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Aplastic Anemia Post Liver Transplant Due to Graft-versus-host Disease

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ABSTRACT

INTRODUCTION:

The patient was a 64-year-old male presented with a 2 day history of increasing fevers and altered mental status. He underwent orthotopic liver transplant for cryptogenic cirrhosis, probably secondary to non-alcoholic steatohepatitis, 45 days before. The head and neck imaging showed negative changes. CBC at admission showed pancytopenia with WBC 0.6 x 109 /L., hemoglobin 6.8 g/dL and platelet 29 x 109 /L.

METHOD:

Bone marrow biopsy demonstrated marked hypocellular marrow. Bone marrow culture showed no acid fast bacteria or fungal growing. EBV in-situ hybridization, CMV immunohisto-chemical (IHC) stain, Grocott's methenamine silver stain and Ziehl–Neelsen stain on bone marrow were all negative. CD3 and CD20 IHC stains showed significant increase ofT cell but no B cell in bone marrow. HLA typing test of the bone marrow demonstrated chimerism with the presence of both liver donor and recipient lymphocytes, which is diagnostic for graft-versus-host disease (GVHD). No third HLA typing present ruled out transfusion-associated GVHD. The biopsy of skin rash on left arm showed vacuolar interface dermatitis with intraepidermal necrotic keratinocytes.

CONCLUSION

The differential diagnosis of aplastic anemia post liver transplant include: anaplastic anemia associated with non-A, non-B, non-C fulminant hepatic failure, medication, viral infection including parvovirus B19, CMV and EBV, post transplant lymphoproliferative disease, GVHD and some other etiology such as iron deficiency, renal insufficiency, hypersplenism, hemolysis. The incidence of GVHD post liver transplant is <1% and the mortality is 75-90%. The presentation includes fever, skin rash, diarrhea and pancytopenia. The diagnosis is demonstration of chimerism with the presence of both donor and recipient lymphocytes in PB and BM. The treatment includes immunosuppression and bone marrow transplant, but is usually ineffective.

CLINICAL COURSE

The patient is a 64-year-old male presented with a 2 day history of increasing fevers and altered mental status. His past medical history includes orthotopic liver transplant for cryptogenic cirrhosis, probably secondary to non-alcoholic steatohepatitis, 45 days ago. The clinical course was uneventful after the liver transplantation. He was found to be C. difficile positive and was put on appropriate antibiotics. He still spikes every night, up to 102 F; accompanied with tremors and decreased mental status. The head and neck imaging is negative. His liver function test is close to the normal range. CBC shows pancytopenia with WBC 0.6 x 109/L, Hb 6.8 g/dl, MCV 82 fL, reticulocytes 0.3%, reticulocytes absolute 6 x 109/L, and platelet 29 x 109/L.

