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Absence of peripheral blood chimerism in graft-vs-host disease following orthotopic liver transplantation: case report and review of the literature

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Abstract

Background—Graft-vs-host disease (GVHD) is a rare and often fatal complication of orthotopic liver transplantation (OLT). The skin is frequently involved early in disease progression, but clinical and histopathological features may be nonspecific, presenting a diagnostic challenge. While the detection of peripheral blood chimerism has been proposed as a diagnostic criterion for post-OLT GVHD, it is not known whether peripheral blood chimerism is an absolute requirement for the diagnosis.

Materials and methods—We report a case of a 57-year-old man who developed post-OLT GVHD with cutaneous, enteric, and bone marrow involvement. We also review the epidemiology, pathogenesis, clinical presentation, histopathology, molecular diagnostic techniques, and treatment of GVHD following liver transplantation.

Results—In our patient, analysis of the peripheral blood by short-tandem repeat polymerase chain reaction did not detect circulating donor lymphocytes. Donor lymphocytes were detected in the buccal mucosa, however, confirming the diagnosis. A review of chimerism patterns in 63 previously published cases of post-OLT GVHD reveals that this is the first reported case in which chimerism was absent in the peripheral blood but present in another site.

Conclusions—Peripheral blood chimerism may be absent in cases of post-OLT GVHD. A combination of clinical, histopathological, and molecular features is therefore required to make this challenging diagnosis.

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Introduction

Graft-vs-host disease (GVHD) is a rare and often fatal complication of solid organ transplantation, whereby lymphocytes that accompany the transplanted organ react against antigens expressed by the recipient. In liver transplantation, about 10^9 donor lymphocytes are transferred to the recipient, equivalent to the quantity transferred in a bone marrow transplant.[1,2] However, unlike stem cell transplantation, in which an objective is to repopulate an ablated lymphoid compartment, solid organ transplantation requires a more tenuous balance: neither the host immune system should reject the organ nor should the transferred lymphocytes react against the host.

When GVHD occurs following liver transplantation, the targeted host tissues include the skin, gastrointestinal tract, and bone marrow. Death occurs in approximately 80% of cases, often from sepsis, multi-organ failure, or hemorrhage.[3] The high mortality rate reflects not only the difficulty of treating the disease but also the challenge of diagnosing it, as the initial presentation can be indistinguishable from a severe drug reaction or viral infection, and no definitive diagnostic test exists. The demonstration of peripheral blood chimerism – the presence of both donor and recipient circulating lymphocytes – has been proposed as a diagnostic marker of GVHD following liver transplantation, but the pathophysiological significance of peripheral chimerism remains a matter of debate.[4]

Herein, we present a 57-year-old man who developed severe GVHD following orthotopic liver transplantation (OLT) in the absence of documented peripheral blood chimerism, and we review the previously published cases of post-OLT GVHD in adults in which chimerism was investigated.

Case report

A 57-year-old man underwent OLT for end-stage liver disease secondary to alcoholic cirrhosis. The donor was a 56-year-old man with a 6-antigen mismatch at the HLA A, B, and DRB1 loci. The intraoperative and postoperative courses were uneventful, with demonstration of excellent hepatic synthetic function. Standard triple therapy post-operative immunosuppression was used, consisting of prednisone, mycophenolate mofetil, and tacrolimus. Prednisone was tapered rapidly to 10 mg daily by post-operative day (POD) 12 to minimize steroid-associated psychosis.

Beginning on POD 16, the patient developed persistent fevers, respiratory failure, and pancytopenia. Computed tomography imaging of the chest demonstrated a right-sided pleural effusion, and broad-spectrum antibiotic therapy was initiated for presumed pneumonia. However, microbiological studies from the blood, urine, pleural fluid, bronchoalveolar lavage, and cerebrospinal fluid were all negative for bacteria, viruses, and fungi. On POD 23, the patient developed diarrhea and a macular erythematous eruption on the dorsal feet that subsequently generalized. No transaminitis was observed. Withdrawal of medications considered high risk for a drug eruption did not alter his disease progression. Additional viral studies including human herpes virus 6, adenovirus, parvovirus B19, Epstein–Barr virus, and cytomegalovirus serum polymerase chain reaction (PCR) were all negative.

