

LETTER TO THE EDITOR

Mesenteric inflammatory veno-occlusive disease (MIVOD) after allogeneic peripheral blood stem cell transplantation (PBSCT)

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Abdominal pain is a common and non-specific symptom after allogeneic PBSCT. Diagnosis frequently requires invasive diagnostic procedures. We report a patient with incapacitating abdominal pain of obscure etiology after PBSCT, finally diagnosed after a partial intestinal resection.

A 42-year-old man, diagnosed with AML with erythroid markers, received an allogeneic PBSCT from an HLA-identical sibling in the first CR. Conditioning included oral BU 4 mg/kg/day for 4 days and CY 60 mg/kg/day for 2 days. CsA and MTX (days +1, +3, +6 and +11) were used as GVHD prophylaxis. A positive tuberculin skin test prompted the administration of daily oral isoniazid after engraftment.

On day +71, the patient developed clinical grade II acute intestinal GVHD, documented by colonic biopsy, which responded to methylprednisolone (2 mg/kg/day) therapy.

On day +97, he was readmitted to the hospital due to epigastric pain, diarrhea, severe weight loss and increased liver enzymes. An upper GI endoscopy showed non-specific gastroduodenitis, and a CT scan disclosed diffuse concentric thickening of the small bowel wall (Figure 1). An extensive chronic GVHD, with liver and gastrointestinal involvement was suspected. He was still taking CsA with therapeutic levels, which was maintained at the same dose and he resumed full-dose methylprednisolone therapy, which yielded rapid clinical improvement. The patient developed CMV antigenemia that promptly responded to ganciclovir treatment. Isoniazid prophylaxis was discontinued to decrease liver toxicity.

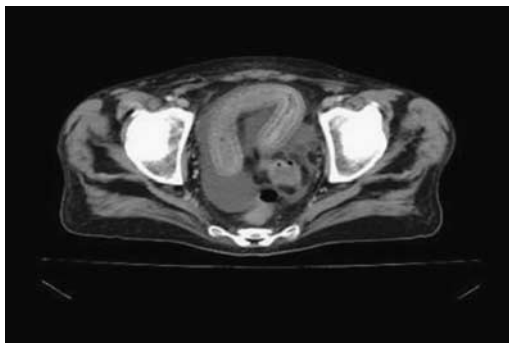


Figure 1 CT showing diffuse concentric thickening of the small bowel wall.

On day +149, the patient was readmitted to the hospital due to further diarrhea, bouts of abdominal pain suggesting partial obstruction, which worsened with solid oral intake and weight loss. The abdominal pain required analgesia including opiate derivatives. Total parenteral nutrition (TPN) was necessary. At this time, CMV antigenemia was negative. A new CT scan revealed increased thickening of the small bowel wall with cecal involvement. A further upper GI endoscopy disclosed non-specific duodenitis, shown to be chronic inflammation on histology. A colonoscopy confirmed severe terminal ileum stenosis. Fibrosis and mononuclear infiltrates were present in colonic biopsies. Although staining for acid-fast bacilli was negative in the biopsy, a positive PCR for tuberculosis was reported. Treatment with isoniazid, rifampicin and pyrazinamide was started resulting in only mild clinical improvement. Lowenstein cultures set up from the colonic biopsy were negative for *Mycobacterium tuberculosis*.

After one month of treatment and TPN, his abdominal symptoms worsened and small bowel radiologic studies showed severe distal ileum stenosis with dilatation of the proximal loops. The patient underwent a surgical resection of the terminal ileum, and rapid and complete resolution of the gastrointestinal symptoms was achieved. A few days later, TPN was stopped and oral intake resumed.

Histology of the surgical specimen (Figure 2) showed extensive areas of ulcerated mucosa and transmural thickening of the bowel wall and mesentery with sclerosis. There was both selective and generalized involvement of small and medium-sized veins with severe stenosis of the lumen and occasional venular obliteration. Additionally, venous inflammation, myointimal hyperplasia and signs of recanalization were frequent. However, no fibrinoid necrosis or thrombi were documented. Strikingly, arteries remained uninvolved. There were no histologic findings of GVHD. Gram, PAS and Zhiel–Nielsen stains as well as PCR for *M. tuberculosis* were all negative. All these findings were consistent with the diagnosis of the rare clinicopathologic entity: mesenteric inflammatory veno-occlusive disease (MIVOD).

Up to date, 24 months after PBSCT, the patient remains asymptomatic. In spite of the clinical improvement, he completed 6 months of anti-tuberculosis therapy.

