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Case Report
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Evans Syndrome: A Rare Complication of a Living Related Pediatric Liver Transplantation

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Abstract

Introduction: Liver transplantation is considered a lifesaving procedure for patients with decompensated liver cirrhosis, when there are no available medical and surgical treatment options. The improvement in outcomes has led to the advent of an increased incidence of both acute and long-term complications after liver transplantation. Evans syndrome is a rare hematological disorder associated with a positive direct antiglobulin (Coombs) test, Autoimmune Hemolytic Anemia (AIHA) with Immune Thrombocytopenia (ITP) in the absence of any underlying etiology.

Case Report: Here, we present a five-and-a-half-year-old patient who underwent a related living-donor liver transplantation and presented with Evans syndrome as a post-transplant related complication. The patient was initially treated with prednisolone 2 mg/kg and during tapering had a relapse after which intravenous immunoglobulin was added to his therapy, with a good response. After a year of follow up, our patient maintained his hemoglobin level and platelet count on 0.25 mg/kg (5 mg) of prednisolone and tacrolimus as immunosuppressive medication. Our patient demonstrated a few transplant-related complications including Epstein Barr virus related post-transplant lymphoproliferative disorder and late portal vein thrombosis. These may have contributed to our patient developing Evans syndrome.

Conclusion: There was an acceptable response to first-line therapy of Evans syndrome and close follow up is required to timeously identify relapses. Surgical options like splenectomy would be limited in our patient especially during the COVID-19 pandemic and shunt surgery for correction of the portal vein thrombosis is being considered.

Keywords: Pediatric liver transplantation; Autoimmune hemolytic anemia; Portal vein thrombosis; Post-transplant lymphoproliferative disorder; COVID-19 pandemic; Splenectomy

Abbreviations

AIHA: Autoimmune Hemolytic Anemia; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; Hb: Hemoglobin; ITP: Immune Thrombocytopenic Purpura; IVIG: Intravenous Immunoglobulin

Introduction

Liver transplantation is considered a lifesaving procedure for patients with decompensated liver cirrhosis, acute liver failure, some metabolic disorders and liver malignancies when there are no available medical and surgical treatment options [1-3]. Living related donor liver transplantation has increased the donor pool and is increasingly being performed in low-middle income countries like South Africa, with a paucity of deceased organ donation [4,5].

Since 1963, when the first three human liver transplantations were performed at the University of Colorado, there have been considerable advances in liver transplantation, including recipient and donor selection, operative technique in either living or deceased donor transplantation, immunosuppressive medications and postoperative intensive care unit care. All these have significantly contributed to a marked improvement in outcomes [6-8].

This improvement in outcome has however led to the advent of an increased incidence of

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both acute and long-term complications after liver transplantation. Here, we present a patient who underwent a related living-donor liver transplantation and presented with Evans syndrome as a post-transplant complication.

Evans syndrome is a rare hematological disorder associated with a positive direct antiglobulin (Coombs) test, Autoimmune Hemolytic Anemia (AIHA) with Immune Thrombocytopenia (ITP) in the absence of any underline etiology [9-11]. It can run a chronic course in transplant recipients with frequent episodes of exacerbation and remission [12-14]. The patient's family provided written informed consent before the start of the study, which was approved by the Ethics Committee of University of the Witwatersrand.

Case Presentation

The patient is a 5½-year-old boy with weight and height between 0 and -1 Z score for his age. He had a living related ABO compatible liver transplant at sixteen months of age for his primary disease, biliary atresia. The procedure was complicated by recurrent infections and hypoxic cardiac arrest leading to microcephaly and mild developmental delay. His post-transplant course was complicated by a prolonged intensive care unit admission for sepsis and a tracheostomy was inserted for prolonged mechanical ventilation which was decannulated two years post insertion.

