

Coombs Positive Thrombotic Thrombocytopenic Purpura: A Challenging Case Report and Clinical Review

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Abstract

Evans syndrome (ES), a hematologic disorder defined by autoimmune destruction of at least 2 hematologic cell types.

The association of immune thrombocytopenic purpura (ITP) and autoimmune haemolytic anemia (AIHA). Some cases of Evans syndrome (ES) were associated, mainly in adults, with various medical conditions such as autoimmune diseases, common variable immunodeficiency and malignancies.

ES has a chronic and relapsing course, and patients are usually dependent on prolonged immunosuppressive treatments [1].

Here, we report a case of a young patient with a known history of immune thrombocytopenic purpura who presented with severe cytopenia and end-organ damage in terms of acute renal impairment and hepatic dysfunction. Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy often caused by deficiency of von Willebrand (vW) factor cleaving protease, ADAMTS-13, leading to large vW multimers and intravascular platelet aggregation. Hemolysis in TTP is mechanical and nonimmune mediated, thus Coombs testing is usually negative. We report a case of an adolescent with thrombocytopenia and Coombs positive anemia, diagnosed with Evans syndrome, but ultimately found to have TTP.

Keywords: Evans Syndrome (ES); Immune Thrombocytopenic Purpura (ITP); Autoimmune Haemolytic Anemia (AIHA); Von Willebrand (vW)

Introduction

Evans syndrome is an autoimmune disorder characterized by simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) and/or immune neutropenia.

ES can be idiopathic (primary); in the absence of underlying condition and thus a diagnosis of exclusion or secondary to an underlying cause as; systemic lupus erythematosus, lymphoproliferative disorders or primary immunodeficiency.

Its diagnosis need to exclude the conditions with careful evaluation of peripheral blood smear and analysis of DAT.

Case Presentation

This is a 26 year-old gentleman who was diagnosed with Idiopathic Thrombocytopenic Purpura in 2012. He received multiple lines of therapy including steroids, Rituximab and underwent splenectomy.

He had a good response and continued to follow in our clinic with baseline platelets count of 140,000 platelets per microliter of blood. He was last seen in the clinic in January 2018.

In April 2018, he presented to our Emergency Department complaining of abdominal pain, vomiting, diarrhea, itching and yellowish discoloration of the sclera and skin. His symptoms were associated with fever reaching up to 38°C.

He has developed the aforementioned symptoms 3 days ago after eating undercooked meat.

He had no history of loss of consciousness, abnormal movements, headache, or blurred vision. He denied any symptoms of chest pain, cough, shortness of breath, hemoptysis and gastrointestinal bleeding. He had negative history of decreased urine output, hematuria, weight loss, night sweats, joints pain and skin rash.

No reported history of previous blood transfusion, recent antibiotics or herbal medications intake, or an episode with similar symptoms previously.

On physical examination, he was febrile with body temperature of 38°C, tachycardic with a heart rate of 110 beats per minute, normotensive with blood pressure of 122/55 mmHg, saturating well (93%) breathing ambient air.

He was conscious, alert and oriented to time, place and person. He however looked pale and jaundiced with no palpable lymph nodes.

His chest exam revealed vesicular breathing, audible first and second heart sounds with no added sounds or murmurs.

His abdomen was soft and lax with right upper quadrant tenderness elicited by deep palpation. Post laparoscopic scars were noted but no other skin changes or organomegaly.

Neurological examination showed no abnormalities with negative meningeal signs.

The patient's laboratory investigations showed leukocytosis (WBC of 26,200 per microliter), normocytic anemia with hemoglobin of 6.7 g/dL (his baseline hemoglobin was 14.0 g/dL), normal platelets count of 378,000 platelets per microliter of blood, and reticulocytosis.

The rest of investigations also revealed indirect Hyperbilirubinemia (Total Bilirubin of 300 µmol/L, Direct Bilirubin of 22 µmol/L), mild transaminitis (ALT of 74 U/L), markedly elevated LDH of 1450 U/L and low Haptoglobin with otherwise normal coagulation profile, electrolytes and BUN/creatinine levels.

