

Letters to the Editor

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Resolution of Behcet's disease after non-myeloablative allogeneic stem cell transplant for acute myeloid leukaemia

SIR, Behcet's disease (BD) commonly affects younger patients. The diagnosis is generally made from a cluster of symptomatology, including recurrent orogenital ulcers, skin rash, seronegative arthritis and uveitis. The diagnosis requires the presence of recurrent oral ulceration with two of four minor criteria that include anterior uveitis and papulopustular skin lesions. Although usually an indolent course, BD can result in life-threatening complications such as meningitis, stroke, pulmonary haemorrhage and thromboembolic disease. Anti-inflammatory drugs and immunosuppressive agents are the main therapeutics; in advanced BD, high-dose chemotherapy followed by autologous haematopoietic stem cell transplants (HSCTs) resulted in some successes [1–3], indicating that immune ablation could modify the course of this disease. The lack of uniform successes, however, suggests that the reconstituted immune repertoires after autologous HSCT in some patients remain perturbed. Allogeneic HSCT that provides a new and diverse immune repertoire may, therefore, be more effective. However, literature on allogeneic HSCT in patients with BD is scanty. A patient whose BD relapsed after autologous HSCT successfully underwent an allogeneic HSCT and achieved a remission that lasted 2 yrs [4]. Resolution of BD also occurred in three patients who underwent umbilical cord blood transplants for myelodysplastic syndrome [5–7]. Unlike these previous cases that involved the use of myeloablative conditioning regimens, we report here the first case of BD that resolved following a non-myeloablative allogeneic HSCT for acute myeloid leukaemia (AML).

A 43-yr-old Caucasian man presented in 2005 with a 3- to 4-yr history of recurrent oral ulcerations associated with a maculopapular rash on the lateral aspect of his arms and back, an anterior uveitis and intermittent acute arthritis of his ankles and knees. Each acute episode lasted 6–8 weeks and occurred every 3–4 months. The symptoms worsened progressively. Autoimmune serological studies were negative. His HLA types were: HLA-A2, 11; B15, 55 and DRB1 0401, 1401. Based on the classification criteria set by the International Study Group [8], he was diagnosed with BD. Because his disease was limited, he was managed with NSAIDs.

In March 2006, he presented with further oral ulcers. He was, on this occasion, also pancytopenic. Further investigations including a bone marrow examination led to a diagnosis of AML-M₀. Cytogenetics was normal. He received standard therapy with daunorubicin (60 mg/m²/day for 3 days) and ARA-C (200 mg/m²/day for 7 days) but did not achieve a remission of his AML. Bone marrow 2 weeks after completing induction chemotherapy showed that it was still hypercellular with >90% blast cells. He proceeded to a further chemotherapy, this time with fludarabine (25 mg/m²/day for 5 days) and high-dose ARA-C (2 g/m²/day for 5 days) and achieved a complete remission. He was consolidated with another course of fludarabine and high-dose ARA-C before proceeding to a non-myeloablative allogeneic HSCT from his HLA-matched brother. Conditioning regimen consisted of intravenous fludarabine 30 mg/m²/day for 5 days and melphalan 100 mg/m²/day for 1 day. This was followed by the infusion of peripheral blood

stem cells mobilized by G-CSF collected from his HLA-matched brother. CSA was used for graft-vs-host disease (GVHD) prophylaxis. Peri-transplant period was uneventful. He was engrafted by day 15. He developed Grade III skin GVHD, without any visceral involvement, and this was successfully treated with corticosteroid. The dose was tapered and he discontinued the corticosteroids by 2 months and CSA by 6 months after the transplant. With a follow-up of 24 months, he has remained leukaemia-free, off all immunosuppressive agents, and without evidence of GVHD or further attacks of BD.

Although theoretical consideration favours allogeneic HSCT for treatment of autoimmune diseases, the high risk associated with myeloablative allogeneic HSCT makes this therapeutic approach one of limited applicability in BD. However, the outcome of our patient indicates that BD remission can be achieved using non-myeloablative allogeneic HSCT. Obviously, it should be noted that our patient only had limited BD. Therefore, whether a non-myeloablative allogeneic HSCT can induce disease regression in patients with aggressive BD remains unknown. Furthermore, it remains to be determined if BD regression could be achieved solely from an aggressive and prolonged period of immunosuppression, such as that used for our patient, involving fludarabine during induction and consolidation phase of his AML treatment and during the conditioning period for the transplant, followed by the administration of CSA and corticosteroids, or that BD regression requires a distinct and new immune repertoire from the healthy donors. Although the answer to this question may be addressed in a randomized study, any definitive results will only be attained if there are enough patients available for the study and also if there is a robust system to accurately predict the clinical course of the disease in these patients. However, since the toxicity associated with a non-myeloablative transplant is low, rheumatologists may now be more comfortable for their patients to participate in such a randomized study.

Rheumatology key message

- Regression of BD following non-myeloablative stem cell transplant for AML.

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Cyclophosphamide-associated complications: we need to be aware of SIADH and central pontine myelinolysis

SIR, We report a case highlighting a rare complication that rheumatologists might come across while using cyclophosphamide.

A 49-yr-old lady with dcSSc for 2 yrs, presented with cough and dyspnoea on exertion of 4 months duration. Clinical examination, HRCT-thorax and pulmonary function test revealed interstitial lung disease with severe restrictive abnormality. She was started on monthly pulses of intravenous cyclophosphamide (500 mg) and oral prednisolone (20 mg/day).

A day after the second pulse, she presented with extreme fatigue and restlessness. There was no history of fever, chest pain or headache. Investigations revealed hyponatraemia (serum Na 106 meq/l) and she was started on 0.9% normal saline. Over the next 12 h her consciousness deteriorated. She had two episodes of generalized tonic-clonic seizures and became comatose. Serum sodium did not improve.

At this time, the urine osmolality was found to be high (620 mOsmol/kg) with low-plasma osmolality (248 mOsmol/kg) and normovolaemia. These features were consistent with syndrome of inappropriate antidiuretic hormone secretion (SIADH) possibly related to cyclophosphamide infusion since no other underlying cause could be identified. Fluids were restricted. As she had altered consciousness and seizures, we tried to correct hyponatraemia with hypertonic saline. Sodium deficit was calculated and 3% saline initiated at 15 ml/h. The consciousness improved 24 h after initiating hypertonic saline, but again deteriorated over the next 24 h. CSF examination was normal. Blood and urine cultures were negative. MRI-brain at this stage was normal. She remained in coma despite the serum sodium becoming normal. There were no further seizures. A repeat MRI done after a week showed typical features of central pontine myelinolysis (CPM) (Fig. 1). The patient continues to be comatose till the time of writing this report which is about 3 months after the event.

SIADH is the most frequent cause of normovolaemic hyponatraemia [1]. Cyclophosphamide can also produce SIADH [2]. This is, however, usually known with higher doses used in oncology practice [3]. In the present case, this complication was seen at a relatively lower dose (500 mg). There are only a few reports of low-dose intravenous cyclophosphamide causing SIADH [4, 5].

CPM is a well-known complication encountered while correcting hyponatraemia [6]. Both prolonged hyponatraemia as well as rapid correction of it can cause CPM [7]. In this case, both might have contributed to this complication. But what this case highlights is that SIADH, although uncommon with low-dose cyclophosphamide, is nevertheless an important complication one



FIG. 1. T₂-weighted image showing triangular area of hyperintensity in the basis pontis suggestive of central pontine myelinolysis.

should keep in mind while using this drug irrespective of the dosage.

Rheumatology key message

- SIADH and CPM can occur despite using cyclophosphamide in low dose.

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