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Concise report

Bone marrow transplantation for Behçet's disease: a case report and systematic review of the literature

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Abstract

Objectives. Behçet's disease (BD) can be life threatening and may be refractory to corticosteroids and immunosuppressives. There has been some experience with haematopoietic stem cell transplantation (HSCT) in BD either for severe, refractory disease or for a haematological condition. The objectives of this study were to describe a BD patient undergoing HSCT and to evaluate the outcomes of BD patients who underwent HSCT.

Methods. We report a BD patient with refractory gastrointestinal (GI) involvement who had HSCT for concomitant myelodysplastic syndrome (MDS). We also performed a systematic literature search regarding HSCT for either refractory disease or concomitant haematological conditions in BD patients.

Results. A 30-year-old woman with refractory GI BD involvement with trisomy 8 MDS underwent a successful myeloablative allogeneic HSCT resulting in complete resolution of both BD and MDS. Additionally we identified 14 manuscripts providing data on 19 patients with BD who had HSCT. Among these 20 patients, including ours, refractory disease was the indication of transplantation in 9, while 11 patients were transplanted because of accompanying haematological conditions. Transplant indications for the nine patients (four male, five female) with refractory BD were neurological involvement in five, pulmonary artery aneurysm in two, GI disease in one and not reported in one patient. Three patients with neurological disease, both patients with pulmonary artery aneurysm and the patient with intestinal involvement achieved complete remission of their disease. Six patients transplanted for haematological conditions, including the presented case, also had GI involvement of BD. All of these patients achieved complete remission of GI findings after HSCT.

Conclusion. When considering HSCT, the potential adverse events and complications, which can be fatal, need to be kept in mind.

Key words: Behçet's syndrome, Behçet's disease, refractory autoimmune disease, haematopoietic stem cell transplantation, blood stem cell transplantation, myelodysplastic syndrome.

CLINICAL SICENCE

Introduction

Behçet's disease (BD) is a condition of unknown aetiology with different proposed pathogenetic pathways underlying various clinical presentations. It involves the skin, mucosa and joints, causing oral ulcers, genital ulcers, nodular lesions, papulopustular lesions and pathergy phenomenon as well as serious organ involvement including the eyes, vascular system, nervous system and the gastrointestinal (GI) system. The pattern of disease expression of BD might differ among different locations,

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with fewer cases of intestinal disease in the Mediterranean region. Intestinal disease is most common among patients in the Far East, particularly in Japan [1].

BD is usually treated with colchicine when the main problem is mucocutaneous disease or arthritis. When there is serious organ involvement, immunosuppressives, biologic agents and corticosteroids may be required, zdepending on the severity of the disease. There may be occasional patients who may be refractory to all of these measures [2, 3].

Haematopoietic stem cell transplantation (HSCT) has been used in the treatment of severe autoimmune and inflammatory conditions unresponsive to approved therapies, most commonly multiple sclerosis, systemic sclerosis, SLE, RA, JIA, Crohn's disease and haematological immune cytopenia [4, 5]. Encouraging results are reported especially in SLE, multiple sclerosis and systemic sclerosis patients who were refractory to conventional treatment modalities [6, 7]. In BD, HSCT has been reported in a number of case reports, performed either for refractory BD or accompanying haematological conditions [8].

In this report we aim to describe a case of GI BD with trisomy 8–positive myelodysplastic syndrome (MDS) refractory anaemia with excess blasts type 2 (RAEB-2) undergoing a successful myeloablative allogeneic transplantation resulting in complete remission of both BD and MDS. We also review all published data on patients with BD who have undergone HSCT for either refractory disease or concomitant haematological conditions, with special emphasis on the outcome regarding efficacy in BD manifestations and safety.

Materials and methods

Our multidisciplinary BD outpatient clinic has >9000 recorded patients. We report here a BD patient who had HSCT due to MDS, but who also had severe GI involvement refractory to treatment with immunosuppressives, corticosteroids and biologic agents. Informed consent was obtained from the patient to report her findings.

