Graft-versus-host disease after liver transplantation complicated by systemic aspergillosis with pancarditis

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BRIEF COMMUNICATION

J Romagnuolo, LD Jewell, NM Kneteman, VG Bain. Graft-versus-host disease after liver transplantation complicated by systemic aspergillosis with pancarditis. Can J Gastroenterol 2000;14(7):637-640. Acute graft-versus-host disease (GVHD) is a common complication after bone marrow transplantation, with characteristic rash and diarrhea being the most common features. After liver transplantation, however, this phenomenon is very rare. Most transplant patients are on a variety of medications, including immunosuppressants; therefore, the differential diagnosis of skin rash or diarrhea is broad. A 37-year-old man who underwent liver transplantation for primary biliary cirrhosis, and developed a rash and watery diarrhea, is presented. Skin and colonic biopsies confirmed acute GVHD. A pulse of intravenous steroids was given. The skin rash improved, but he developed pancytopenia. His course was complicated by central line infection, jugular and subclavian vein thrombosis, pseudomembranous colitis, recurrent bacteremia, cholesterolosis on total parenteral nutrition and cytomegalovirus infection. After the onset of pleuritic chest pain and clinical sepsis, spiral computed tomography scan of his chest showed no evidence of sepsis. The patient developed septic infarcts in multiple organs. Despite empirical treatment with amphotericin B, he died of multigorgan dysfunction syndrome within 72 h. Autopsy revealed systemic aspergillosis with pancarditis, endocardial vegetations, and septic pulmonary, splenic, hepatic and renal infarcts. The pathogenesis and experience with this rare, but often fatal, complication of liver transplantation are reviewed. In contrast to GVHD after bone marrow transplantation, pancytopenia is common and liver dysfunction is rare. One should have a high level of suspicion in the liver transplant recipient presenting with rash and/or diarrhea.

Key Words: Aspergillosis; Cytomegalovirus; Esophagitis; Graft-versus-host disease; Immunosuppression; Liver; Myocarditis; Primary biliary cirrhosis; Skin disease

Réaction du greffon contre l’hôte après transplantation hépatique compliquée par une aspergillose systémique et une pancardite

RÉSUMÉ : La réaction aiguë du greffon contre l’hôte est une complication courante après la transplantation de moelle osseuse, qui se manifeste typiquement par des éruptions cutanées et de la diarrhée. Après la transplantation hépatique, par contre, ce phénomène est très rare. La plupart des receveurs de transplantation prennent divers médicaments dont des immunosupresseurs. Le diagnostic différentiel des éruptions cutanées ou de la diarrhée est donc vaste. On présente ici le cas d’un homme de 37 ans qui a subi une transplantation hépatique pour cirrhose biliaire primaire et qui a développé une éruption cutanée et de la diarrhée. Les biopsies cutanées et coloniques ont confirmé une réaction aiguë du greffon contre l’hôte. Des corticostéroïdes par voie intraveineuse ont été administrés en bolus. L’éruption cutanée s’est améliorée, mais le patient a développé une pancréatite. Son état s’est compliqué d’une infection de son cathéter central, d’une thrombose veineuse jugulaire et sous-clavière, d’une colite

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psuedo-membrane, of a bacteriemia recurrent, of a cholestase led to the nutrition parenteral totale and of an infection by cytomegalovirus. Après le déclenchement d’une douleur thoracique d’origine pleurale and d’une septicémie clinique, une tomodensitométrie spiralée of the thoraix and of the abdomen revealed des infectus septiques affecting de multiples orga-

nes. Malgré un traitement empirique à l’ampiclotrimocine B, le patient est dé-
cédé d’une défaillance pluri-organique dans les 72 heures. L’autopsie a révélé une aspergillose systémique avec pancardite, vaccinations endocardi-
ques and infectus septiques au niveau of the poumon, de la rate, du foie and of du
rein. La pathogenèse and the manifestations of this complication rare, mais
souvent fatale, of the transplantation hépatique are passed in review.

Comparativement to the reaction of the greffon against the hôte who sui the trans-
plantation of moelle osseuse, la pancytopénie est courante and the dysfonc-
tion hépatique is rare. Il faudrait donc entretenir un fort degré de sur-
spication face à un receveur of transplantation hépatique qui présente une éruption cutanée and (ou) of the diarrhée.