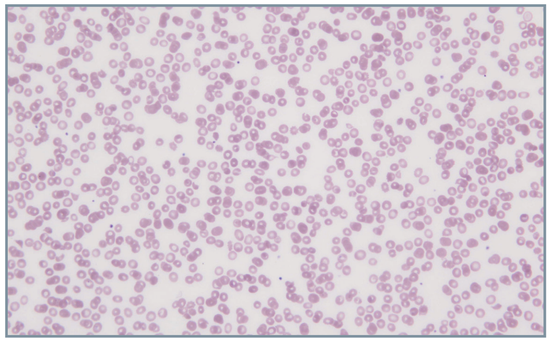

Figure 1: Peripheral blood smear shows severe pancytopenia

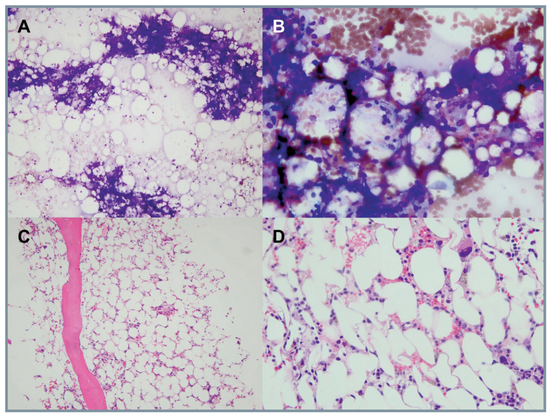

Figure 2: Bone marrow aspirate and biopsy. Bone marrow aspirates (A. 200X magnification and B. 400X magnification) show hypocellular spicules in bone marrow composed mostly by stromal cells. Bone marrow biopsy (C. 200X magnification and D. 400X magnification) shows severe hypocellular (variable, 1-10% cellularity) bone marrow with trilineage maturation.

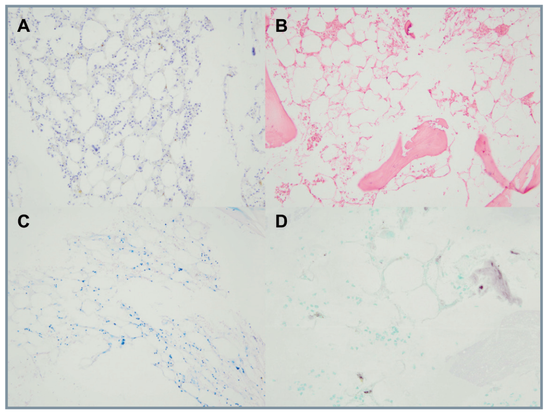

Figure 3: Immunohistochemical staining for CMV (A), in-situ hybridization for EBER (B), special stains for AFB (C) and GMS (D) show no infectious process involving the bone marrow.

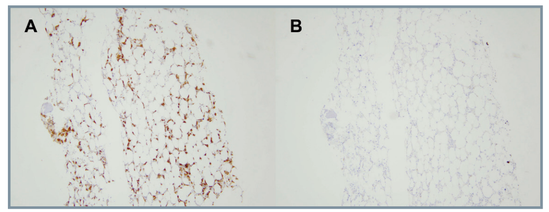

Figure 4: Immunohistochemical staining for CD3 (A) and CD20 (B) demonstrate increased T cells infiltrating the bone marrow.

	Patient's buccal mucosa	Transplant liver	Patient's current Bone Marrow
HLA A	A02, A29	A02, A26	A02, A26
HLA B	B58, B44	B38, B52	B44, B58, B38, B52
HLA C	C07, C16	C12, C-Bw4	C07, C16, C12
HLA DRB1	DR07, DR15	DR4, DR15	DR07, DR15, DR04
HLA DQB1	DQ02, DQ06	DQ06, DQ08	DQ02, DQ06, DQ08

Table 1: By PCR-sequence specific primer (SSP), HLA typing of transplant liver (donor), patient's buccal mucosa and patient's bone marrow are identified.

FINAL DIAGNOSIS

Liver transplant-associated GVHD

DIFFERENTIAL DIAGNOSES

- Transfusion-associated GVHD
- Viral infection (Parvovirus B19, CMV, EBV)
- Medications (Tacrolimus, cyclosporine A, Sirolimus, MMF, Azathioprine)
- Aplastic anemia (non-A, non-B, non-C fulminant hepatitis due to unknown viral infection)
- Hemolysis following ABO-incompatible liver transplant
- Hypersplenism
- PTLD: 2% of liver transplant; poor prognosis
- Renal insufficiency: drug effect, diabetes, HTN

RISK FACTORS FOR GVHD AFTER LIVER TRANSPLANTATION

- Close HLA matching as a significant risk factor for GVHD
- Multiple HLA class I mismatches protect against GVHD
- More frequent in older patients (age >65 years) with younger donors (age difference of >40 years)

TREATMENT OF GVHD

- Increased immunosuppression with high-dose steroids and antibody preparations such as antithymocyte globulin, antilymphocyte globulin and Prednisolone.
- Broad antibiotic and antifungal prophylaxis
- Restoration of the host's immune system.

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