His immunosuppressive medication comprised of intraoperative induction with methylprednisolone and then tapered prednisolone over three months with twice daily tacrolimus as maintenance therapy to prevent rejection. The patient also developed an Epstein Barr Virus (EBV) driven Post-transplant Lymphoproliferative Disorder (PTLD) sixteen months after transplantation which was confirmed on histology of the tonsillar tissue as polymorphic non-destructive type and was managed with reduction of immunosuppression where tacrolimus was stopped for a year and restarted at low dose (levels 1-2) thereafter, when his enzymes started increasing.

Three years post liver transplantation; our patient started to have

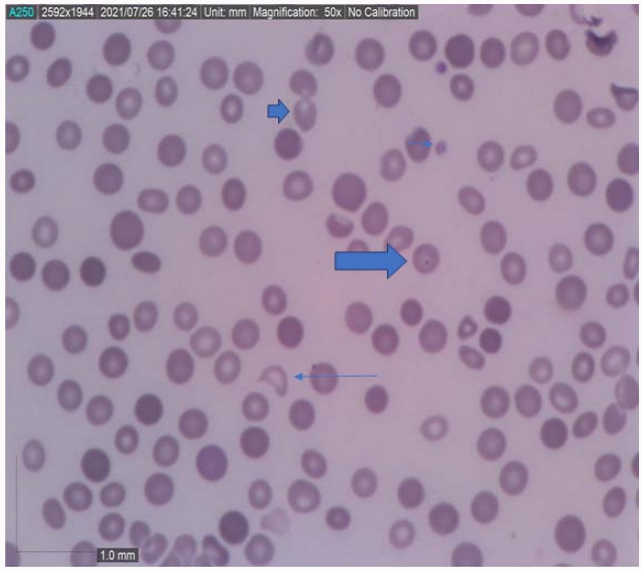

Figure 1: Peripheral blood smear at time of diagnosis of Evans syndrome in our patient.
Peripheral blood smear showing nucleated red blood cells (long thick arrow), occasional teardrop cells (short thick arrow), and red cell fragments (long thin arrow and occasional giant platelets (short thin arrow).

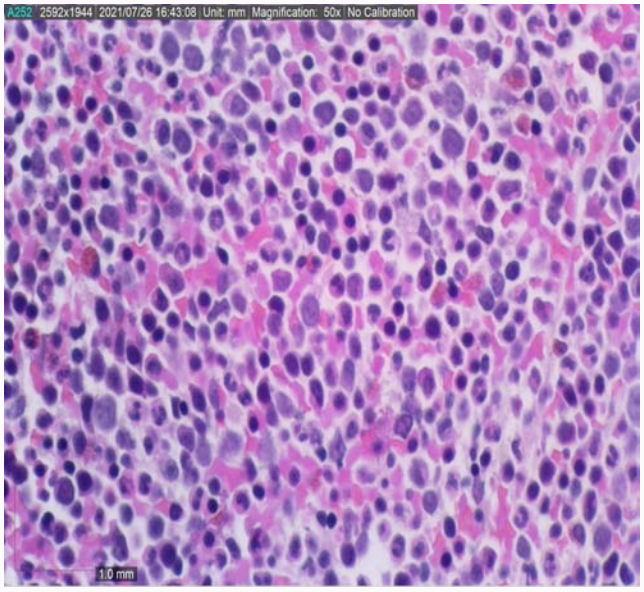

Figure 2: Bone marrow biopsy showing a hypercellular bone marrow with well represented tri-linear hemopoiesis.

increased splenomegaly and was subsequently diagnosed with portal hypertension secondary to portal vein thrombosis based on Doppler abdominal ultrasound and contrast Computerized Tomography (CT) scan of the abdomen. This led to hypersplenism and esophageal varices (not actively bleeding) which required frequent packed red blood cell transfusion and the commencement of propranolol as prophylactic management of esophageal varices.

