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Fever and Pancytopenia in a Liver Transplant Recipient: Going Against the Rules of Occam's Razor

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Abstract: The syndrome of fever and pancytopenia is not infrequently encountered postliver transplant, and a broad differential list of infectious and noninfectious aetiologies can be invoked. A transplant patient is susceptible to more than 1 opportunistic infection or disease process. We described the diagnostic conundrums in managing our patient who ran a complex protracted course postliver transplant. He was diagnosed to have both disseminated tuberculosis and graft-versus-host disease, a rare complication after solid organ transplantation.

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The main causes of fever and pancytopenia in a liver transplant recipient include infections from the herpesviridae, such as cytomegalovirus posttransplant lymphoproliferative disease, and adverse drug events. In addition, a high index of suspicion for mycobacterial infections and endemic mycoses, such as histoplasmosis and penicilliosis, should be maintained especially in patients with epidemiological risk factors. We report a case of disseminated tuberculosis (TB) diagnosed after extensive investigation. The patient ran a protracted unusual course despite TB treatment, which led us to pursue a coexisting diagnosis of graft-versus-host disease (GVHD).

Case Report

A 62-year-old Vietnamese-born man with diabetes mellitus and untreated genotype 6 chronic hepatitis C cirrhosis with a baseline Hepatitis C viral load of 5 log underwent deceased-donor liver transplantation for hepatocellular carcinoma. Baseline hepatitis B and human immunodeficiency virus serology were negative. He did not drink alcohol and denied intravenous (IV) drug use. The route of acquisition of hepatitis C was unknown. He had been living in Australia for the past 30 years and worked as a tailor. Three months before transplant, he had a pleurodesis for a left pleural effusion which was transudative in nature with negative microbiology (including acid-fast bacilli [AFB] smear, cultures and TB polymerase chain reaction [PCR]). Posttransplant medications included induction basiliximab, tacrolimus and mycophenolate mofetil, prophylactic sulfamethoxazole-trimethoprim and valganciclovir.

The liver donor was a 63-year-old Indian-born woman who was deceased after brain death from an intracranial haemorrhage. No donor-specific antibodies were identified and T cell and B cell crossmatch were negative. The HLA mismatches involved A24, B18, B51, DR8, and DR13.

Two months posttransplant, he presented with fever, hypotension, left pleural effusion, and pancytopenia (white cell count, $0.4 \times 10^9/L$ [reference range, 4.0-10.0]; hemoglobin, 62 g/L [reference range, 120-150]; platelets, $48 \times 10^9/L$ [reference range, 150-400]). He was commenced empirically on IV piperacillin-tazobactam. Medications contributing to pancytopenia (mycophenolate mofetil, sulfamethoxazole-trimethoprim, and valganciclovir) were ceased. Microbiological cultures (including AFB smear and cultures) from the blood, sputum, and left pleural effusion were unyielding. Nucleic acid tests for cytomegalovirus, Epstein Barr virus, human herpesvirus-6, and ParvoB19 in the blood were negative for acute

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infection as were histoplasma and Brucella serology. The bone marrow was hypocellular with features of mild hemophagocytosis. Although there was initial uncertainty in attributing the presentation wholly to hemophagocytic lymphohistiocytosis, a raised ferritin of 3679 $\mu\text{g/L}$ (reference range, 20-300) and the absence of any alternative diagnosis prompted treatment with IV immunoglobulin (IVIg), a weaning dose of dexamethasone together with granulocyte colony-stimulating factor support which resulted in gradual improvement in his blood counts (white cell count, $4.0 \times 10^9/\text{L}$ [reference range, 4.0-10.0]; hemoglobin, 77 g/L [reference range, 120-150]; platelets, $173 \times 10^9/\text{L}$ [reference range, 150-400]) and fever. Having also received harvoni (ledipasvir/sofosbuvir), hepatitis C viral load was negative at this point.