On POD 31, the patient developed bullae on the palms and soles, epidermal denudation of the trunk and extremities, and extensive mucosal erosions (Fig. 1a). A biopsy from non-denuded skin revealed epidermal atrophy, vacuolar alteration of the basal layer, satellite cell necrosis, and foci of subepidermal vesiculation (Fig. 2). Sigmoid biopsy showed crypt dropout and epithelial apoptosis. Analysis of the peripheral blood was negative for chimerism; however, a buccal swab revealed 2% donor lymphocytes by short-tandem repeat PCR (chimerism was not assessed from the skin biopsy).

The patient was given a diagnosis of grade IV GVHD with cutaneous, enteric, and bone marrow involvement. Pulse-dose methylprednisolone was initiated on POD 34, and rabbit anti-thymocyte globulin was administered on POD 37–40, along with increased doses of mycophenolate mofetil and tacrolimus. The patient's fevers subsided, and his pancytopenia and skin findings improved rapidly (Fig. 1b). A bone marrow biopsy performed on POD 64 revealed a normocellular marrow with mixed hematopoeiesis; chimerism studies were not performed on this bone marrow sample. The patient was discharged from the hospital to a rehabilitation facility on POD 74. At 19 months post-transplant, he was alive and well with no recurrence of GVHD.

Comment

GVHD following liver transplantation was first reported in 1988 and, since that time, nearly 100 additional cases have been published.[5] The incidence of post-OLT GVHD observed in large case series ranges from 0.3% to 2%.[1,3,4,6,7] Mortality is high, about 75–85% among adults (compared with 35% among pediatric patients), and is most often attributable to sepsis, but respiratory failure, multi-organ dysfunction, and fatal hemorrhage have also been described.[1,3]

The mechanisms leading to GVHD following liver transplantation reflect interactions between lymphocytes transferred with the donor organ and the host's native immune system. In essence, these interactions can lead to three potential outcomes: if the host's immune system predominates and reacts against the donor organ, graft rejection ensues; if the donor lymphocytes predominate and react against host tissue, GVHD ensues; and if the two systems are in balance, allograft function without GVHD can be established.[8] The scenario leading to GVHD therefore requires both relative immunocompromise of the host and relative immunoreactivity of the donor lymphocytes. Based on these preconditions, Taylor *et al.* have proposed a three-phase model summarizing the pathogenesis of post-OLT GVHD: first, the recipient is relatively immuno-compromised due to pre-transplantation liver disease, the physiological stress of surgery, and the use of post-transplantation immunosuppressants; second, donor lymphocytes become activated upon interaction with host antigen-presenting cells, triggering IL-2-dependent proliferation with predominantly Th1 differentiation, which overwhelms the host's compromised immune system; and third, the cytotoxic donor T-lymphocytes target antigens expressed by host tissue, leading to cell death and tissue dysfunction.[1] A reinforcing feedback loop can then be established, whereby destruction of the host's bone marrow, skin, and mucosal epithelium leads to additional immunocompromise, and cytokines released by targeted host cells further activate donor lymphocytes.[1]

Risk factors for developing post-OLT GVHD are thus related to both donor and host immune profiles. Early studies of post-OLT GVHD revealed that donor lymphocytes are reactive not only against host tissues but also against cultured cells with HLA expression patterns similar to the host, suggesting that HLA expression contributes to GVHD risk.[9] Multiple cases of post-OLT GVHD occurring in the setting of complete HLA matching between donor and recipient have provided evidence that HLA similarity, rather than mismatching, is an important risk factor.[10,11] When HLA types are closely matched, the relatively immunocompromised recipient may not recognize donor lymphocytes as foreign, while the donor lymphocytes may still be able to react against minor host antigens, shifting the immune balance in favor of GVHD. In a large case series by Smith *et al.*, the risk of developing post-OLT GVHD increased 10-fold (from 1% to 10.3%) if the donor and recipient had no more than one mismatch in HLA-A or HLA-B alleles; the risk was 22.2% if the donor and recipient also shared at least one HLA-DR allele.[6] Similarly, Key *et al.* found that HLA-B matching independently carried a risk of post-OLT GVHD of 21%, compared with 0.4% among donor–recipient pairs who were fully mismatched at HLA-B.[12] Recipient age also contributes to GVHD risk, presumably because it is a marker of immunocompetence: recipient age >65 years carries a ninefold increased risk of developing post-OLT GVHD, and recipient age more than 40 years older than donor age carries a 10-fold increased risk.[6] Of course, HLA matching and advanced age are not prerequisites for disease development, as our case demonstrates, but rather should heighten suspicion if early clinical signs of GVHD arise.