Three and half year's post liver transplantation, the patient presented with fatigability and pallor with yellow discoloration of sclera. On examination he was jaundiced with severe pallor and ecchymosis over his lower limbs with moderate splenomegaly. His medication comprised of tacrolimus 0.5 mg twice daily and propranolol. Blood workup showed severe anemia with a hemoglobin count of 5.4 g/dl, platelet count of 7×10^9/L, high reticulocyte count of 24% and normal white cell count of 5.6 cells/L with an unconjugated hyperbilirubinemia and other biomarkers supporting hemolysis (low haptoglobin, raised lactate dehydrogenase) (Table 1). Further investigations for hemolysis revealed a positive direct Coombs test for IgG, a peripheral blood smear showing nucleated red blood cells, occasional teardrop cells, red cell fragments and occasional giant platelets (Figure 1). Bone marrow biopsy showed a hypercellular bone marrow with well represented tri-linear hemopoiesis (Figure 2).

The patient subsequently received a transfusion of leucodepleted packed cells of 15 ml/kg and a single donor mega unit of platelets. His Hemoglobin (Hb) level and platelet count improved to 9.5 g/dl and 31 $\times 10^9$/L respectively. Cytomegalovirus (CMV) viral loads, Parvovirus PCR were negative and EBV viral load was 14,500 copies/ml (Table 1). He was diagnosed as having a Coombs positive Autoimmune Hemolytic Anemia (AIHA) with Immune Thrombocytopenic Purpura (ITP) consistent with Evans syndrome. After 48 h the patient's hemoglobin and platelet started to drop again to 6.3 g/dl 9×10^9/L, necessitating another transfusion of leucodepleted packed red blood cells and a mega unit single donor platelet transfusion. The patient was subsequently started on prednisolone 2 mg/kg and maintained his Hemoglobin (Hb) and platelet count. He was then discharged with weekly follow-up and tapering of the prednisolone according to

Table 1: Blood count, liver functions and EBV and CMV viral load during the course of diagnosis and treatment of Evans syndrome.

	4 weeks before presentation	At presentation	24 hours post presentation	48 hours post presentation	6 weeks post presentation	1 year post presentation
Tacrolimus level ug/l	3.3	3.7			4	1.2
CMV IU/ml	LTD				LTD	
EBV IU/ml	14500				8406	
Hb g/dl	9	5.4*	9.5	6.3#	4.7*##	14.2
WBCs × 10^9/l	1.81	5.2	2.4	2.34	6.7	4.1
Neutrophil Count × 10^9/l		1.97	2.03	1.59	3.09	3.04
PLT count × 10^9 /l	47	7*	31	24	4*	114
Retics %		24	16		16	
TB umol/l	46	130			128	11
DB umol/l	10	12			21	3

*Patient received PRBC and PLT transfusion; #patient started on Prednisolone; ##patient started on IVIG
Abbreviations: TB: Total Bilirubin; DB: Direct Bilirubin; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; Hb: Hemoglobin; PLT: Platelet; Retics: Reticulocytes; WBC: White Blood Cell; IVIG: Intravenous Immunoglobulin

his blood results over 6 weeks until he reached a maintenance dose of 0.5 mg/kg. At this point, he became symptomatic once again with unconjugated jaundice, anemia and thrombocytopenia with normal liver enzymes. With a Hb level of 4.7 g/dl and platelet count of 4 × 10^9/L he required repeated transfusion of both packed cells and platelets requiring an increased dose of prednisolone once again to 2 mg/kg. When this failed to control the autoimmune process, he was started on 1 g/kg Intravenous Immunoglobulin (IVIG) over 2 days, and scheduled for a splenectomy in the future. Our patient showed a good response to Intravenous Immunoglobulin (IVIG) resulting in normalized Hb level and platelet counts with no further hemolysis being observed.

After a year of follow up, our patient maintained his hemoglobin level and platelet count on 0.5 mg/kg prednisolone and tacrolimus as immunosuppressive medication. Splenectomy was deferred as a result of the COVID-19 pandemic and the patient being stable on first line therapy with minimal adverse effects.

