Trisomy-8-Positive Hematologic Malignancies Associated with Intestinal Behçet's Syndrome: Keep This Entity in Mind

Ayşe Salihoglu Teoman Soysal

Division of Hematology, Department of Internal Medicine, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey

Keywords

Trisomy · Behçet's syndrome · Hematologic malignancy

Behçet's syndrome (BS), a multisystem vasculitis first defined by Hulusi Behçet in the 1930s, is characterized by recurrent oral and genital ulcerations, eye and skin lesions, and ocular, vascular, gastrointestinal, and nervous system involvement with positive skin pathergy test. It is mainly seen along the ancient Silk Road expanding from the Mediterranean Sea to the Far East. The prevalence of gastrointestinal tract involvement varies from 3 to 25% and has a distinct geographical variation. There are typically ulcerations in the ileocecal area [1]. Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders presenting with ineffective hematopoiesis, increased bone marrow cellularity, myeloid lineage dysplasia, and peripheral cytopenia with an increased risk of developing acute myeloid leukemia. MDS can have overlapping features with myeloproliferative neoplasms (MPN). Trisomy 8 has a frequency of 10–15% in MDS/MPN patients, and its isolated form is included in the MDS intermediate cytogenetic risk group. There is an established report describing MDS patients with trisomy 8 associated with BS involving the gastrointestinal tract [2]. BS can occur at the same time, before, or after MDS diagnosis. The pathogenesis of the relationship between MDS, BS, and

trisomy 8 may include several mechanisms. The high cytokine stimuli in BS may contribute to the development of MDS. Trisomy 8 may play an important role in its pathogenesis, and its presence results in overexpression of several cytokine genes. The production of proinflammatory cytokines and reactive oxygen species may be the cause of intestinal ulcers.

In the current issue of *Acta Haematologica*, Narazaki et al. [3] report a patient diagnosed with trisomy-8-positive primary myelofibrosis (PMF) and intestinal BS, highlighting the previously reported association of MDS with trisomy 8 and BS in other groups. The patient was diagnosed with Janus-kinase-2 positive PMF and was commenced on ruxolitinib. After 2 years, BS symptoms, including fever and ulcers in the terminal ileum, occurred. She experienced 2 episodes of intestinal perforation while on ruxolitinib. Following discontinuation of ruxolitinib, further BS symptoms, namely uveitis and recurrent oral aphthous ulcers, developed. Steroid therapy was initiated. Following a short duration of remission, the patient experienced the third episode of intestinal perforation resulting in short bowel syndrome. Azathioprine and infliximab provided control of BS symptoms. Trisomy 8 is also one of the most common cytogenetic abnormalities observed in MPN patients including PMF. The reported case of PMF associated with trisomy 8 and this particular phenotype of ulcerative digestive disease provides valuable information.

BS associated with underlying trisomy-8-positive MDS frequently does not fulfill usual diagnostic criteria and forms a distinct subset of patients. Ocular involvement is of low frequency, and HLA-B51 positivity has a lower rate. In contrast, ulcerative gastrointestinal involvement is quite common. Clinical presentation of the intestinal involvement is similar to Crohn's disease, and patients present with symptoms including fever, abdominal pain, weight loss, diarrhea, or intestinal hemorrhage. Intestinal lesions are mostly located in the ileocecal region and deep in the small intestine. Histologic findings of biopsy specimens often indicate chronic active inflammation with or without vasculitis [4]. Intestinal involvement can result in perforation, and intestinal surgery may be required as in the reported case.

Isolated trisomy 8 in the absence of morphological criteria in the bone marrow is not considered definitive evidence of MDS. This is in part because trisomy 8 can be a constitutional condition. Chromosome analyses of peripheral blood lymphocytes and nonhematological cells, such as skin fibroblasts or oral mucosa cells, reveal that some of the cells have 3 copies while other cells have the usual 2 copies of chromosome 8. Constitutional trisomy 8 mosaicism (CT8M), also known as Warkany syndrome, is reported in 1/25.000 to 1/50.000 live births and has physical stigmata, including abnormal pigmentation and facial abnormalities. Patients usually have mild intellectual deficits, and joint, urinary, cardiac, and skeletal anomalies. Hematologic malignancies and BS have been reported in CT8M. In the presence of the aforementioned abnormalities and trisomy 8, one may suspect CT8M [5]. Trisomy 8 as the acquired condition occurs in hematological disorders, especially MDS, and is restricted to malignant cells. It can be either isolated or associated with other chromosomal anomalies.

In conclusion, the association of BS with underlying trisomy-8-positive MDS/MPN leads to an intersection

between hematologists, rheumatologists, and gastroenterologists. Clinicians must maintain a high index of suspicion for this entity. Although BS is less prevalent in Europe and the USA, increased recognition of the symptoms and migration from prevalent countries have led to an increased frequency of the syndrome. Patients with this entity have distinct features compared to general BS or MDS/MPN populations. Gastrointestinal involvement is very common. Symptoms regarding the gastrointestinal system and concomitant cytopenia may raise suspicion of this entity. Administration of immunosuppressive agents (prednisolone, cyclosporine A, and TNF- α inhibitors) is mostly not sufficient to completely control BS. Relapse and serious comorbidities, including intestinal perforation and massive bleeding, often occur during the course of refractory BS. Treatment of the underlying hematological condition should be considered. Patients undergoing allogeneic hematopoietic stem cell transplantation for hematological conditions may achieve complete remission of both BS and gastrointestinal symptoms after transplantation, and selected patients should be offered this treatment option [6].

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

We did not receive any funding.

Author Contributions

Both of the authors contributed equally to the editorial comment.

References

- 1 Esatoglu SN, Kutlubay Z, Ucar D, Hatemi I, Uygunoglu U, Siva A, et al. Behçet's syndrome: providing integrated care. *J Multidiscip Healthc*. 2017 Aug;10:309–19.
- 2 Ahn JK, Cha HS, Koh EM, Kim SH, Kim YG, Lee CK, et al. Behçet's disease associated with bone marrow failure in Korean patients: clinical characteristics and the association of intestinal ulceration and trisomy 8. *Rheumatology (Oxford)*. 2008 Aug;47(8):1228–30.
- 3 Narazaki T, Shiratsuchi M, Tsuda M, Tsukamoto Y, Muta H, Masuda T, et al. Intestinal Behçet's disease with primary myelofibrosis involving trisomy 8. *Acta Haematol*. 2019, DOI: 10.1159/000501019.
- 4 Esatoglu SN, Hatemi G, Salihoglu A, Hatemi I, Soysal T, Celik AF. A reappraisal of the association between Behçet's disease, myelodysplastic syndrome and the presence of trisomy 8: a systematic literature review. *Clin Exp Rheumatol*. 2015 Nov-Dec;33(6 Suppl 94):S145–51.
- 5 Saumell S, Solé F, Arenillas L, Montoro J, Valcárcel D, Pedro C, et al. Trisomy 8, a Cytogenetic Abnormality in Myelodysplastic Syndromes, Is Constitutional or Not? *PLoS One*. 2015 Jun;10(6):e0129375.
- 6 Soysal T, Salihoglu A, Esatoglu SN, Gültürk E, Eşkazan AE, Hatemi G, et al. Bone marrow transplantation for Behçet's disease: a case report and systematic review of the literature. *Rheumatology (Oxford)*. 2014 Jun;53(6):1136–41.