The clinical signs of acute post-OLT GVHD include fever, rash, diarrhea, and pancytopenia. Onset typically occurs 2–8 weeks after transplantation, but rare cases occurring up to eight months beyond the transplant date have been reported.[4,6,13] The initial sign may be fever without an identified source, as was the case with our patient, though in many instances the skin represents the first organ system involved.[14,15]

The eruption of acute GVHD consists of erythematous to violaceous macules coalescing into patches, appearing on the head and neck, chest, back, and extremities, with a particular predilection for the palms and soles.[16] A centripetal progression from acral to central sites is characteristic but not always observed. As the rash evolves, bullae and full-thickness denudation may develop, along with hemorrhagic crusting at mucosal orifices.[17]

Destruction of the intestinal mucosa results in a loss of absorptive capacity, leading to diarrhea.[1] Bone marrow involvement can manifest as pancytopenia, which carries a poor prognosis due to the risk of hemorrhage and an increased susceptibility to infection.[4] The development of pancytopenia is more characteristic of post-OLT GVHD than of GVHD following hematopoietic stem cell transplant, because in the latter scenario the repopulated marrow is of donor origin. Conversely, the liver is relatively unaffected in post-OLT GVHD, unlike in cases following hematopoietic transplantation.[16]

On skin biopsy, the histopathological findings are identical to those observed in acute GVHD following hemato-poietic stem cell transplantation and include epidermal atrophy, dyskeratotic keratinocytes with adjacent lymphocytes in the epidermis (satellite cell necrosis), and vacuolar alteration of the basal layer.[15] Unfortunately, these histopathological

patterns are not specific to GVHD and can also be observed, for example, in severe drug reactions such as toxic epidermal necrolysis.[18] In fact, in a study of 179 skin biopsies from 137 patients who were suspected of GVHD following bone marrow transplantation, there was no statistically significant difference in the rate of dyskeratosis, satellitosis, or basal vacuolization observed in patients who ultimately were confirmed to have GVHD compared with those who were found to have an alternate diagnosis.[19]

Due to the lack of clinical or histopathological features specific to post-OLT GVHD, considerable interest has turned to the use of molecular techniques to confirm the diagnosis. In particular, identification of donor lymphocytes in the recipient's peripheral blood, skin, or bone marrow has been proposed as a distinguishing feature of post-OLT GVHD. Currently, the presence of donor lymphocytes is most commonly assayed by HLA typing through serological or PCR-based techniques, or by PCR-based assays of highly polymorphic short tandem repeats within genomic DNA, but in cases of donor–recipient sex mismatch, fluorescence *in situ* hybridization directed at the Y-chromosome has also been used.[20–22]

Does the identification of donor lymphocytes in the host provide diagnostic confirmation of post-OLT GVHD? By necessity, there must be at least transient peripheral chimerism for GVHD to occur, as donor lymphocytes must be exposed to antigens on target tissues to initiate a cytotoxic response. However, transient chimerism may be a nonspecific finding in OLT recipients. In the first week after liver transplantation, peripheral blood chimerism has been found in the majority of OLT recipients studied, with the proportion of lymphocytes of donor origin ranging from 1% to 24%, with an average of approximately 5%.[23–25] These values typically decline over the following 2–4 weeks. It is unclear whether persistence of peripheral blood chimerism correlates with an elevated risk of developing GVHD: Jonsson *et al.* found that patients who developed GVHD had lower levels of peripheral blood chimerism than control patients, while several subsequent studies have found that persistent peripheral blood chimerism is seen more commonly and at higher levels in patients who develop GVHD.[24–28] (In theory, transient peripheral blood chimerism could also be detected following transfusion of non-leukore-duced blood products; no evidence of transfusion-associated chimerism was detected in the current case.)