His Direct combs test was strongly positive for IgG and his peripheral blood film showed neutrophilia with severe toxic granulation, mild left shift, and few reactive lymphocytes and no blasts. Red Blood Cells (RBCs) showed mild anisocytosis with small RBCs agglutinates with no significant schistocytes, spherocytes or polychromasia. Thrombocytosis was present with frequent platelet clumps and giant forms.

The patient's virology screen was negative for Hepatitis A, B, C and HIV.

A diagnosis of Evans Syndrome induced by septicemia was postulated and consequently the patient was started on IV methylprednisolone as well as broad spectrum antibiotics and was transfused least incompatible blood. However, his condition continued to deteriorate and he became confused, febrile and dyspneic.

His labs showed further drop in hemoglobin and platelets along with rising WBCs count. He also developed acute kidney injury (AKI), acute liver injury and disseminated intravascular coagulation (DIC). Furthermore, his LDH level continued to rise.

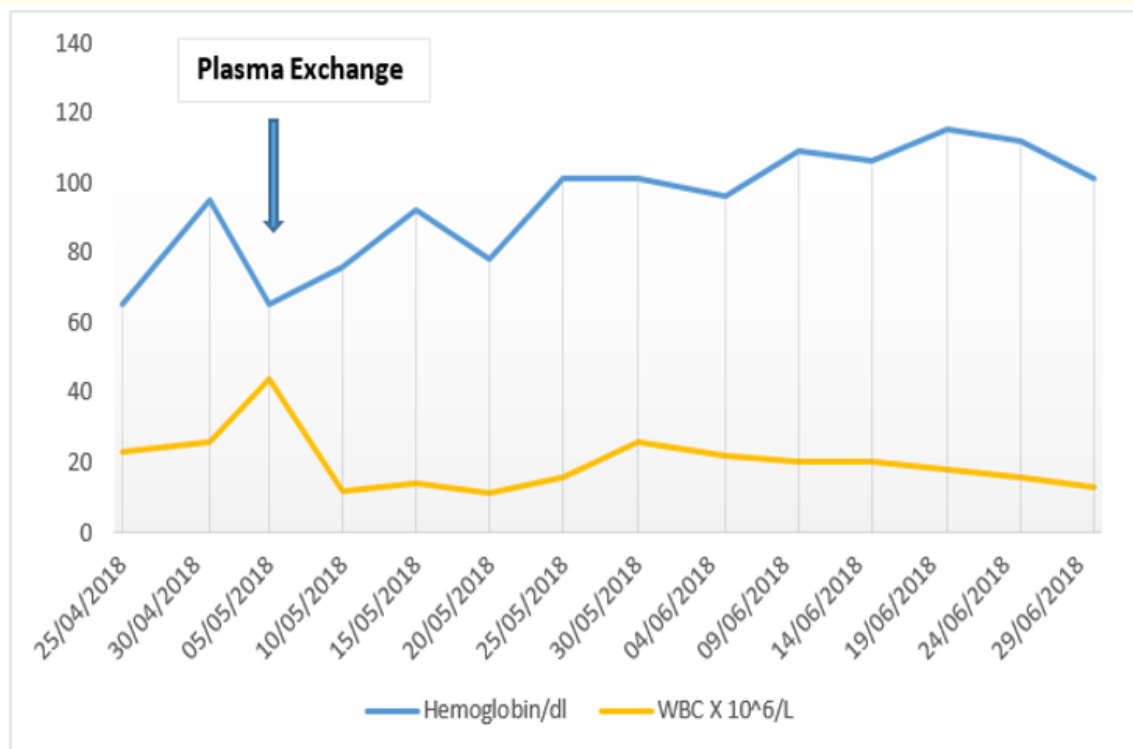
The patient required intubation and inotropic support and on day 2 post Intensive care unit admission, he became anuric and started on CRRT and ICU team was discussing his code status. At that time, suspicion of TTP/atypical HUS was raised and the patient was started on plasmapheresis, Rituximab and IVIG, after which his condition markedly improved.