We performed a systematic literature search in PubMed using the terms Behçet's syndrome OR BD OR refractory autoimmune disease AND HSCT OR blood stem cell transplantation OR myelodysplastic syndrome. We retrieved 323 articles published in English in PubMed through March 2013. Articles not reporting on BD patients ($n = 249$) and on transplanted BD patients ($n = 31$) were excluded after reading the title and abstract. Three articles that were duplicates and 25 articles that did not report transplanted BD patients were excluded after reading the full text. The full text of one article was not available. The remaining 14 articles were analysed (Fig. 1).

Results

Case report

In September 2006, a 25-year-old woman without any previous diagnosis was admitted to the hospital for fever, nausea, vomiting and diarrhoea that had started in the preceding 3 months. On physical examination she was pale with mild abdominal tenderness in the periumbilical region. On laboratory examination she had macrocytic anaemia. Colonoscopy revealed multiple, deep and round ulcers, 5–20 mm in diameter, with clearly demarcated margins, in the right side of the colon and also in the splenic flexure and rectum. Biopsy results showed moderately active colitis without granulomas. Contrast-enhanced CT demonstrated mural thickening of the terminal ileum. Further review of the medical history revealed a 4-year history of recurrent oral and genital ulcers and arthralgia. Intestinal BD was diagnosed based on these findings. Her complaints resolved after treatment with methylprednisolone and AZA. In May 2007 she presented with pancytopenia. Despite discontinuation of AZA, pancytopenia persisted. Bone marrow biopsy and aspiration revealed normocellular marrow with dysplasia. Conventional cytogenetic analysis of the bone marrow showed a composite karyotype including trisomy 8, 9 and 19. Close follow-up and re-evaluation of the marrow in case of complete blood count changes were planned. The GI symptoms of the patient progressed and infliximab was initiated.

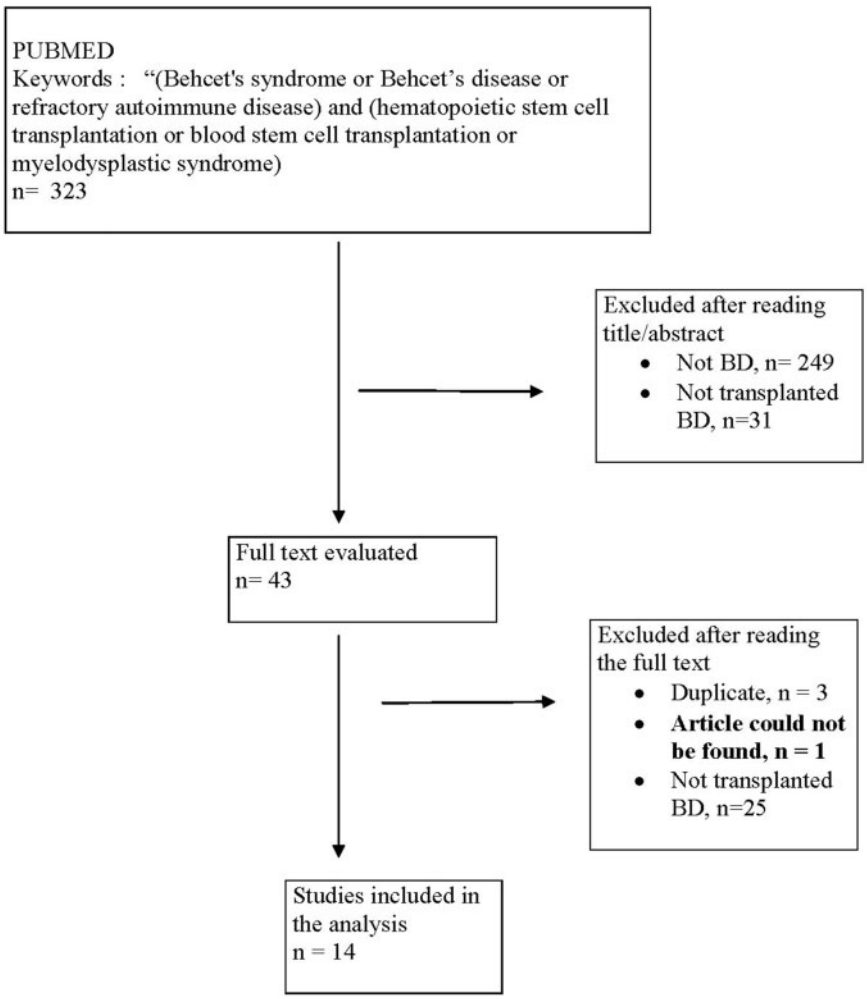
The patient remained symptom free for 1 year. In December 2009 intestinal symptoms worsened while on infliximab. Treatment was switched to adalimumab, however, her fever and abdominal pain continued. Erythema nodosum-like lesions appeared. She was considered refractory to adalimumab and methylprednisolone was added. In March 2011 the thrombocytopenia and anaemia worsened. Thalidomide was initiated. In April 2011 her GI symptoms and cytopenias worsened. The repeated bone marrow examination was consistent with MDS/RAEB 2. In July 2011 we decided to proceed with myeloablative allogeneic transplantation, taking into account the availability of a 6/6 HLA-matched sibling donor. Cholestatic liver disease developed after 6 months of transplantation while tapering ciclosporin, but was self-limited. The transplantation was successful, resulting in complete remission of MDS/RAEB 2. A control colonoscopy performed 8 months after transplantation appeared completely normal. Twenty months after transplantation the patient is in good general condition without any symptoms of BD and complete blood count parameters are within the normal ranges without any medications.

