**Case report**

**Behçet’s disease, myelodysplastic syndrome, trisomy 8, gastroenterological involvement – An association**

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**ABSTRACT**

Only a limited number of cases of Behçet’s disease and hematological malignancies have been reported in the literature. We report the case of a 45 year old female patient with Behçet’s disease who developed myelodysplastic syndrome, refractory anemia with excess blasts in transformation subtype, with complex chromosomal abnormalities, including excess of chromosome 8, following several years of treatment with chlorambucil for Behçet’s disease. As has been described in most such cases, gastrointestinal involvement was most prominent. This case is described and the occurrence of myelodysplastic syndrome in Behçet’s disease reviewed.

**Introduction**

Behçet’s disease is an inflammatory disorder of unknown etiology, characterized by recurrent oral and genital ulceration, arthritis, ophthalmic and skin lesions. Involvement of the intestines, central nervous system, other visceral organs and vascular system can also occur (1). In addition to colchicine and low dose steroids, Behçet’s disease patients are often treated with immunosuppressive therapy, such as azathioprine, and occasionally drugs like chlorambucil and cyclosporine A. Current therapy options also include alpha-interferon and anti-TNF agents (2-3).

Only a limited number of cases of Behçet’s disease and hematological malignancies, all lymphomas, have been reported in the literature (4-8), except for an unlikely cluster of patients with an association of myelodysplastic syndrome (MDS) and Behçet’s disease. We present the case of a patient with Behçet’s disease who developed myelodysplastic syndrome which evolved to secondary acute leukemia following immunosuppressive treatment, review the literature and discuss the relevant issues.

**Case report**

A 45 year old female patient, first presented to the rheumatology clinic in 1995 with persistent arthritis of both ankles and knees as well as erythema nodosum. She reported rheumatic symptoms on and off for 15 years, but no details or medical records were available. An evaluation of her arthritis, including evaluation of inflammatory bowel disease was unrevealing. She was treated with low dose steroids, hydroxychloroquine and colchicine. The symptoms were controlled with this regimen.

In January 1997, while under therapy, the patient presented with a flare of her disease: oral and genital ulceration, erythema nodosum and disabling arthritis of multiple upper and lower extremity joints. The cardiovascular, respiratory, abdominal and ophthalmologic examinations were unremarkable. Initial laboratory work revealed antinuclear antibodies, rheumatoid factor negative; C3 and C4 normal. A pathergy test was not performed.

The diagnosis of Behçet’s disease was made (9) and the patient treated with increased steroids. Attempts at treatment with methotrexate, sulfasalazine, cyclosporine A and azathioprine failed due to adverse reactions. As the patient continued to suffer from non-scarring, intractable oral and genital ulcers and arthritis and required high dose steroids for control, treatment with chlorambucil 4 mg per day was initiated.

From 1998 to the end of 2003 her disease was managed in the community and controlled under a regimen of chlorambucil 4 mg/d, colchicine 1 mg/d
and prednisone 15 mg/d. Repeated blood counts were normal. In September 2003, treatment with colchicine and chlorambucil was withdrawn due to pancytopenia. The patient was asymptomatic at that time. The course of her disease, laboratory tests and treatments from this point are summarized in Table I. The patient returned to the hospital 2 weeks later with an upper respiratory tract infection. Her temperature was normal. The blood count showed persistent pancytopenia. Chest and sinus X rays were interpreted as normal. Antibiotic treatment with cefuroxime was started. Two weeks later the patient was admitted to the hospital suffering from severe watery diarrhea, abdominal pain and fever, 38°C, still under prednisone 20 mg/d. Abdominal and chest X ray were interpreted as normal. Stool culture grew Campylobacter jejuni. The patient was treated with azithromycin with relief of her symptoms and fever. A week later, while still under treatment, her condition deteriorated with profuse watery diarrhea and abdominal pain, this time accompanied by polyarthritis and oral and genital ulceration with a fever of 39°C. Laboratory work revealed worsening of pancytopenia, hypokalemia, hypoalbuminemia, CRP-494 mg/l (normal less than 6 mg/ml) and positive occult blood in the stool. Small bowel series showed multiple filling defects in the ileum, suggestive of ulceration. Due to her poor general condition an endoscopic evaluation was not performed. A bone marrow aspiration and biopsy established the diagnosis of myelodysplastic syndrome, FAB subtype-refractory anemia with excess of blasts.