This is, to the best of our knowledge, the first case of MIVOD reported to have occurred following haematopoietic stem cell transplantation (HSCT). MIVOD is a rare entity that clinically mimics inflammatory bowel disease or intestinal ischemia.¹ The main complaints are usually recurrent and non-specific bouts of abdominal pain. The

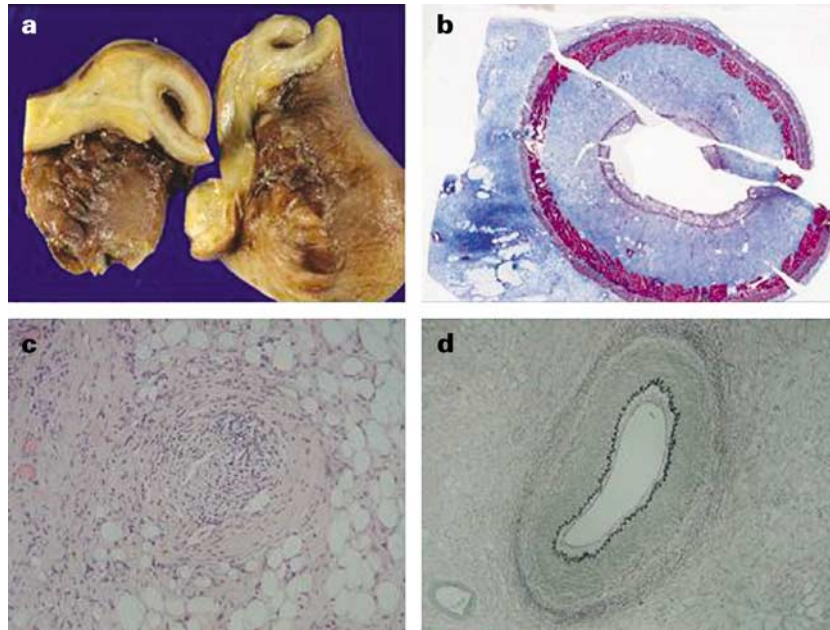


Figure 2 Histopathological findings. (a and b) Surgical specimen (panel a) and macromicroscopic whole-mount preparation (panel b) of the specimen showing transmural and mesenteric thickening due to fibrosis. (c and d) Microscopic details showing venulitis with obliteration and partial recanalization of the lumen (panel c) and spared arterial vessels (panel d).

intensity of symptoms is usually out of proportion to the physical findings. Diarrhea, nausea and vomiting are common. Flaherty *et al.*² first reported this clinical entity in 1994, in 7 patients, although since 1989 similar occurrences have been reported using other terms.³ The largest series (17 cases) was reported by Lie *et al.*⁴ in 1997. The diagnosis is made on histopathology and relies on selective vasculitis of mesenteric veins and venules, although, occasionally, the involved vessels may be missed on endoscopic biopsy. Characteristic features are marked myointimal hyperplasia with predominant lymphocytic or granulomatous inflammation, and the presence of thrombi that finally leads to fibrous obliteration of veins. Chronic ischemic changes may result in symptomatic strictures, as in our patient. Medical treatment has been unsuccessful in all cases, surgical resection of the involved segment always being effective. No progression to systemic disease has been described and recurrence is extremely rare, with only one such case published to date.⁵

The etiology of MIVOD remains unclear. Cases relating to primary CMV infection⁶ or drugs such as Rutoside⁵ have been described, but most of the reported patients had autoimmune diseases⁵ such as rheumatoid arthritis, lupus erythematosus,⁷ Behçet disease or Buerger's disease, or they presented with idiopathic disease. In our opinion, the immune dysregulation that follows a PBSCT, particularly in the context of previous GVHD, played the main role in the development of MIVOD in the patient reported here. We cannot rule out that delayed drug toxicity was also involved, but diagnosis was relatively far from conditioning therapy on day +149, and the patient was only treated with two chemotherapy courses before PBSCT. Furthermore, CMV viremia was present on day +97, but not during the last severe episode, so its association with

MIVOD in our patient is less clear unless a secondary autoimmune reaction had occurred.

To summarize, MIVOD, in spite of its rarity, should be considered in the differential diagnosis of patients with recurrent and otherwise unexplained abdominal pain after an HSCT. In this situation, after common pathological processes causing abdominal pain have been excluded, clinicians should bear in mind that MIVOD is a possible diagnosis and therefore the patient may require surgery. This entity could be more frequent than expected due to the under diagnosis of mild and perhaps reversible forms of the disease. As indicated above, endoscopic biopsy specimens may miss the involved vessels and only severe cases, which need surgery and undergo an extensive surgical histological examination may be fully identified.

AM Pérez-Corral¹, D Serrano¹, J Menarguez-Palanca²,
R Carrión¹, I Barreiro³, A Gómez-Pineda¹, I Buño¹,
P Balsalobre¹ and JL Díez-Martín¹

¹Servicio de Hematología, Hospital General Universitario Gregorio Marañón, Madrid, Spain;

²Servicio de Anatomía Patológica, Hospital General Universitario Gregorio Marañón, Madrid, Spain and

³Servicio de Radiología, Hospital General Universitario Gregorio Marañón, Madrid, Spain

E-mail: aperezc.hgugm@salud.madrid.org

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