Systematic literature review

In the 14 reported studies, data on 20 HSCT procedures (9 autologous [9–15], 5 allogeneic [16–19], 3 cord blood [20–22], 3 not defined [16, 23]) performed in 19 BD patients (11 female and 8 male) were provided. One patient who was transplanted for refractory BD had first autologous (ASCT) and later allogeneic stem cell transplantation (allo-SCT) [9, 17]. Demographic findings, clinical features, treatment modalities and outcomes of these patients, including our patient, are summarized in the Table 1.

The mean age at diagnosis of BD was 29.5 years (range 4–54). The mean interval between BD diagnosis and transplantation was 48.3 months (range 3–120). The mean follow-up of the reported patients after transplantation

FIG. 1 Systematic literature search in PubMed



Depiction of the flow of articles through the PubMed search and screening process.

was 34.2 months (range 2–78). The previously used medications were AZA in four patients [11, 12, 14, 23], ciclosporin in three [11, 14, 23], infliximab in three [11, 14, 17] , CYC in seven [9–12, 14, 17] and not specified in two [16] (Table 1). Among the 20 patients including our case, the indication for transplantation was refractory BD in 9 [9–13, 17, 18] and accompanying haematological disorders in 11 [14, 16, 19–23].

Outcome in patients transplanted for refractory BD

Among the nine patients who received 10 HSCT procedures (8 autologous and 2 allogeneic) for refractory BD, five were transplanted for neurological involvement [9, 12, 13, 17], two were transplanted for pulmonary artery aneurysms, including one patient with concomitant intracardiac thrombosis [10], and one was transplanted for GI involvement [11]. Among the 11 patients who had HSCT for haematological conditions, 7 patients also had severe BD involvement, 6 in the GI tract [16, 20, 21] and 1 in the eyes [14].

Among the five patients who were transplanted for refractory neurological involvement, three were reported to have complete remission without relapses during a mean follow-up of 44 months [12, 13]. One remained refractory to autologous HSCT and underwent allo-SCT but relapsed after remission for approximately 2 years [9, 17]. One did not achieve remission after HSCT [12]. Two patients with refractory pulmonary artery aneurysms had complete remission of aneurysms. However, one of the patients continued to have mucocutaneous lesions after transplantation [15]. The patient who was transplanted for refractory GI involvement also had complete remission and did not relapse during a follow-up duration of 24 months [11].

The patient with two transplantations experienced no complications during ASCT, while grade 4 GI and liver graft-*vs*-host disease (GVHD) occurred after allo-SCT [9, 17]. Two patients had mild GI side effects [10, 15], three had no complication [11, 13] and neutropenic fever developed in two patients after ASCT [12].