**CASE PRESENTATION**

A 37-year-old married man with primary biliary cirrhosis, hypercholesterolemia and type II diabetes mellitus presented with a one-week history of skin rash and diarrhea 23 days after having undergone OLT. The rash was a pruritic, symmetrical, erythematous, maculopapular skin eruption on his neck, back and chest, with prominent involvement of his palms and soles. The rash was perifollicular, and there were some coalescing patches of erythema and target lesions. As well, he complained of three days of large-volume, watery, nonbloody diarrhea with urgency and tenesmus, but denied having fever, abdominal pain or nausea. His other medications included ranitidine, insulin, prednisone 20 mg orally once daily, and cyclosporine 375 mg orally bid, with an admission trough level of 470 \( \mu \text{g}/\text{L} \). In addition, he had been enrolled in a double-blinded study receiving either placebo or basiliximab, a chimeric (mouse/human) anti-interleukin (IL)-2 receptor monoclonal antibody.

The OLT surgery went without complication (Table 1). Methylprednisolone 100 mg intravenously bid, cyclosporine 7.5 mg/kg/day orally, and the oral study drug were given post-
operatively. No azathioprine was used. He was started on trimethoprim-sulphamethoxazole for pneumocystis prophylaxis.

A skin punch biopsy was consistent with GVHD. His creatinine level was 410 \( \mu \text{mol}/\text{L} \) and fell to 144 \( \mu \text{mol}/\text{L} \) with intravenous fluids. Sigmoidoscopy and gastroscopy revealed 30 cm of severe colitis with multiple shallow ulcers, ulcerative esophagitis, gastritis and duodenitis. All biopsies revealed evidence of acute GVHD, with apoptosis and glandular dropout (Figure 1). Repeated human leukocyte an-
tigen (HLA) typing did not reveal chimerism. Cytomegalovirus (CMV)uffy coat, stool cultures and Clostridium difficile toxin assays were negative. The prednisone dose was increased to 60 mg/day.

After one week, he developed thrombocytopenia (62x10^9/L), and intravenous methylprednisolone sodium succinate 500 mg was given daily and then slowly tapered. After an additional week, his rash improved but the diarrhea
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GVHD after liver transplantation

Figure 2) Spiral computed tomography chest scan showing a non-enhancing peripheral wedge-shaped region of increased attenuation in the right lung parenchyma consistent with pulmonary infarction from embolism.

Figure 3) Left: Autopsy specimen of lung tissue showing aspergillus with pulmonary necrosis and alveolar edema (hematoxylin and eosin stain, original magnification x220). Right: Autopsy specimen of heart tissue showing aspergillus myocarditis with invasion of a myocardial vessel. (Gomori's methanamine silver stain, original magnification x350)

pered. A dose of intravenous immunoglobulin was given. His course was complicated by pseudomembranous colitis, recurrent Gram-negative bacteremia, jugular/subclavian vein thrombosis related to line infection, CMV disease, severe pancytopenia (requiring platelets and granulocyte colony-stimulating factor) and cholestasis (total parenteral nutrition-related).

Forty-two days after admission, as he began to improve, he started having brief episodes of pleuritic right-sided chest pain without shortness of breath. A chest x-ray revealed an infiltrate below the right hilum and small nodular opacities peripherally in the left midlung zone. Lung biopsy could not be performed because of refractory thrombocytopenia. He quickly deteriorated and blood cultures grew Enterobacter species. With the suspicion of systemic aspergillosis, intravenous amphotericin B was begun and his cyclosporine was held. After an asystolic cardiac arrest, he was resuscitated and a pacemaker was inserted. He underwent an unrevealing bronchoscopy (no fungi, no pneumocystis), but a spiral computed tomography was consistent with multiple pulmonary emboli (Figure 2). Unfortunately, over the next 12 h, he became pacemaker- and inotrope-dependent, his white blood cell count was 55x10^9/L, his lactate level was 25 mmol/L and he was anuric on continuous venous-venous hemodialysis. Supports were withdrawn.

Autopsy revealed severe aspergillus pancarditis with transmural, widespread necrosis (Figure 3), fibrinous pericarditis, infective (aspergillus) endocarditis with vegetations on the left and right atrial endocardium, and probable septic emboli with renal and splenic infarcts. There was evidence of angioinvasive pulmonary aspergillosis with infarction (Figure 3).