One week later, fever recurred and the blood counts declined again (white cell count, $1.2 \times 10^9/\text{L}$ [reference range, 4.0-10.0]; hemoglobin, 72 g/L [reference range, 120-150]; platelets, $115 \times 10^9/\text{L}$ [reference range, 150-400]). The patient had *Pseudomonas aeruginosa* pneumonia based on imaging and positive blood culture. Despite prompt clearance of bacteraemia with IV meropenem, there was persistent high fever. A positron emission tomography-computed tomography scan revealed multiple bilateral lung nodules associated with supraclavicular and mediastinal lymphadenopathy. Despite previous negative TB investigations, a high index of suspicion for TB based on epidemiological risk factors prompted urgent biopsy of supraclavicular lymph node and a repeat sputum examination for TB. AFB smear and TB PCR on both the supraclavicular lymph node and sputum were positive, and AFB cultures subsequently yielded pan-sensitive TB.

Treatment for TB comprising rifabutin, isoniazid, ethambutol, and moxifloxacin together with pyridoxine was commenced promptly. Pyrazinamide was substituted by moxifloxacin to minimize liver dysfunction on top of the potentially hepatotoxic backbone of rifabutin and isoniazid. Tacrolimus levels were monitored closely in view of potential drug interactions with rifamycins and kept between 8 and 12 ng/mL.

Unfortunately, there was ongoing intermittent fever and pancytopenia despite 4 weeks of TB treatment. A repeat bone marrow examination now revealed a positive TB PCR. Tacrolimus was ceased at this point because he was deemed to have no immunological capability for organ rejection and to ameliorate the net immunosuppression. A progress CT chest showed improvement in the lymph nodes and lung lesions, deeming paradoxical reaction from TB treatment unlikely.

Six weeks after commencement of TB treatment, he developed a generalized desquamating rash (without erythema multiforme-like target lesions) with cheilitis and buccal erosion. Throughout this, he had persistent fever and pancytopenia but maintained normal serum transaminases. A drug-related adverse event was felt to be most likely. A delayed β -lactam-induced drug eruption was favored given that rash was nonprogressive despite continuation of TB treatment. Pellagra was also possible in view of progressive malnutrition despite aggressive nasogastric dietary supplements. A skin biopsy was performed (Figure 1).

Unfortunately, the patient continued to deteriorate significantly. He had high spiking fevers up to 39°C with refractory pancytopenia despite granulocyte colony-stimulating factor support. He had an episode of gastrointestinal bleed amidst

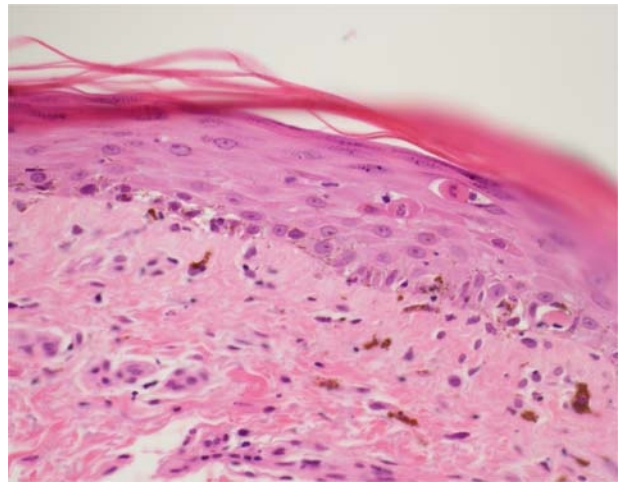


FIGURE 1. Skin biopsy, hematoxylin and eosin stain, $\times 400$ magnification. The epidermis showed apoptotic keratinocytes accompanied by lymphocytes, basal vacuolar change, and a sparse lymphocytic infiltrate in the dermis.

intercurrent infections with pneumonia and *Enterococcus faecium* line sepsis and subsequently developed multiorgan failure leading to his demise 8 weeks after starting TB treatment.

The skin biopsy (Figure 1) revealed apoptotic keratinocytes predominantly in the stratum basalis reaching into stratum spinosum with minor basal vacuolar damage and lymphocyte exocytosis. There was no full thickness epidermal necrosis or granulomas. The biopsy raised the possibility of grade 3 GVHD or an erythema multiforme-like drug eruption. The presence of apoptotic keratinocytes was not an expected finding of pellagra.