Table 1 Characteristics of patients receiving HSCT for accompanying haematological conditions (1–11 patients) and refractory BD (12–20 patients)

Patient no.	Age/sex	Country	Interval, months[a]	BD symptoms	Treatment for BD before HSCT	Indication for HSCT	Trisomy 8	Follow-up time, months	Clinical response	Reference
1	10/F	Japan	10	O, S, I, Fv	CS	AML	–	17	CR	[20]
2	27/F	Japan	120	O, G, S, Fv	NSAIDs, Col, CS	MDS	+	23	CR	[22]
3	28/F	Japan	3	O, I, Fv	Antibiotics, total parenteral nutrition	MDS	+	16	CR	[21]
4	36/M	Korea	NR	O, G, S, A, I	CS, Col	MDS	–	25	CR	[16, 23]
5	31/F	Korea	NR	O, G, S, A, P, I	CS, Col, SSZ	MDS	–	4	CR	[16, 23]
6	34/F	Korea	NR	O, G, S, A	CS, Col, AZA, CsA	MDS	NR	NR	NR	[23]
7	35/F	Korea	NR	O, G, S, P, I	CS, immunosuppressive therapy	AA	+	78	CR	[16]
8	43/M	Korea	NR	O, G, S	CS, immunosuppressive therapy	AA	+	58	CR	[16]
9	43/M	Caucasian	12	O, S, A, U	NSAIDs	AML-M0	–	24	CR	[19]
10	54/M	India	84	O, G, S, P, U, V	CS, CsA, AZA, Col, CYC, etoposide, CHB, tacrolimus, infliximab	Plasmacytoma	NR	36	CR	[14]
11	25/F	Turkey	60	O, G, S, I	CS, Col, AZA, infliximab, thalidomide	MDS	+	**20**	CR	Present case
12	20/F	Eastern ethnicity/Italy	120	O, G, I, U, CNS	CS, CYC, MMF	CNS disease	N/A	8	Short remission (90 days)	[9]
12	20/F	Eastern ethnicity/Italy	132	O, G, I, U, CNS	CS, CYC, MMF, ASCT, CYC, IFN-α, infliximab,	CNS disease	N/A	28	Relapse after remission for 2 years	[17]
13	48/M	Turkey	15	O, U, Fv, CNS, pulmonary involvement, Coombs'-negative haemolytic anaemia	CS, CYC	Pulmonary disease	N/A	60	PR	[10, 15]
14	28/M	Germany	48	O, S, A, Fv, intracardiac thrombus, pulmonary involvement	CS, CYC, MTX	Pulmonary disease	N/A	60	CR	[10, 15]
15	4/F	Italy	24	O, S, A, Fv, P, I	Total parenteral nutrition, CS, CYC, SSZ, AZA, CsA, tacrolimus, MTX, infliximab	Intestinal disease	N/A	24	CR	[11]
16	18/F	Caucasian	84	O, G, A, S, CNS, RP, interstitial cystitis	CYC	CNS disease	N/A	36	CR	[12]
17	34/F	Asian	24	O, G, S, CNS	CS, AZA, Col, CYC, levamisole	CNS disease	N/A	22	No remission	[12]
18	19/M	Italy	48	CNS	CS, CHB	CNS disease	N/A	48	Without relapse	[13]
19	19/M	Italy	36	CNS	CS, CHB	CNS disease	N/A	48	Without relapse	[13]
20	NR/F	NR	NR	NR	NR	NR	N/A	2	Dead	[18]

F: female; M: male; O: oral ulcers; G: genital ulcers; I: intestinal ulcers; S: skin; Fv: fever; A: arthralgia; P: positive pathergy test; T: thrombosis; U: uveitis; V: vasculitis; Col: colchicine; CHB: chlorambucil; CR: complete remission; PR: partial remission; NR: not reported; N/A: not applicable. [a]Time interval between BD diagnosis and HSCT.

One patient undergoing allo-SCT died from infection after 2 months [18].