**DISCUSSION**

Although the clinical presentations of acute GVHD in OLT and BMT are similar, there are important differences. In BMT, symptoms usually include diarrhea, liver dysfunction and skin rash. The classic rash is characterized by erythema of the palms, soles and ears; truncal perifollicular erythema; targets; and rarely bullae. Fever is sometimes present. Chimerism may be demonstrated often with HLA typing. Sanchez-Izquierdo et al (1) reviewed the English language medical literature in 1996 and found 13 cases of acute GVHD after OLT. There were notable differences when compared with BMT: frequent pancytopenia; early presentation (two to six weeks); and absence of liver involvement. The latter feature presumably is due to the recognition of the liver as ‘self’ by the allograft lymphocytes (perhaps why pancytopenia usually does not follow BMT). Among the 13 patients (1-10), three were women, four had previously rejected transplants – two of whom had been given antithymocyte globulin (ATG) – and 10 (76.9%) patients died (of sepsis in all cases in which cause of death was specified). Disseminated candidiasis occurred in three cases, but aspergillosis was not reported. Only one other case of aspergillus endocarditis complicating OLT was reported in the literature (11). Five further cases of acute GVHD after OLT have been published, two of which were pediatric cases (12-16).

Billingham (17) described the phenomenon of acute GVHD as requiring the following: graft containing immunologically competent cells; alloantigens in the host that are foreign to the donor; and incapability of the host to mount an effective immune response against the graft.

Histologically, the hallmarks of acute GVHD are apoptosis with selective epithelial damage. Particularly, cells that are undifferentiated, and perhaps bear more primitive surface antigens, are targeted (tips of the skin’s rete ridges, the hepatic periductular epithelium, the bases of intestinal crypts) (18).

Lymphocyte migration and mixed chimerism occur in successful organ transplantation, but why some patients develop GVHD is unknown. The process seems to have two phases (18). The afferent phase consists of antigen presentation, IL-1 production, T cell activation involving IL-2, and clonal proliferation and differentiation. The efferent phase is not well understood. There is either direct cytotoxicity or in-
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direct cytolysis via intermediaries such as tumour necrosis factor (TNF). Donor HLA homozygosity (1% to 2% of the population), when the recipient shares a haplotype, may play a role in living-related, pediatric OLT.

Interferon-gamma, TNF-α, IL-1, IL-2 and other cytokines may increase major histocompatibility complex expression in the recipient and upregulation of adhesion molecules, which in turn increases alloreactive T cells’ recognition of host-donor differences (19). In this way, infections, through cytokine release, may perpetuate or trigger GVHD. GVHD does not occur in gnotobiotic (germ-free) mice.

Timing of immunomodulation appears to be crucial. IL-2 given immediately to mice after transplantation decreased mortality from BMT-related GVHD by about 70%. However, when the same cytokine was given one week later, it was able to trigger GVHD (20). An IL-2 receptor blocker, such as basiliximab, although an effective treatment for GVHD, once it has begun, could potentially increase the risk of GVHD if given immediately after transplantation.

Increased immunosuppression is the treatment of choice with the intention of suppressing the alloreactive lymphocytes from the donor (19). However, both donor and recipient systems are affected, leading to the high mortality attributable to infection and to the poor success. High-dose steroids prevent IL-1 production and are lympholytic. Although cyclosporine can cause GVHD in syngeneic murine BMT through thymic effects, it can be an effective treatment for allogeneic GVHD, via the inhibition of IL-2 production and IL-2 receptor expression (21). The mechanism by which intravenous immunoglobulins cause immunosuppression probably involves the binding of the Fc portion to natural killer cells, which targets them for elimination while preventing recognition of target tissue. Other lymphocytotoxic agents, including antilymphocyte globulin and ATG or OKT3, are used in a stepwise manner. Antifungal coverage and aggressive infection surveillance are paramount. Prophylactic measures such as immunosuppression of the donor, pretransplant perfusion of the graft with antilymphoblast globulin, organ irradiation or physical removal of nodal tissue from the donor liver hardly are justified for all OLT, given the rarity of GVHD. Also, eliminating all donor lymphoid cells usually decreases tolerance and leads to more rejection. Potentially, there may be less graft-versus-tumour effect when transplantation has been performed for neoplasia, as has been shown in BMT.

Acute GVHD is an unusual complication of liver transplantation but one with a high fatality rate. It should be suspected in any OLT patient presenting with pancytopenia, diarrhea and/or rash. Our patient had prompt attention to various infections and limited exposure to anaerobic antibiotics (risk factors for fungal infection). In addition, fluconazole was given prophylactically. Despite these measures, he still succumbed to disseminated aspergillosis; therefore, low-dose, amphotericin B prophylaxis should be considered when high-dose steroids are initiated for GVHD.

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REFERENCES