Persistent chimerism *per se* does not imply a diagnosis of GVHD, as it may instead be a marker of immune tolerance.[25,28] Conversely, an absence of peripheral chimerism may reflect dynamic circulating lymphocyte levels and, as our case illustrates, does not exclude the diagnosis of GVHD.[21,29] Nonetheless, in the vast majority of cases in which it has been investigated, peripheral chimerism has been detected in patients with post-OLT GVHD. As Table 1 demonstrates, an absence of peripheral blood chimerism or buccal chimerism has been documented only once each out of 63 previously published cases in adults. Our case is unique for being the first reported in which chimerism was absent in the peripheral blood but present in another site (the buccal mucosa).

Once the diagnosis has been made, the treatment of post-OLT GVHD requires suppression of the activated donor lymphocytes. High-dose corticosteroids are considered the first-line therapy, but post-OLT GVHD appears to be less responsive to corticosteroids than GVHD following hematopoietic stem cell transplantation, and thus additional immunosuppressive

strategies may be necessary.[1] In our case, mycophenolate mofetil and tacrolimus, which were already being used as anti-rejection agents, were continued at increased doses, while anti-thymocyte globulin, which specifically targets T-lymphocytes, was added. Additional options include azathioprine, cyclo-sporine, and tumor necrosis factor-α inhibitors, such as infliximab and etanercept.[3,14,45,46] Newer agents that may hold particular promise include the anti-IL-2 receptor antibodies daclizumab and basiliximab, which block T-lymphocyte clonal expansion.[3] Lastly, some patients have been treated via withdrawal, rather than escalation, of immunosuppression, with the intention of allowing the host's native immune system to target the donor lymphocytes; this strategy has shown success in small trials, but it may not be appropriate in advanced cases of GVHD with significant host pancytopenia.[43]

Conclusion

More than 20 years after its first description, post-OLT GVHD remains a diagnostic challenge. While host risk factors, clinical presentation, and histopathology can all provide supporting evidence, no single feature is specific to the diagnosis. Peripheral chimerism offers additional diagnostic support, but as our case and others have shown, persistence of peripheral chimerism is also neither perfectly sensitive nor specific for post-OLT GVHD. Instead, all of these findings in combination, coupled with an appropriate degree of clinical suspicion, are necessary for a timely diagnosis, with the hope of ultimately reducing mortality from this rare and severe complication of liver transplantation.

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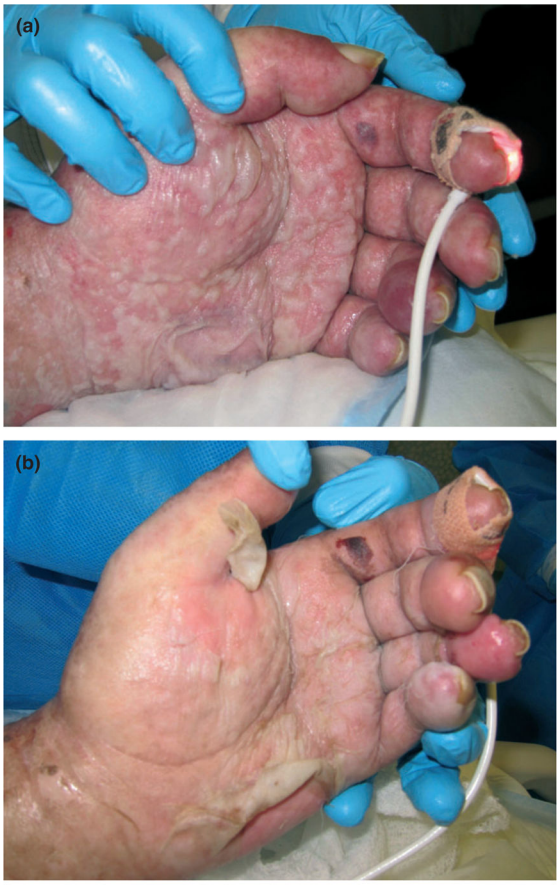

Figure 1.
(a) Erythema, bullae and denudation of the palm. (b) Improved exam after 3 days of anti-thymocyte globulin with significant reduction of erythema and residual denudation

