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Case report

Bronchiolitis obliterans organizing pneumonia and ulcerative colitis after allogeneic bone marrow transplantation

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Summary:

A 37-year-old man with acute myeloblastic leukemia in first remission developed ulcerative colitis and bronchiolitis obliterans organizing pneumonia (BOOP) 7 months after bone marrow transplantation (BMT) from an HLA-matched brother who suffered from severe Crohn's disease. BOOP occurred 20 days after idiopathic interstitial pneumonia, in the context of severe ulcerative colitis. Lung and colon biopsies showed no signs of CMV infection or GVHD. The patient was treated with oral methylprednisolone 1 mg/kg/day and his clinical status and chest X-ray improved slowly. Remarkably, the symptoms of colitis also resolved with prednisone therapy and he is now symptom-free. We hypothesize that ulcerative colitis may have been transmitted from donor to recipient (adoptive autoimmunity) and that it was complicated by BOOP. However, other factors such as CMV may have contributed to the occurrence of BOOP.

Keywords: allogeneic bone marrow transplantation; autoimmune diseases; ulcerative colitis; BOOP; adoptive autoimmunity

Bronchiolitis obliterans organizing pneumonia (BOOP) is a rare cause of diffuse infiltrative lung disease. It may be idiopathic or occur in association with infections, drugs or miscellaneous neoplastic or inflammatory diseases. The first case of BOOP following bone marrow transplantation (BMT) was described in 1990.[1] Since then, six additional cases of BMT-associated BOOP have been reported (Table 1), including two successive episodes in a single patient undergoing two BMT procedures.[2–4] BOOP has also been described in several patients with inflammatory bowel disease.[5] We report a new case of BMT-associated BOOP which developed in the recipient of a marrow transplant from a donor who suffered from Crohn's disease. As the patient simultaneously developed ulcerative colitis and BOOP about 6 months after BMT, this observation could constitute a case of adoptive autoimmunity in which transmission from donor to recipient of inflammatory bowel disease could have contributed to the pathogenesis of BMT-associated BOOP.

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Case report

The patient, a 37-year-old man with acute myeloblastic leukemia in first remission, received a genotypically HLA-identical BMT from his brother in March 1995. The donor was negative for cytomegalovirus (CMV) on serology but had suffered from severe Crohn's disease for the past 15 years, which was treated with sulfasalazine and azathioprine. The latter was stopped 3 weeks before the transplant. The recipient was positive for CMV. Pre-transplant pulmonary function tests were normal. Conditioning consisted of cytarabine 12 g/m^2, cyclophosphamide 120 mg/kg and single dose total body irradiation (TBI) 8 Gy. Graft-versus-host disease (GVHD) prophylaxis was carried out with short methotrexate and cyclosporine (CsA).

The initial post-transplant course was complicated by grade 1 acute skin GVHD that resolved after increasing the dose of cyclosporine. He never developed any sign of clinical or subclinical chronic GVHD. On day 162, he experienced generalized seizures (attributed to severe hypertension and CsA) and was started on phenobarbital and clonazepam while CsA was stopped. Cerebral spinal fluid examination and cerebral CT scan and NMR were all normal. Shortly afterwards, he developed diffuse abdominal pain with bloody diarrhea. Rectosigmoidoscopic examination performed on day 167 showed severe ulcerative and hemorrhagic colitis involving the rectum and whole sigmoid colon. Biopsies (Figure 1) showed ulcerative colitis with no sign of CMV infection or GVHD. Immunohistology demonstrated a mixture of T and B cells with a predominance of B cells. Stool cultures and search for *Clostridium difficile* toxin remained negative. Twenty days later, he developed fever and a rapidly progressive interstitial pneumopathy that required ventilation. Bronchoalveolar lavage (BAL) was noncontributive and *in situ* hybridization, as well as blood and urine cultures, failed to detect CMV, although CMV reactivation had been detected by serology in the preceding 2 months. Treatment with high-dose immunoglobulins, ganciclovir, imipenem, doxycycline