After his demise, chimerism testing on the skin biopsy was performed. Short tandem repeats and sex-specific Amelogenin analysis of the skin tissue revealed 41.6% female DNA, in keeping with the diagnosis of GVHD.

DISCUSSION

This is a complex case of a liver transplant patient with disseminated TB and GVHD. Cases of TB in association with GVHD has been described in the hematopoietic stem cell transplant recipients, whereby intense immunosuppression used to treat GVHD has resulted in reactivation of TB.^{1,2} This is the first report on GVHD in a liver transplant recipient with disseminated TB. To date, there is no well-established immunological link between TB and GVHD in solid organ transplant patients, just as GVHD is poorly understood in solid-organ transplant recipients.

GVHD is thought to be due to the inability of the immunosuppressed transplant recipient to reject immune-active donor lymphocytes in the transplanted graft as foreign, leading to cell mediated tissue destruction.³ GVHD occurs much less frequently in liver transplant recipients (0.1-2%) than in haematopoietic allogeneic stem cell transplant recipients (30-50%).⁴ The average time between liver transplant and first symptom is 60.6 days.⁴ Clinical manifestations include rash in 94.2%, fever in 66.6%, diarrhea in 54%, and pancytopenia in 54%, classically not affecting the liver function.⁴ Our patient had all the above features except diarrhea.

Risk factors for developing GVHD in solid organ transplant recipients described in the literature include close HLA

matching between donor and recipient, recipient aged 65 years or older, recipient donor age difference of 40 or greater, glucose intolerance, autoimmune hepatitis, alcoholic liver disease, and pretransplant hepatocellular carcinoma.^{5,6}

As disseminated TB and GVHD have overlapping clinical manifestations, it was difficult to ascertain definitively the onset of GVHD in this patient until the rash occurred. However, we postulated that the initial treatment for possible hemophagocytic lymphohistiocytosis with steroids and IVIG could have hastened the reactivation of TB but it could have also partially treated an undiagnosed GVHD, as evidenced by the transient improvement in the pancytopenia and the fever.

Diagnosis of GVHD rests heavily on histological features in affected end organs like the skin and gut and is confirmed by chimerism testing—the demonstration of donor lymphocytes in recipient tissues.⁴

Treatment of GVHD in solid organ transplant recipients is not well established. Corticosteroids, antithymocyte/lymphocyte globulin, IVIG, basiliximab, rituximab, alemtuzumab, and TNF- α antagonists have been used. It is not also clear if immunosuppression should be ceased to allow recipient cells to mount a response against foreign cells. Mortality remains as high as 67.8% to 91.6%,⁴ the majority dying from sepsis, multiorgan dysfunction, and gastrointestinal bleed.

Although we tread into no man's land dealing with GVHD in a liver transplant patient, the other contention lies in the strategies for TB prevention in a solid organ transplant patient. Most experts would recommend screening and treating latent TB in a solid organ recipient,⁷ but our liver transplant center, with low prevalence of TB, adopts a strategy of close follow-up and prompt evaluation for TB in patients with strong epidemiological risk factors as opposed to screening and offering isoniazid prophylaxis upfront, given its risk of hepatotoxicity and unfavorable cost-benefit ratio. This was based on a number-needed-to-harm of 15 to 27 (hepatotoxicity in age group of 50-64 years)⁸ with isoniazid treatment as opposed to a number-needed-to-treat of 49.7 to 79.5⁹ to prevent 1 case of TB. Due effort was made to exclude active TB before transplant in this patient. He had an unremarkable

CT chest and a negative AFB smear, AFB culture and TB PCR on sputum. Donor-derived infection was less likely because the liver donor had no symptoms or radiological features of TB and the other organ recipients from this donor did not develop TB posttransplant.

In conclusion, this was an immunosuppressed patient who ran a complex, protracted, and unusual course posttransplant. Often, the pursuit of additional or alternative diagnoses may require repeated and multiple invasive diagnostic sampling. Although infections may explain many complications after transplant, noninfective (drug, malignant, or immunological) etiologies may coexist, much against the principle of Occam's Razor.

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