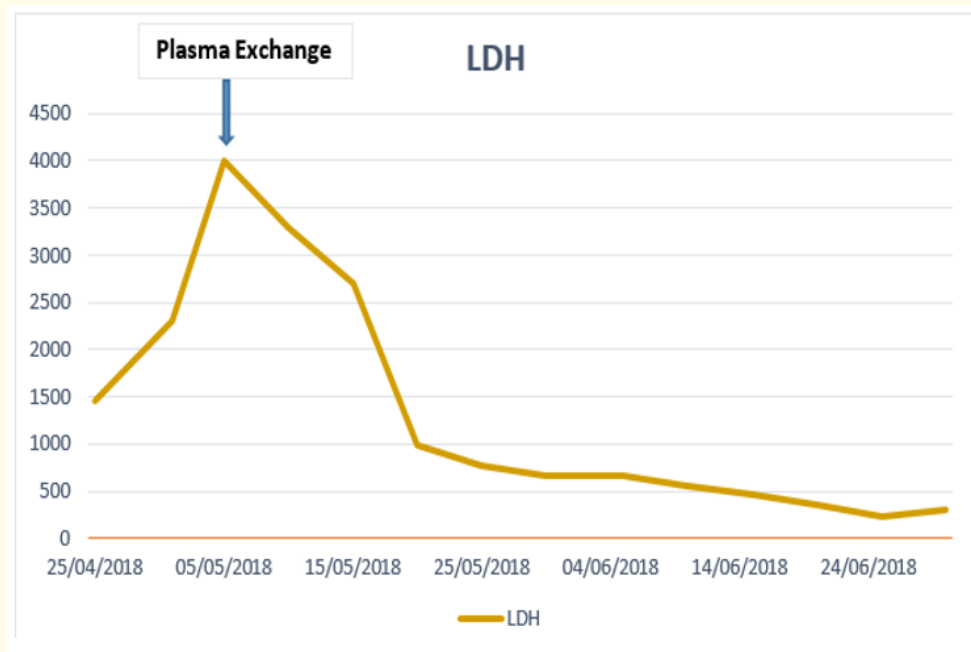
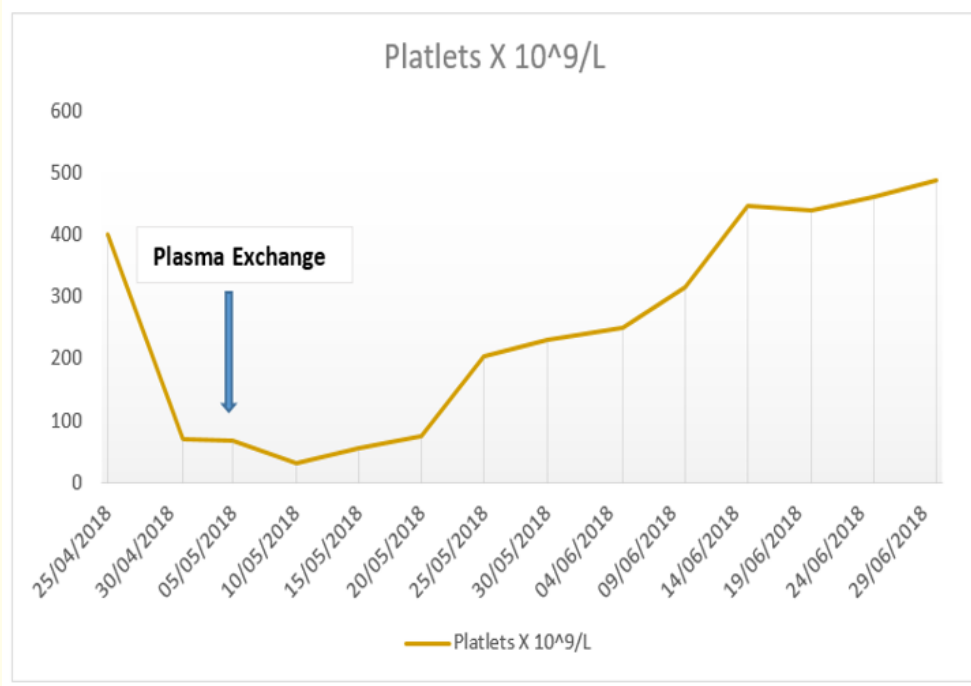
His conscious level and hemodynamics have improved as well. In addition, his WBCs count started to normalize, his Hemoglobin became stable and his platelets started to increase. His coagulaopathy was corrected, LDH significantly dropped, his renal and liver functions started to improve. However, Coombs test was still strongly positive.