Treatment with broad spectrum antibiotics, piperacillin-tazobactam, gentamicin, metronidazole later replaced by meropenem, vancomycin, and amphotericin B was ineffective. She was resuscitated with IV fluids, electrolyte replacement and blood transfusions. All blood, urine and stool cultures were negative for bacteria, viruses and parasites. As the patient’s condition continued to deteriorate under the treatment, her symptoms could be attributed to a flare of Behçet’s disease, possibly related to progressing MDS. She was treated with intravenous pulse methylprednisolone 1 gr/d with only transient improvement in her condition. A short term trial of treatment with infliximab also failed. A second bone marrow biopsy was interpreted as Refractory Anemia (RA) with excess of blasts, in transformation to acute leukemia. Bone marrow chromosome analysis showed complex chromosomal abnormalities: 55,XX,-5q-,+i(8q),+i(8q),+11,+13,+14,+19,+22,+X,+dm. Due to her poor general condition and uncontrolled Behçet’s disease she was not felt to be a candidate for chemotherapy treatment for her progressing MDS. Despite intensive treatment the patient’s condition deteriorated and she died with multi-organ system failure.

**Discussion**

The association of Behçet’s disease with malignancies has rarely been reported, and even less so with hematolo-

**Table I. Summary of the patient’s terminal illness.**

<table>
<thead>
<tr>
<th>Clinical picture</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>30/9/2003 Asymptomatic pancytopenia (Hb 9, WBC 2.5, PLT76)*</td>
<td>Colchicine and chlorambucil stopped</td>
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<td>↓</td>
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<tr>
<td>13/10/2003 Upper respiratory tract infection</td>
<td>Cefuroxime Tx</td>
</tr>
<tr>
<td>Pancytopenia (Hb 8.8, WBC 2.1, PLT90)</td>
<td>Observation</td>
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<tr>
<td>Sinus and chest x-ray normal</td>
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<tr>
<td>3/11/2003 GI symptoms, fever</td>
<td>Azythromycin Tx</td>
</tr>
<tr>
<td>Pancytopenia (Hb 7.6, WBC 3, PLT30)</td>
<td>Prednisone dose increased</td>
</tr>
<tr>
<td>Stool culture – C. jejuni</td>
<td></td>
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<td>↓</td>
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<tr>
<td>10/11/2003 GI symptoms, fever, arthritis, oral and genital ulcers</td>
<td>Pipracillin-tazobactam</td>
</tr>
<tr>
<td>Pancytopenia + electrolyte abnormalities</td>
<td>+ gentamicin + metronidazol</td>
</tr>
<tr>
<td>Small bowel passage – filling defects</td>
<td>Vancomycin + meropenem + Ampho B</td>
</tr>
<tr>
<td>Bone marrow biopsy – RAEB</td>
<td>IVpulse steroids</td>
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<tr>
<td>20/11/2003 No response</td>
<td>IVsteroids, IVinfliximab</td>
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<tr>
<td>Blood, urine, stool cultures – negative</td>
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<tr>
<td>5/12/2003 Clinical and laboratory deterioration</td>
<td>Blood products and supportive care</td>
</tr>
<tr>
<td>Bone marrow biopsy – RAEB-t</td>
<td></td>
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<tr>
<td>20/12/2003 Patient died with multi-organ system failure.</td>
<td></td>
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</tbody>
</table>

*WBC x 10⁹/L; Hb in mg/dL; PLT x 10⁹/L.
gical malignancies. We present a case of Behçet’s disease in association with MDS in transformation to acute leukemia, which raises a number of issues: the relationship of MDS to Behçet’s disease and the role of gastrointestinal involvement and chromosome abnormalities there in.

The association of MDS and immunological abnormality disorder has been well described in the literature. Clinical manifestations of such phenomena may include systemic vasculitic syndrome, skin vasculitis, fever, arthritis, inflammatory bowel disease and even classical connective tissue disorders (10). The prevalence of these manifestations among MDS patients has been estimated at between 10-18.5% (11-12). MDS associated with vasculitis has been reported to affect mostly cutaneous vessels or joints. The literature also includes case reports on Takayasu’s arteritis (13), Henoch-Schonlein purpura (14) and other vasculitic syndromes.