Table 1 Reported cases of BMT-associated BOOP

Case number	*1*	*2*[a]	*3*[a]	*4*	*5*	*6*	*7*	*8*
Author	*Chien*[1]	*Thirman*[2]	*Thirman*[2]	*Mathew*[3]	*Mathew*[3]	*Mathew*[3]	*Przepiorka*[4]	*Baron (this report)*
Age	31	37	42	15	10	12	23	37
Sex	M	M	M	M	M	M	F	M
Disease	AML	CML	CML	ALL	AML	ALL	ALL	AML
Graft								
Type	Sibling	Sibling	Sibling	Unrelated	Unrelated	Sibling	Sibling	Sibling
HLA mismatches	0	0	0	0	0	2	1	0
Conditioning	NR	Cy + TBI	Bu Cy + AraC	AraC + Cy + TBI	AraC + Cy + TBI	AraC + Cy + TBI	Cy + Thiotepa + TBI	AraC + Cy + TBI
GVHD prophylaxis	NR	MTX + ATG + PDN	CsA	PDN	PDN	PDN	CsA + PDN + aCD5	CsA + MTX
aGVHD								
Grade	NR	1	3	0	0	0	2	1
Resolved	Yes	Yes	Yes				Yes	Yes
cGVHD								
Organ	NR	Liver	Skin	None	Skin	None	None	None
Day		210	190		155			
Treatment		NR	CsA + PDN		PDN			
Outcome		resolved	improved		resolved			
Previous lung involvement	Yes	No	No	No	No	No	No	Yes
Etiology	CMV							?
Day	64							185
Treatment	ganciclovir + IVIg							ganciclovir + IVIg + AB
Resolved	Yes							Yes
GI involvement	Yes	No	Yes	NR	NR	NR	NR	Yes
Symptoms	diarrhea		bleeding					diarrhea + bleeding
Etiology	aGVHD		CMV					ulcerative colitis
BOOP								
Day	180	240	128	94	89	110	140	205
BAL	lymphocytosis	NR	sterile	parinfluenza	NR	parinfluenza	sterile	sterile
Biopsy	BOOP	BOOP	Non-diagnostic	BOOP	BOOP	BOOP	BOOP	BOOP
Treatment	Steroids	Steroids	Steroids	Sterois + IVIg	Steroids	Steroids + IVIg	Steroids	Steroids
Outcome	Resolved	Resolved	Resolved	Resolved	Resolved	Death from MOF	Death from RF	Resolved

[a]Same patient

NR = not reported; MOF = multiple organ failure; RF = respiratory failure; IP = interstitial pneumonia; AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; CML = chronic myelogenous leukemia; Cy = cyclophosphamide; AraC = arabinoside cytosine; Bu = busulfan; TBI = total body irradiation; aGVHD = acute GVHD; cGVHD = chronic GVHD; BAL = bronchoalveolar lavage; GI = gastrointestinal; PDN = prednisone; CsA = cyclosporine; MTX = methotrexate; ATG = antithymocyte globulin; aCD5 = anti-CD5 monoclonal antibody; IVIg = intravenous immunoglobulins; AB = antibiotics.

and amphotericin B resulted in progressive improvement and extubation 3 days later, followed by progressive normalization of his chest X-ray film. However, he continued to suffer from bloody diarrhea and a second rectosigmoidoscopy confirmed the previous diagnosis of ulcerative colitis.

On day 205, a routine chest X-ray film showed interstitial infiltration of the lower right lobe, which rapidly progressed to diffuse acino-interstitial infiltrates despite treatment with ganciclovir, erythromycin, amphotericin B and polyvalent immunoglobulins. The patient had no fever, but a non-productive cough, hypoxemia at rest and inspiratory crackles on chest examination. Bronchoalveolar lavage was non-contributory but open lung biopsy showed BOOP (Figure 2). *In situ* hybridization did not demonstrate the presence of CMV. The patient was started on oral methylprednisolone 1 mg/kg/day and improved slowly. Methylprednisolone 40 mg daily was continued for 3 months and then tapered over a few weeks. Since stopping steroids 18 months ago, he has remained in good clinical condition without recurrence of BOOP. Remarkably, the symptoms of colitis resolved with the prednisone therapy and he his now symptom-free.

Discussion

We report a patient who simultaneously developed BOOP and ulcerative colitis 6 months after allogeneic BMT. Although its physiopathology remains unclear, BOOP has been observed in the context of various autoimmune disorders and in particular inflammatory bowel diseases.[5] The pathogenesis of ulcerative colitis remains unclear but autoimmunity has been highlighted among genetic, allergic,

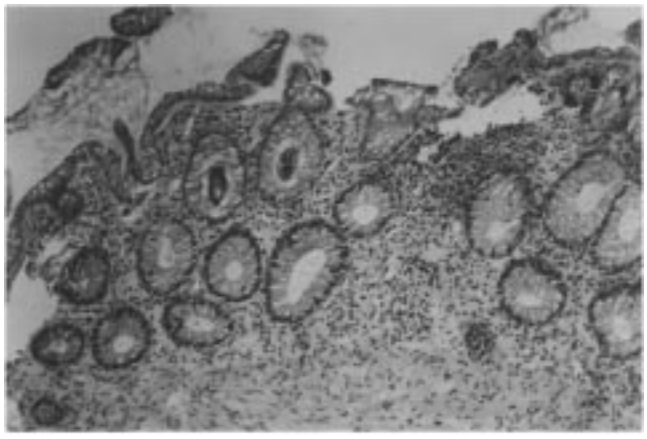

Figure 1 Colon biopsies showing diffuse superficial cell degeneration with severe congestion of the lamina propria. Crypts showed derangement of their normal architecture as well as goblet cell depletion and a diffuse moderate inflammation of the lamina propria.