Outcome in patients transplanted for accompanying haematological conditions

Among the 11 patients who were transplanted for haematological conditions, 6, including the presented case, also had GI BD involvement. All of these patients achieved complete remission of GI findings after HSCT [16, 20, 21]. One patient had recurrent uveitis and mucocutaneous lesions despite CYC, AZA and corticosteroids. While infliximab use was being considered, a plasmacytoma was diagnosed and the patient had a complete remission of both ocular and mucocutaneous manifestations after autologous HSCT [14]. Outcome data regarding the haematological condition were available in 10 of the patients and all had remission of their haematological condition after HSCT and did not relapse during the mean follow-up of 30 months before they were reported.

Transplantation procedures included three cord blood transplantations, seven allo-SCT and one ASCT. Three patients transplanted with cord blood experienced grade 1–2 GVHD of the skin, grade 2 GI GVHD, pneumatosis cystoides intestinalis, neutropenic fever and cytomegalovirus viraemia (CMVv) [20–22]. One patient had grade 3 skin GVHD [19]. The presented case had grade 1 skin GVHD and CMVv. Complications regarding the transplantation were not reported in six patients.

Discussion

BD can be a life-threatening condition, especially when it involves the vascular, nervous and GI systems [24]. Although we now have more treatment options, including TNF-α antagonists, IL-1 and IL-6 blocking agents, there is still an unmet need for more effective treatment modalities for patients who are refractory to biologic agents. However, one must make sure that the benefit outweighs the risks when developing a management strategy for these patients.

When considering HSCT as a treatment option for BD, one must consider the possible risks and benefits. HSCT itself can be a costly, and if complications develop, it can be a life-threatening procedure. Farge *et al.* [4] analysed outcomes of autologous HSCT for autoimmune diseases. Transplant related mortality at 100 days from the 900 patients was found to be 5% and varied according to the original diagnosis and was lower in experienced institutions. Infections were the most common cause of transplant-related mortality. Major complications of allo-SCT are infections, GVHD and hepatic, renal and pulmonary damage [25]. Daikeler *et al.* [18] reported data for 35 patients receiving allo-SCT for autoimmune diseases. Treatment-related mortality was 22% at 2 years. However, improved risk assessment and supportive care have reduced transplant-related mortality in allo-SCT in recent years. Among the 20 patients, only 1 patient with allo-SCT developed grade 4 GVHD [17] and 1 patient died due to an infectious cause [18]. ASCT, which may be preferred for refractory BD patients, seems to be a relatively safe treatment modality. Of the nine patients with ASCT in our survey (one with plasmacytoma, eight with refractory BD), none experienced a serious transplant-related complication. No BD flares occurred following G-CSF administration.

The effect of GVHD or graft *vs* autoimmunity on BD outcome after transplantation is not addressed in this study because only two patients with refractory BD experienced allo-SCT. One of them had grade 4 GVHD and BD relapsed after a remission period of <2 years. The other patient died from infection 2 months after allo-SCT.

The possibility that the intense immunosuppression following HSCT may be providing remission in BD patients, rather than the HSCT itself, has been discussed. It could be questioned whether the disease-free status of our patient after transplantation is related to the prolonged CsA treatment (50 mg/day) given for cholestasis related to GVHD. However, this seems unlikely since her GI involvement had been refractory to AZA, corticosteroids, infliximab and adalimumab prior to transplantation. The resolution of both BD and MDS in our patient seems to be induced by transplantation by changing the behaviour of the disease through resetting of the entire immune response.

In conclusion, HSCT may be an effective alternative in BD patients with severe organ involvement, especially GI involvement refractory to immunosuppressives. Because of the higher transplant-related morbidity and mortality of allo-SCT, mostly autologous transplants have been performed in BD patients, and non-myeloablative regimens may be preferred to myeloablative ones.

Rheumatology key messages

- Haematopoietic stem cell transplantation (HSCT) may be a treatment option for Behçet's disease refractory to other treatment modalities.
- Potential adverse events and complications related to HSCT need to be kept in mind.

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