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Severe Thrombocytopenia Associated With Helicobacter Pylori Infection after Liver Transplantation: Cases Report and Literature Review

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Liver transplantation; Immune thrombocytopenia; Helicobacter Pylori

1. Abstract

Thrombocytopenia is a common complication following Liver Transplantation (LT). Immune Thrombocytopenia (ITP) associated with Helicobacter Pylori (HP) infection following LT has never been reported. We reported two cases of post-LT ITP refractory to corticosteroid therapy successfully treated with anti-HP therapy after detection of HP infection. The underlying mechanism was analyzed and related literature was reviewed. HP detection is recommended in the management of post-LT ITP cases.

2. Introduction

Liver Transplantation (LT) has been used for patients with end-stage liver disease and hepatic malignancy. Thrombocytopenia is a common complication following LT. Chatzipetrou et al. reported in a study including 541 LT recipients that90.9% of the cases had 56.5%+/-23.5% fall in platelets within the first 2 weeks and may exceed preoperative levels during 3rd or 4th post-operative weeks. Nadir of post-LT thrombocytopenia may be on Postoperative Days (PODs) 3-5 [1, 2]. The suggested mechanism for post-LT thrombocytopenia includes hemodilution, decreased Thrombopoietin (TPO) production, increased platelet sequestration in the liver graft or spleen, immunological reactions, platelet consumption due to venous thrombosis or Disseminated Intravascular Coagulation (DIC), Thrombotic Micro Angiopathy (TMA), drug-induced, various infections and complex factors [3]. Among them, alloimmune reaction initiated by passenger lymphocytes carried by graft can cause Immune Thrombocytopenia (ITP) following LT [4]. Based on Taylor's investigation in 1105 LT recipients, the prevalence of new-onset ITP were 0.7%. Post-LT ITP is one of the causes of severe symptomatic thrombocytopenia requiring hospitalization and treatment [5-10]. Reports up to date showed that post-LT ITP may be idiopathic, drug-induced, lymphoma or infection associated [11-15].

ITP has long been associated with Helicobacter Pylori (HP) infection [16, 17]. But new-onset ITP associated with HP infection after LT has never been reported. Here, we present two cases with severe post-LT thrombocytopenia associated with HP which occurred at different post-LT time. The corresponding pathophysiology and management measures were analyzed. Written informed consent was obtained from the patients for the publication of this study. The livers transplanted to the recipients reported here were donated from car accident victim's diagnosed brain death after active rescue treatment, organs from executed prisoners were not used.

3. Cases Presentation:

3.1. Case 1:

A 63-year-old male patient was admitted due to progressively enlarged intrahepatic nodule for 21 months without any symptoms. A small intrahepatic nodule with a diameter of 7mm and slightly peripheral augmentation by contrast enhanced Computed Tomography (CT) was found at the 5th segment of the patient's right hepatic lobe 21 months before. But the patient neglected it. On a recent chest CT, the nodule had enlarged into a 55mm-diameter space occupying lesion. Mean while, his alpha-Fetus Protein (AFP) and CA19-9 levels both increased to 9.06ng/ml and 31.19U/ml re-

spectively. The lesion was considered primary hepatic cancer. He had a past history of hepatitis B for 30 years and had taken oral lamivudine intermittently. He was found to have asymptomatic cholecystolithiasis for several years.

At presentation, the patient was in good condition. His blood, urine and stool routine test, coagulation tests, serum biochemistry analysis including transaminase levels, bilirubin levels, blood urea nitrogen and creatinine test results were all within normal range.