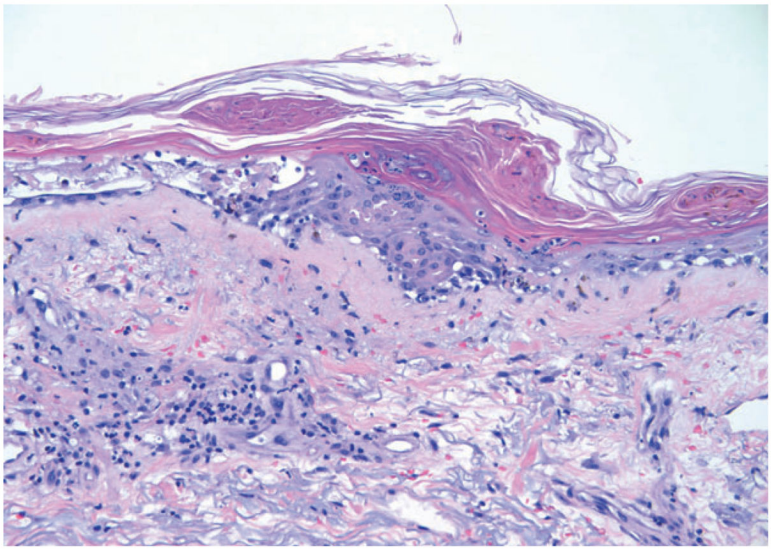

Figure 2.

Skin biopsy revealing atrophy of the epidermis, intraepidermal lymphocytes associated with dyskeratotic keratinocytes (satellite cell necrosis), vacuolar alteration of the basal layer and subepidermal vesiculation (hematoxylin-eosin, original magnification × 40)

Table 1

Summary of post-OLT GVHD cases in adults in whom chimerism was investigated

			Organ systems involved			Chimerism			
Recipient age (years)/sex	**Donor age (years)/sex**	**HLA loci mismatched (A+B; DR)**	**Skin**	**GI**	**Bone marrow**	**Blood**	**Other**	**Outcome**	**Reference**
51/M	NS/M	4/4; 2/2	+	+	+	+	+ Marrow	Survived	(5)
56/M	20/M	4/4; 2/2	+	+	+	+	NS	Died	(30)
55/M	22/M	3/4; NS	+	+	+	+	NS	Survived	(2)
57/M	22/M	4/4; NS	+	+	+	+	NS	Died	
44/M	NS/NS	2/4; 0/2	+	+	+	NS	+ Autopsied solid organs	Died	(31)
55/M	NS/NS	NS	+	+	+	NS	+ Autopsied solid organs	Died	
53/M	NS/NS	NS	+	+	+	+	NS	Died	
52/F	NS/M	4/4; 0/2	+	+	+	+	NS	Died	(32)
18/F	NS/M	NS	+	+	+	NS	+ Marrow	Died	(33)
53/M	NS/NS	1/4; 2/2	+	+	+	+	+ Skin	Died	(34)
52/F	NS/NS	NS	+	+	+	+	NS	Survived	(16)
65/F	17/M	2/4; 2/2	+	+	+	+	NS	Died	(9,35)
30/M	NS/NS	4/4; 0/2	+	+	+	+	NS	Died	(36)
52/F	32/F	1/4; 1/2	+	+	+	NS	+ Skin, marrow	Died	(10)
49/F	NS/NS	4/4; 2/2	+	−	−	+	NS	Died	(37)
50/F	NS/M	NS; 1/2	+	+	+	NS	+ Marrow	−	(17)
42/M	35/M	4/4; 1/2	+	+	+	+	NS	Died	(38)
56/M	NS/NS	3/4; 2/2	+	−	+	+	+ Skin	Survived	(39)
63/M	23/M	3/4; 2/2	+	+	+	NS	+ Skin	Died	(40)
68/M	74/M	3/4; NS	+	+	+	+	NS	Died	(41)
68/M	NS/NS	NS	+	+	−	+	NS	Died	(14)
38/F	NS/M	3/4; 1/2	+	+	+	+	+ Skin, marrow	Died	(20)
37/M	NS/NS	NS	+	+	−	−	NS	Died	(29)
29/M	18/M	3/4; 2/2	+	−	+	+	+ Marrow	Survived	(42)
NS/NS	NS/NS	4/4; 1/2	+	+	+	+	NS	Died	(6)
NS/NS	NS/NS	2/4; 2/2	+	−	+	+	NS	Died	
NS/NS	NS/NS	2/4; 2/2	−	−	+	+	NS	Survived	