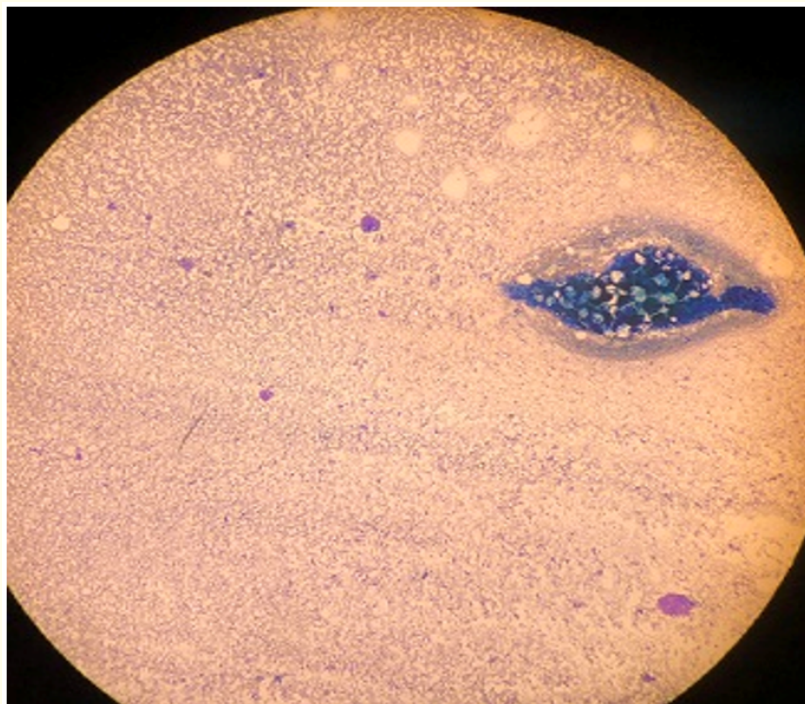
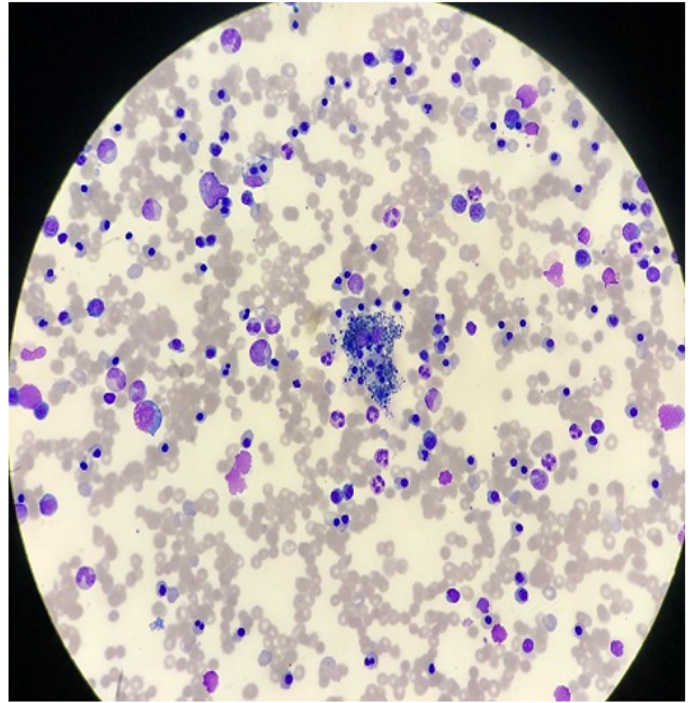
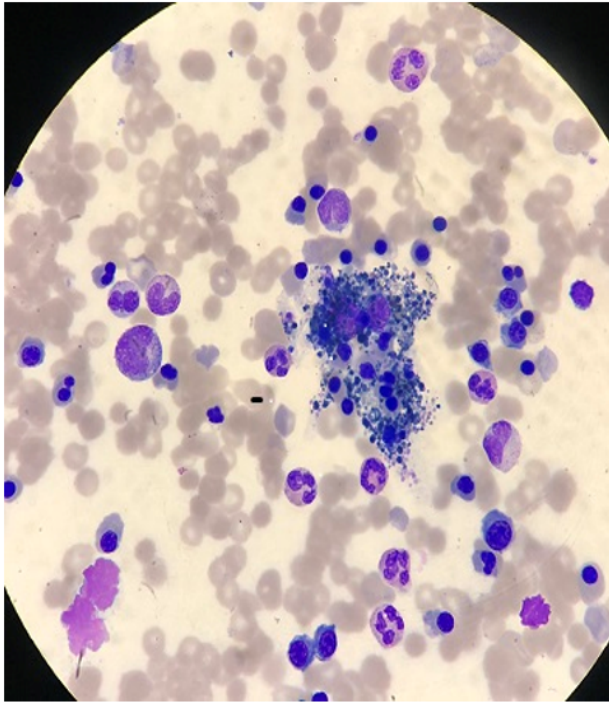
His virology screen (Hepatitis A, B, C, HIV, CMV, EBV and Parvo B19 virus) as well as *E. coli* 0:157 serology and auto-immune serology were all negative.