As the foci was close to the right hepatic pedicle and was a solitary one, hepatectomy together with liver transplantation was advised and accepted by the patient and his family members. The patient was evaluated to be fit for the operation. A week later, he got the chance of liver transplantation from a young male donor who was diagnosed brain death after a car crash accident. The donor has also donated his two kidneys to two other patients who had fully recovered after operation without complications. With adequate preparation, our patient received hepatectomy and orthotropic liver transplantation during which 1200ml of plasma was infused and blood loss of 1300ml was recorded. Tacrolimus and sirolimus were used to prevent Graft Versus Host Disease (GVHD). Lab test results on the second day indicated that his hepatic function recovered well with only moderate increased transaminase levels, bilirubin levels and INR whereas his platelet count decreased from 130×109/L before operation to 51×109/L. As his liver function gradually recovered to normal, his platelet count dropped further to 11×109/L on the 3rd post-operation day. He developed cough and bloody sputum. He was refractory to every day platelet transfusion with platelet count dropped to 4×109/L on the 5th post-operation day. Tests for hepatitis B or C virus, cytomegalovirus, Epstein-Barr virus replication were all within normal range. With antibiotic prophylaxis, no evidence of active bacterial infection was detected. As allo-antibody against his platelet was detected by ELISA method and bone marrow smear analysis demonstrated active marrow and megakaryocyte proliferation with rare platelet-producing megakaryocyte, diagnosis of post-transplantation immune thrombocytopenia was made. Every day platelet transfusion was discontinued. He was administered high-dose intravenous immunoglobin (IVIG), corticosteroid, recombinant human thrombopoietin (rhTPO) and vasopressor for pulmonary bleeding control. His cough and bloody sputum alleviated after the 6th post-transplantation day, but his platelet count remained less than 10×109/L. On the 11th day, Helicobacter Pylori (HP) was detected by a 14C-urea breath test and anti-HP therapy was given. On the 13th day, his platelet count rose up to 18×109/L and kept on increasing afterwards. His platelet count came back to normal (140×109/L) on the 25th post-transplantation day and did not drop again since then even after corticosteroid tapering. It is now a year after the transplantation and the patient is in good condition with normal platelet count.

3.2. Case 2

A 66-year-old male patient presented with frequent skin purpura, and gum bleeding for 2 years. He was diagnosed liver cirrhosis secondary to schistosomiasis and received cholecystectomy due to cholecystitis more than ten years before. He received splenectomy 9 years before due to hypersplenism after which his blood routine results recovered from pancytopenia to normal. He received liver transplantation from a deceased donor of car accident 7 years before and was administered mycophenolate mofetil and tacrolimus for GVHD prevention. He recovered well without GVHD or liver function abnormality. With recurrent mucocutaneous hemorrhage and thrombocytopenia (platelet count<10×109/L) 2 years ago, he was diagnosed immune thrombocytopenia in another hospital. He was treated with corticosteroid, IVIG, rhTPO supported by platelet transfusion and recovered with normalized platelet count. His anti-GVHD regimen was adjusted to cyclosporin alone. But his purpura and gum bleeding recurred one month before when his platelet count was 15×109/L and was admitted to the same hospital. He did not respond to the same treatment as his thrombocytopenia aggravated and hematuria presented resulting in moderate anemia. He was referred to our hospital. On admission, PE showed that he was vitally stable except slight hypertension, ptosis of his upper eyelid and mucocutaneous bleeding was noticed. Lab results included normal white blood cell count, moderate anemia and platelet count of 2×109/L. Other lab test results included positive anti-human globulin test (Coombs test), positive autoantibody and alloantibody against platelets by ELISA method, no deficiency in ferritin, vitamin B12 or folic acid, normal thyroid function and serum hepatitis B or C virus negative. Bone marrow morphology showed proliferative marrow, macrocytosis of erythroid cell lines, decreased megakaryocyte count with maturation defect signs. Bone marrow biopsy pathologic analysis demonstrated normal megakaryocyte proliferation. A diagnosis of Evans Syndrome (ES) was made and the patient was administrated high-dose corticosteroid, immunoglobulin and oral eltrabopag which took effect very slowly. His platelet count could reach 44×109/L. Further treatment with three courses of low dose decitabine (3.5mg/Kg/day for 3 days) did not work even in combination with IVIG, methylprednisolone and eltrabopag. Then, apostive14C-urea breath test result confirmed HP infection. Two weeks after initiation of anti-HP therapy, his hemoglobin level and platelet count came back to normal. Since then, his platelet count fluctuated between 43×109/L and 227×109/L with combination therapy of eltrabopag, low dose (5mg per day) prednisone and cyclosporine treatment. On the recent follow-up a year after his discharge from hospitalization, both his hemoglobin level and platelet count were still within normal range.

4. Discussion

Both cases reported here have presented with severe, symptomatic thrombocytopenia and were diagnosed ITP after LT. It has been

