinflammatory syndromes by others.
- In patients with BD who present with leukopenia or thrombocytopenia, an underlying hematologic disorder should be suspected.
- Myelodysplastic syndromes (MDS) are a heterogeneous group of stem cell disorders characterized by multilineage dysplasia and refractory chronic hemocytopenias. In many cases, there exist underlying cytogenetic abnormalities, including trisomy 8 (10–20%).
- BD association with myelodysplastic processes, although uncommon, has been previously described.
- The percentage of trisomy 8 in MDS associated to BD is greater than in single MDS. This chromosome abnormality is the most frequently seen in patients with BD and MDS (78–87%).
References

Papers of special note have been highlighted as:
- of interest; • of considerable interest

Suggests that allogeneic hematopoietic stem cell transplantation may be an effective therapy in patients with high-risk aggressive Behçet’s disease.