			Organ systems involved			Chimerism			
Recipient age (years)/sex	**Donor age (years)/sex**	**HLA loci mismatched (A+B; DR)**	**Skin**	**GI**	**Bone marrow**	**Blood**	**Other**	**Outcome**	**Reference**
NS/NS	NS/NS	3/4; 2/2	+	−	+	+	NS	Died	
NS/NS	NS/NS	1/4; 1/2	−	−	+	+	NS	Died	
NS/NS	NS/NS	1/4; 1/2	+	+	+	+	NS	Died	
NS/NS	NS/NS	3/4; 1/2	+	+	+	+	NS	Died	
NS/NS	NS/NS	4/4; 1/2	+	+	+	+	NS	Died	
NS/NS	NS/NS	1/4; 1/2	+	−	+	+	NS	Died	
NS/NS	NS/NS	4/4; 2/2	+	+	+	+	NS	Died	
NS/NS	NS/NS	3/4; 2/2	+	+	+	+	NS	Died	
NS/NS	NS/NS	0/4; 1/2	+	+	+	+	NS	Died	
48/M	20/M	0/4; 0/2	+	+	+	+	+ Marrow	Died	(11)
49/M	NS/NS	NS	+	NS	NS	+	NS	Survived	(27)
56/M	NS/NS	NS	+	NS	NS	+	NS	Died	
59/F	NS/NS	NS	+	NS	NS	+	NS	Died	
59/M	NS/NS	NS	+	NS	NS	+	NS	Died	
61/M	NS/NS	NS	+	NS	NS	+	NS	Died	
63/M	NS/NS	NS	+	NS	NS	+	NS	Survived	
68/M	NS/NS	NS	+	NS	NS	+	NS	Died	
52/M	53/F	3/4; 2/2	+	+	+	+	NS	Died	(13)
66/F	NS/M	0/4; 0/2	+	+	−	+	+ Skin, GI, marrow	Died	(21)
53/M	50/M	3/4; 1/2	−	−	+	+	NS	Survived	(43)
58/M	24/M	0/4; 1/2	+	−	+	+	+ Skin	Survived	
62/M	8/M	4/4; 1/2	+	+	+	+	NS	Died	
59/F	NS/NS	NS	+	NS	NS	+	NS	Died	(3)
66/F	NS/NS	NS	+	NS	NS	+	NS	Died	
55/M	NS/NS	NS	+	NS	NS	+	NS	Died	
48/F	NS/NS	NS	+	NS	+	+	NS	Died	
64/M	NS/NS	NS	+	+	+	+	NS	Died	
67/M	NS/NS	0/4; 2/2	+	NS	+	+	3 Buccal	Survived	(44)
30/M	64/M	4/4; 1/2	+	+	+	+	NS	Died	(4)
44/F	60/M	2/4; 2/2	+	+	−	+	NS	Died	

			Organ systems involved			Chimerism			
Recipient age (years)/sex	**Donor age (years)/sex**	**HLA loci mismatched (A+B; DR)**	**Skin**	**GI**	**Bone marrow**	**Blood**	**Other**	**Outcome**	**Reference**
61/M	51/M	4/4; 2/2	+	−	+	+	NS	Died	
64/F	36/F	3/4; 1/2	+	−	+	+	NS	Died	
67/M	42/F	4/4; 2/2	+	+	+	+	NS	Died	
49/F	NS/M	0/4; 0/2	+	+	+	NS	+ Skin, marrow	Died	(22)
65/M	74/F	2/4; 1/2	+	+	+	+	+ Skin, marrow	Survived	(45)
67/M	61/M	4/4; 2/2	+	+	+	+	NS	Survived	(46)
57/M	56/M	4/4; 2/2	+	+	+	−	+ Buccal	Survived	Current case

+: present; −: absent; GI, gastrointestinal; NS, not stated.