The association between malignant diseases and Behçet’s disease has not been widely investigated. The present literature suggests an increased risk of malignancies in connective tissue diseases, with a more marked increment in dermatomyositis and mixed connective tissue disease and a slight increase in systemic lupus erythematosus, rheumatoid arthritis and polymyositis reported (15-17). The autoimmune nature of the diseases and the immunosuppressive drugs used in their management are regarded as underlying this association. In reference to Behçet’s disease and malignancy the literature is sparse. Cengiz et al. reported on 13 patients with only 3 of the patients having hematological malignancies (18).

Notably, most of the cases of Behçet’s disease and hematological malignancy reported in the literature are of MDS. Until now, 26 patients with this association have been reported in the literature (19-38). Their main clinical and laboratory findings are summarized in Table II together with those of the current study patient. Most of the patients reported are from Japan. Their median age is 45 years, range 10-74. The majority of the patients had oral and genital ulcers, gastrointestinal (GI) symptoms, fever and skin lesions. Eye lesions and arthritis were infrequently reported. MDS was diagnosed before or concomitantly with Behçet’s in most of the patients. Only one patient whose MDS was diagnosed after Behçet’s disease received immunosuppressive (chlorambucil and cyclosporine) treatment before the diagnosis.

Whereas trisomy 8 has been the most common chromosomal abnormality reported in MDS associated with Behçet’s disease, 18 out of 23 patients investigated, its reported incidence is only 10-20% among untreated general MDS patients with chromosomal abnormalities (39). Thus the percentage of trisomy 8 in MDS patients with Behçet’s disease is markedly higher than in patients with MDS alone. In addition considering the high frequency of trisomy 8 in this setting with associated GI manifestations, Shinya et al. suggested that trisomy 8 might predispose patients with MDS and Behçet’s disease to intestinal ulceration (33).

GI involvement of Behçet’s disease typically affects the ileocecal region and colon. The frequency of GI involvement varies in different countries, with a lower frequency in Israel (14-25%) (40) as compared to Japan (50-60%) (41). Our patient’s severe GI involvement, unusual for her locale, dovetails well with the patients reviewed in the literature who had prominent GI symptoms when MDS was present with Behçet’s disease.

Although the relationship between trisomy 8 and GI manifestations of Behçet’s disease is reported frequently in the literature, as stated above, the mechanism of this relationship remains unclear. Shinya suggested that the presence of trisomy 8 facilitates cytokine production in both lymphocytes and supporting tissues and that their elevated level may result in the findings (33). Another proposed mechanism related to an increase in reactive oxygen species (ROS) production. In Behçet’s disease there is increased production of ROS by activated neutrophils and these functions may be increased in the subgroup of MDS patients with trisomy 8 and thus may play an important role in the complications associated with Behçet’s disease and MDS (26).

A relationship between malignancies and immunosuppressive treatment in rheumatic diseases has been demonstrated in studies (42). Specifically an increased risk of malignancies of the immune system, lymphoma and multiple myeloma, has been observed in rheumatic disease patients treated with azathioprine as compared to untreated patients (43). Other studies, have observed an increased risk of leukemia in rheumatoid arthritis patients treated with chlorambucil (44). A causal relationship between alkylating agents, such as chlorambucil and secondary malignancies, in general, is well established (45). These agents form DNA cross links that interfere with replication, repair and translation of DNA and may thus be mutagenic.

There is evidence in the literature that the use of immunosuppressive drugs is associated both with chromosomal abnormalities as well as with myelodysplastic syndrome (47-48). Le Beau et al. reported a series of patients with therapy-related MDS, 97% of them demonstrating chromosomal abnormalities, 87% with abnormalities of chromosome 5 and/or 7 (48). Our patient also had deletion of the long arm of chromosome 5 (del 5q). It has been suggested that the cytogenetic abnormalities induced by the drugs are more important than the mere prolonged use of immunosuppressive therapy in the pathogenesis of MDS. Due to the complex chromosomal abnormalities in our patient it is not possible to infer clear causality between the immunosuppressive therapy and development of MDS in the present case.

In summary, we present a case of a woman with Behçet’s disease who developed pancytopenia, diagnosed as MDS, after immunosuppressive treatment of her underlying condition. Cytopenias are common in patients with rheumatic diseases and may be the consequence of varying etiologies. Prior immunosuppressive treatment should raise the possibility of evolving secondary hematological malignancy. In Behçet’s disease, the peculiar association with MDS, trisomy 8 and gastrointestinal involvement is highlighted.
References


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