Discussion

Hematological complications post liver transplantation has a wide range of different causes and are relatively common. These include anemia, neutropenia and thrombocytopenia or even pancytopenia which are usually secondary to immunosuppressive and/or antiviral medications used during transplantation [15,16]. In our patient, the combination of a positive direct antiglobulin test Autoimmune Hemolytic Anemia (AIHA) with Immune Thrombocytopenia (ITP) in the absence of other underlying etiology, as evidenced by a normal bone marrow biopsy, confirms the diagnosis of Evans Syndrome [10,17]. To the best of our knowledge this is the first reported pediatric case of Evans syndrome post living-donor liver transplantation in South Africa.

The etiology of Evans syndrome is not typically understood and largely unknown but in post liver transplant patients, viral infections like CMV and EBV as well as the role of immunosuppressive drugs or development of autoantibodies secondary to frequent blood transfusions should be considered [12,13,15,18-20]. Our patient demonstrated multiple complications of pediatric liver transplantation, all which may be contributory factors to the development of Evans syndrome. Early PTLD which was managed with reducing immunosuppression at the time resulted in sustained increased EBV viral load levels. Late portal vein thrombosis, which although rare, in our patient was associated with significant hypersplenism resulting in repeated transfusions of both packed blood cells and platelets ultimately contributing to Evans syndrome [21]. Neutropenia was also found in our patient and is associated with 20% of patients with Evans syndrome [10,22,23].

There are limited clinical trials comparing different treatment modalities for Evans syndrome. Most treatment options are extrapolated from those of AIHA and ITP and as Evans syndrome showed period of exacerbations and then relapse, the effect of treatment varies even within the same individual [9,10,24].

There are different stages of treatment. Corticosteroids and IVIG are the first line therapy for Evans syndrome. This is followed by immunosuppressive medication changes to Mechanistic Target of Rapamycin (MTOR) inhibitors, cyclosporine or rituximab as second line therapy if first line therapy failed [9-11]. Splenectomy is usually considered if medical therapy fails, but is not considered a definitive treatment as sustained steroid free remission cannot be guaranteed [10,12,14,22]. In children less than 6 years of age it is not considered an option as the infection risk is greater. The availability of a larger variety of medical therapy from rituximab to bortezomib in recent years in addition to the increased relapse rate post splenectomy has made bortezomib a third line therapy [19]. In the case of our patient, splenectomy although considered, would not be the preferred therapy as this would decrease our surgical shunt options for the management of his portal vein thrombosis.

Evans syndrome is a rare hematological complication following solid organ transplantation. On review of the literature, we found four pediatric cases of Evans syndrome after liver transplantation: Three patients were treated with medical treatment only (steroids, IVIG, and/or rituximab), and one patient required surgical intervention (splenectomy) [12,25].

Our patient showed an acceptable response with first line therapy of Evans syndrome with a maintenance of low dose steroid (5 mg daily) and keeping low trough level of tacrolimus between 2 ug/l to 4 ug/l to maintain his biochemical parameters within normal limits. The patient continues being monitored closely at follow up with regular viral loads for monitoring for EBV, CMV and Parvoviral infection.

Conclusion

We would like to highlight this case to increase awareness of

rare complications of pediatric liver transplantation like Evans syndrome which our patient demonstrated and highlight the necessity and importance of conservative management. During the COVID-19 pandemic, surgical management options requiring prolonged hospital admissions are less favored especially in the case of immunosuppressed pediatric patients. Optimizing first line therapy in this patient and delaying splenectomy has offered us an opportunity to review options for correction/management of the portal vein thrombosis.

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Author Contributions

IE Hassan provided the first draft of the manuscript. C Hajinicolaou and P Walabh provided expert opinions from Hepatology and Transplant perspectives. All authors contributed to the drafting of subsequent and final drafts and approval of the final draft for publication.

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