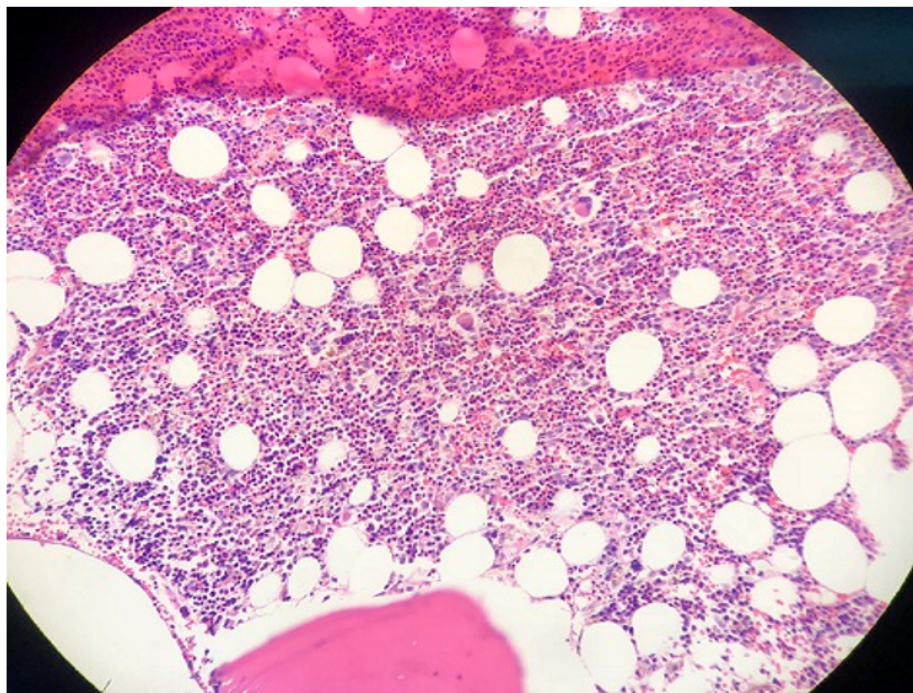
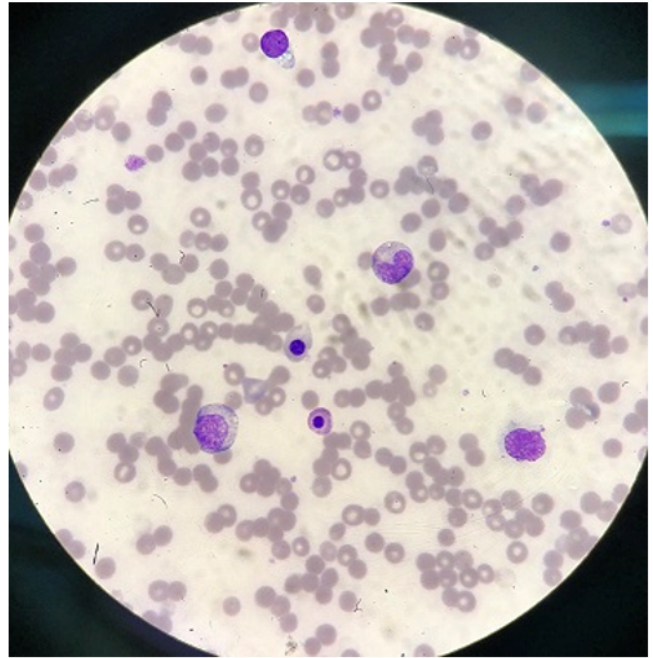
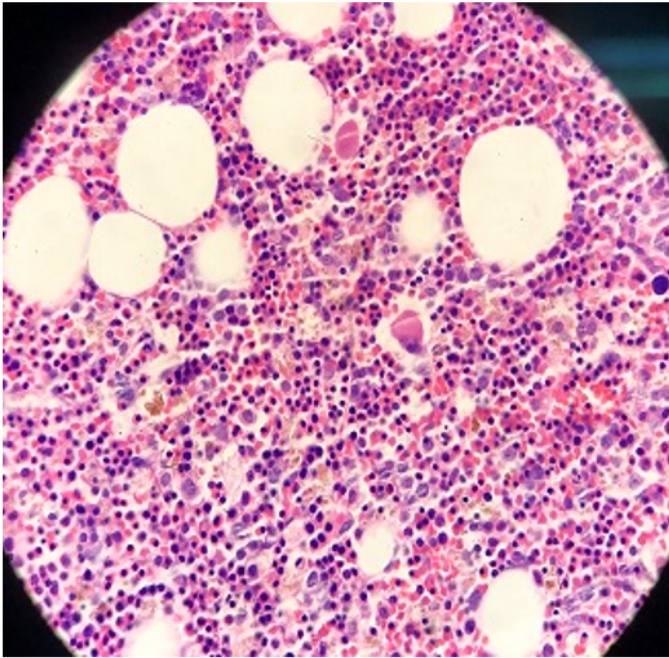
Later on, his repeat peripheral blood smear showed circulating blasts and his bone marrow revealed mildly hyper cellular marrow, increased Megakaryocytes with many young forms and erythroid hyperplasia with no evidence of malignant involvement. BCR-ABL was negative.