reported that platelet count fell in up to 90% of post-LT patients [1]. The putative mechanisms and factors include hemodilution, immunologic reactions, decreased TPO production, sequestration of platelets in the liver graft, increased platelet consumption, drug induced, various infections associated or complex factors [3]. TPO, a cytokine produced mainly in the liver, plays an important role in megakaryocyte maturation, regulation of the amount, growth, and size of megakaryocyte ploid. Its blood concentration may decrease in patients with advanced liver diseases due to reduced messenger RNA expression. Goulis et al. have demonstrated that platelet count decreased further in the first days after LT. Just after the nadir of thrombocytopenia, TPO concentration increased and reached a peak on OPD5 followed by subsequent rise in platelet count which return to normal within further 4 to 6 days. Commonly, the platelet count decreased by 30% to 50% after LT due to platelet entrapment in the graft and decreased TPO level [18-20].Very severe or delayed recovery of thrombocytopenia may be caused by other factors including ITP, TMA, drug induced or lymphoma, etc [10]. The platelet count of Case 1 reported here also decreased following similar pattern but with much more severity and longer course refractory to platelet transfusion. With life-threatening pulmonary bleeding, salvage therapy was imperative. Response to IVIG, corticosteroid and detection of allo-antibody to platelets suggested the presence of ITP. Case 2 developed thrombocytopenia 7 years after LT. Initial response to corticosteroid, IVIG and the detection of auto-antibody to platelet glycoprotein verified the diagnosis of ITP, too. With positive anti-human globulin test result, case 2 was further diagnosed ES which is the combination of ITP and Autoimmune Hemolytic Anemia (AIHA). Several cases of post-LT ES had been reported, most of which were associated with chronic GVHD not seen in our patient. [21-26].

For adult patients with ITP, the International Consensus Report and the McMaster ITP Registry approach have suggested to detect evidence of HP infection and its eradication was recommended [27]. HP is a spiral-shaped, microaerophilic, gram-negative bacillus transmitted via the fecal-oral or oral-oral route and colonizes the gastric mucosal lining of the infected individuals for a lifetime. It is prevalent in more than half of the world's population but mainly people in developing countries. The 14C urea breath test was used to confirm active infection [28]. Higher incidence of HP infection has been reported in patients with liver cirrhosis and hepatocellular carcinoma developed from chronic HBV or HCV infection comparing with healthy controls [29, 30]. Cases of HP infection after LT have been reported and have been associated with the development of peptic ulcer and lymphoma [31, 32]. But ITP associated with post-LT HP infection has never been reported.

Several mechanisms have been implicated in the pathogenesis underlying HP infection associated ITP. Molecular mimicry between the highly antigenic cytotoxin-associated gene A (CagA) of HP and platelet-associated IgG (PAIgG) can cause cross-reaction between Anti-cagantibodies and GPIIb/IIIa platelets surface antigen resulting in accelerated immune complex formation and clearance of platelets in the host Reticuloendothelial System (RES). It was also suggested that the interaction of HP-bound Von Willebrand Factor (VWF) with platelet surface Ag (GPIb) lead to increased platelet activation and clearance. Another mechanism is the enhancement of platelet phagocytosis due to decreased inhibitory Fc-γ receptor IIB on monocytes from HP-positive patients. The vacuolating cytotoxin A (VacA), another virulence factor of HP may block the proliferation of helper T cells by interfering with the T-cell receptor interleukin 2 (IL-2) pathway. The binding of VacA to multimerin-1 on platelets may result in enhanced platelet activation and clearance [17]. But the exact role of HP in the interference of immune reaction against platelets in the context of LT and anti-GVHD therapy following LT underlying refractory ITP need to be further studied.

HP infection is acquired mainly during childhoods who are mostly asymptomatic and usually persists unless treated. The prevalence of HP infection is geographically variable, from 6% in developed countries to more than 60% in developing countries [33]. HP eradication has been reported to be associated with a platelet count rise in up to 50%of HP–positive patients with ITP [34-36]. Although the two patients reported here had their ITP occurred at different period after LT, they were both refractory to corticosteroid therapy. Case 1 was also refractory to rhTPO therapy and case 2 was refractory to multi-line therapy including rhTPO, eltrobopag and low-dose decitabine. But both had their platelet count recovered after anti-HP therapy in combination with other therapy. Case 1 had complete recovery of thrombocytopenia even after corticosteroid tapering and case 2 had his ESrecovered with sustained response to eltrobopag and very low-dose of corticosteroid. We suggest that larger-scale of investigation over HP infection prevalence in patients with ITP following LT be conducted. Based on our experience in the management of these cases, we strongly recommend the addition of HP detection lab test to the diagnostic algorithm for post-LT refractory thrombocytopenia associated with severe or refractory ITP or ES.

In summary, we have reported two cases with post-LT ITP with one of which complicated with ES successfully treated with anti-HP therapy after failure of multi-line treatment. We recommend the detection and treatment of HP infection in patients with post-LT ITP or ES.

5. Author Contribution

Xu Ye has collected the case records and been involved in the care of the patients and wrote the article.

6. Statement of Ethics

We state that the patients reported here have given their written informed consent to publish this report. Our study protocol was approved by the hospital's committee on human research.

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