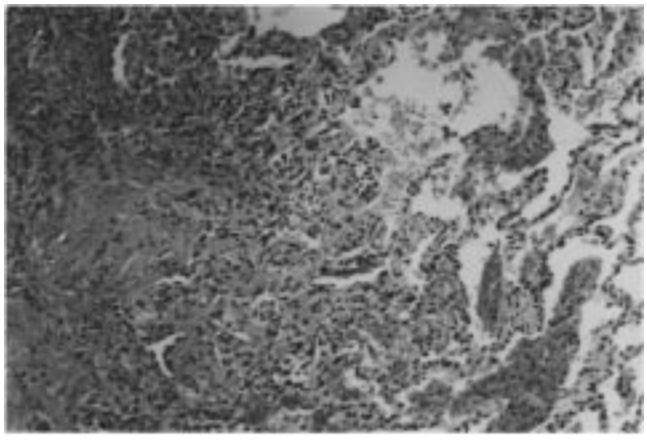

Figure 2 Open lung biopsy showing a regularly arranged inflammatory exudate and plugs of connective tissue distributed within terminal bronchi and bronchioles. Alveoli contained foamy macrophages and inflammatory cells.

dietary, infectious and immunologic mechanisms, and immunosuppressive agents such as prednisolone or cyclosporine can improve it. In the context of BMT, these two infrequent diseases may also have a toxic, infectious or GVHD-related etiology.

BOOP has been associated with radiation therapy as well as several drugs, including anti-inflammatory and immunosuppressive agents such as gold, methotrexate and sulfasalazine.[5] In all cases of BMT-related BOOP, the preparative regimen included cyclophosphamide and in seven of eight cases total body irradiation (TBI) (Table 1). However, the delay between conditioning and the onset of symptoms renders this explanation unlikely in our patient. Ulcerative colitis following BMT may also have a toxic origin but exceptionally so after day 100 post-BMT.[6]

The first reported case of BMT-related BOOP followed CMV interstitial pneumonia.[1] Moreover, ulcerative colitis may also be due to viral (such as CMV or HSV) infections. Our patient also developed BOOP after interstitial pneumonitis in the context of serologic CMV reactivation. However, examination of bronchoalveolar lavage, lung and colon biopsies, as well as blood and urine cultures failed to detect CMV or other viral infections.

BOOP has also been associated with chronic GVHD in three of the eight reported cases (Table 1).[2] No case has been described following autologous BMT and this may indicate that host–recipient interactions play an important role in BMT-related BOOP. Necrosis of the intestinal mucosa is typical of acute GVHD, but is unusual after day 100 and is not part of the chronic GVHD syndrome characterized by patchy fibrosis of the lamina propria and striking fibrosis of the submucosa and serosa extending from the stomach to the colon.[6] Moreover, in our patient colon biopsies showed no sign of acute or chronic GVHD.

After allogeneic BMT, there is gradual development of donor-derived immunity, which generally recapitulates immune ontogeny.[7] Two distinct conditions may develop in this setting, ie eradication of pre-existent immune-mediated diseases and conversely, adoptive autoimmunity. Eradication of pre-existent immune-mediated disease has been documented for several disorders, including rheumatoid arthritis, systemic lupus, psoriasis, ulcerative colitis and Crohn's disease.[8–10] Adoptive autoimmunity is well illustrated by the transfer of several autoimmune conditions from donors to their recipients, including myasthenia gravis, autoimmune thyroiditis and type 1 diabetes mellitus.[7,9,10] It is caused by donor-derived pathogenic B, T or stem cell clones after regulatory and suppressive mechanisms are canceled by the conditioning regimen and immune dysregulation in the recipient. Genuine adoptive autoimmunity must be distinguished from autoimmunity occurring in the context of GVHD or in an apparently idiopathic fashion.[9]

To date, no case of transmission of inflammatory bowel disease from a marrow donor to its recipient has been reported. A case of typical ulcerative colitis following BMT has been reported (results of initial biopsies were nonspecific but a repeat biopsy showed typical ulcerative colitis that responded well to topical and systemic corticosteroids) but the donor had no gastrointestinal symptoms.[11] However, this case may have originated from donor-derived cell clones carrying the autoimmune potential. Our patient developed a clinical picture of ulcerative colitis 6 months after engraftment, soon after discontinuation of CsA. Biopsies performed twice excluded diagnoses of virus- or GVHD-induced colitis and all cultures remained negative. Furthermore, the symptoms of colitis began after CsA was discontinued and responded well to corticosteroids. Ulcerative colitis and Crohn's disease are thought to be related diseases or even different manifestations of the same disease.[12] This contention is well supported by epidemiologic similarities and by the increased incidence of both diseases in relatives of patients with Crohn's disease. Therefore, there is a possibility that the immune-mediated colitis seen in our patient derived from the same lymphocyte clones involved in the donor's Crohn's disease, constituting adoptive autoimmunity.

In conclusion, our patient developed two rare diseases, ulcerative colitis and BOOP, 6 months after allogeneic BMT, soon after cyclosporine was stopped. Both resolved with prednisone therapy and 18 months later the patient is symptom-free. These two disorders have been associated

previously in non-transplant settings. We hypothesize that this represents the adoptive transfer of autoimmune ulcerative colitis from donor to recipient complicated by BOOP. However, other factors such as CMV or undetermined infections may have contributed to the occurrence of BOOP.

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