He received a total of 17 sessions of Plasma exchange and 6 doses of Rituximab in which his Clinical condition and Laboratory results were dramatically improved with hemoglobin of 10.5, platelets of 467000, LDH of 198 and negative combs test, he was discharged on Mycophenolate Mofetil 500 mg twice daily and was seen in the clinic 2 weeks later in which he had stable Hb and platelets level and normal LDH level.









Discussion

In our case; patient has the background of ITP, developed Evan syndrome and some evidence of atypical HUS (as presented with impaired renal function and the response to plasma-exchange).

Evan syndrome (ES) is a rare hematological disorder that involves 2 or more immune cytopenias, it usually includes autoimmune hemolytic anemia and autoimmune thrombocytopenia or/and immune neutropenia [1].

Although occasionally associated with immune neutropenia, rare association with disseminated intravascular coagulation (DIC) can happen [2].

Can be classified as primary (idiopathic) or secondary (associated with an underlying disease) as; autoimmune disease (SLE, Sjogren syndrome), immunodeficiencies (common variable immunodeficiency), lymphomas (B-cell non-Hodgkin lymphoma, chronic lymphocytic leukemia, T-cell non-Hodgkin lymphoma), MGUS and Hepatitis-C.

It is very important to distinguish between primary and secondary Evans syndrome as the management and outcome is different [3].

For diagnosis we need to exclude the secondary associated conditions with careful evaluation of peripheral blood smear and analysis of DAT.

Finding of spherocytes on the peripheral blood smear in the presence of thrombocytopenia is a significant clue that immune hemolytic anemia is ongoing, especially if associated with high reticulocytes count.

Coombs test (DAT; Direct Anti-globulin Test) is almost invariably positive and may be positive for immunoglobulin-G (IgG), complement or both. (IAT; indirect anti-globulin test) can be positive in 52 - 83% [4].

Bone marrow aspiration usually indicated for excluding infiltrative process and is usually not indicated in classical cases. Normal level or increased numbers of megakaryocytes confirm that thrombocytopenia is caused by peripheral destruction.

Once confirm the diagnosis of Evan syndrome, patient should be started on corticosteroids. Corticosteroids are the mainstay of therapy, and the typical course of therapy is a dose of prednisone at 1 to 2 mg/kg per day tapered over a few weeks or many months depending on patient response.

IVIg can be used in-addition to steroid to help in washing the auto-antibodies.

For patients not responding to corticosteroids or who are corticosteroids dependent (i.e. requiring a daily dose of prednisone that is more or equal to 15 mg to maintain a remission) should go for the "second-line" therapy which is splenectomy. Other second- or third-line therapies included danazol, oral or intravenous (intravenous pulses) cyclophosphamide (as in patients with SLE or "incomplete" lupus), rituximab [5-7] cyclosporine, azathioprine, mycophenolate and dapsone [1].

Patient may developed serious complications from the disease, Hemorrhage with severe thrombocytopenia reported in 29% of the patients with deaths in severe cases of GI-bleeding and acute intracranial bleed [1] and myocardial infarction as a subsequent result.

Other complications; patient can suffer from serious infection with neutropenia especially if splenectomized, as patients become highly vulnerable to be infected with encapsulated organisms (*Streptococcus pneumoniae*, *Meningococcus*, *Haemophilus*) [8].

Thrombotic microangiopathy (TMA), is a pathologic description, characterized by a clinical presentation with thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and organ injury. It can manifest in a diverse range of conditions and presentations, but AKI

is a common prominent feature because of the apparent propensity of the glomerular circulation to endothelial damage and occlusion. Early recognition is important: TMAs are associated with significant mortality and morbidity, including ESRD, although prompt initiation of supportive and specific management can transform outcome [9].

Haemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia with acute kidney injury. It is currently classified into two main categories: Shiga-toxin producing *E. coli*-hemolytic uremic syndrome (STEC-HUS) which is typically accompanied by bloody diarrhea with The most common serotypes O157:H7 and O104:H4. This form is called EHEC-HUS (enterohemorrhagic *E. coli*, EHEC) or STEC-HUS.

HUS following a respiratory infection with *Streptococcus pneumoniae* (SP-HUS) is very rare, accounting for less than 5% of the cases [10].

If none of these infections is present, there is a suspicion of an atypical hemolytic uremic syndrome (aHUS), also referred to as complement-mediated HUS (cmHUS) [11].

Other types includes; haemolytic uraemic syndrome related to cobalamin C defect, and haemolytic uraemic syndrome secondary to a heterogeneous group of causes (infections, drugs, cancer, and systemic diseases).

Pathophysiologically, in the cases of a genetic defect or an acquired dysregulation of the complement or coagulation system, thrombotic microangiopathy may lead to damage of the affected organs (usually the kidney) even after the trigger (infection, surgical intervention, use of medication) has been controlled or in the absence of a trigger.

This include complement-regulatory defects due to mutations of factor H, factor I, factor B, C3, or membrane cofactor protein (MCP), or to autoantibodies to factor H [12].

Complement activation is initiated by three pathways: the classical pathway is activated by immune complexes and other molecules (e.g. C-reactive protein), and activation of the lectin pathway results from protein interactions with pathogens. The alternative pathway may also be initiated by pattern recognition molecules, but crucially, it is a positive feedback loop that is constitutively active due to spontaneous hydrolysis (tickover) of C3, and is recruited by the classical and lectin pathways; this enables a rapid response against pathogens, but leaves the host vulnerable to bystander damage if the amplification loop is unchecked. The system is therefore tightly regulated by plasma proteins, including FH and factor I (FI), and cell surface proteins, such as membrane cofactor protein (CD46).

Defects in these regulators or in the alternative pathway components can lead to complement dysregulation, with activation of the terminal complement pathway and generation of the anaphylatoxin C5a and the membrane attack complex (C5b-9), resulting in a complement-mediated aHUS [9].

Inherited defects in complement regulation occur more frequently than acquired changes, with the most common being factor H mutations (20 - 30% of all aHUS patients) [13]. Acquired forms of aHUS are very rare and can involve an antibody against factor H (6 - 10% of all aHUS patients).

Under physiological conditions, asymptomatic mutations of the complement regulatory genes can lead to clinical manifestation of thrombotic microangiopathy following a triggering event.

Diagnosis of aHUS requires exclusion of both STEC-HUS (typical HUS, with Shiga toxin detection in stool or blood) and ADAMTS13-mediated thrombotic microangiopathy (TMA) with ADAMTS-13 less than 10% [14].

Diagnostically indicative is finding evidence of thrombotic microangiopathy in renal biopsy.

TTP has diverse clinical features that can make it difficult to differentiate from similar disorders. In pediatrics, TTP is most often confused with hemolytic uremic syndrome (HUS) that commonly presents with abdominal pain and diarrhea or disseminated intravascular

coagulation when there is bleeding, thrombosis, and signs of organ damage. In adults, the differential diagnosis is more extensive as TTP has been associated with drug ingestion, autoimmune disorders, metastatic cancer, pregnancy, and bone marrow transplantation [14].

Plasma exchange (PE) still remains the initial treatment of choice until ADAMTS13 activity is available to exclude TTP as a diagnosis. It should be initiated in adults as soon as the diagnosis of TMA is suspected.

PE will also replace faulty complement regulators and remove FH autoantibodies and hyperfunctional complement components in complement-mediated aHUS [9].

Eculizumab is a recombinant humanized monoclonal antibody that functionally blocks C5, resulting in disruption of the terminal pathway of complement signaling and thereby reduces endothelial injury [15], resulting in improvement of the renal function and hematological parameters after 26 weeks of therapy [16].

In the prospective trials, complete TMA response was achieved in approximately 65% after 26 weeks of eculizumab therapy in both adults [17] and children.

The trials included patients in whom no complement mutation or FH autoantibody had been identified, and the majority responded to complement-inhibiting therapy; therefore, negative genetic and autoantibody investigations do not exclude the diagnosis of complement-mediated aHUS.

The current license for eculizumab is for lifelong treatment, but this is not evidence based. Withdrawal of eculizumab has been associated with relapse exclusively in those with complement mutations.

Rapid reintroduction of eculizumab returned kidney function to baseline suggests that a disease-driven intermittent regime could replace long-term therapy.

The primary concern with terminal complement blockade is increased susceptibility to infection with encapsulated organisms, particularly *Neisseria* infections [18,19]. For this reason, meningococcal vaccination is obligatory prior to initiating therapy with eculizumab.

Conclusion

The final diagnosis in our case was a matter of debate, whether it is a case of refractory Evans syndrome or is it a case of TTP with coombs positivity related to his autoimmune cascade.

His life is saved only by plasma exchange session and by our clinical sense that it goes more with TTP, and the take home message here is always trust your clinical sense even if the frame of the results could not be summed up under one chapter of your book.

In this case, we describe an adolescent male who was first diagnosed with Evans syndrome (ES), which is defined by either simultaneous or sequential combination of immune thrombocytopenia and autoimmune hemolytic anemia with a positive direct antiglobulin test (DAT) in the absence of known underlying etiology. He was later found to have acquired TTP with a positive direct Coombs test, a rare phenomenon that is not previously reported in adolescence.

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