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Case Report

A 5-Year-Old Boy Presenting with Prolonged Lips Bleeding in the Encounter of ALPS (Autoimmune Lymphoproliferative Syndrome): A Case Report

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Abstract

We are reporting an unusual presentation of a child who presented with a prolonged gum bleeding following a minor trauma. The patient was a 5 year-old boy who came with a history of prolonged bleeding. He had fell down followed by a mild gum bleeding which did not stop for 3 days. He was found to have pancytopenia with lymphadenopathy. The child was admitted to the ward for investigations.

Upon a multidisciplinary approach to the case, the impression was Aplastic Anemia due to bone-marrow suppression Vs Leukemia.

He was commenced on aphaeresis PLT transfusion Q 8 hours with minimal improvement, monitored by daily platelets count measurement. His BMA result showed normal cellularity with no evidence of malignancy, the Viral Panel was negative as well. Lymph Nodes biopsy result was not suggestive of lymphoma. So, our patient was given IVIG twice daily instead of PLT transfusion.

Keywords: *ALPS; Autoimmune Lymphoproliferative Syndrome; Cytopenia; Lymphadenopathy; Prolonged Bleeding*

Abbreviations

ALPS: Autoimmune Lymphoproliferative Syndrome; PLT: Platelet; BMA: Bone Marrow Aspiration; IVIG: Intravenous Immunoglobulin

Introduction

Autoimmune Lymphoproliferative Syndrome (ALPS) is an inherited lymphoid disorder which results from mutations in molecules involved in the Fas-Fas ligand pathway [1]. Patients usually present with non-malignant enlargement of the lymphoid organs and features of an autoimmune disorder. Mouse models with Fas mutation (TNFRSF6 gene) and FasL mutations (TNFSF6 gene) cause the lprand gld phenotypes characterized by lympho-proliferation, with autoimmune manifestations, and increased T cell receptor α/β+CD4-CD8- T cells [CD3+double negative (DNT)] [2]. ALPS is the first human disease whose etiology has been attributed to a primary defect in apoptosis or programmed cell death. Awareness of this disease is important as the differential diagnosis includes common autoimmune disorders such as autoimmune hemolytic anemia and immune thrombocytopenia. In a recent retrospective analysis of children with Evan's syndrome, 58% were found to have ALPS [3]. This case has an unusual presentation. So, we have reported and commented on a case that was diagnosed at our center.

Case Description

Our Patient story had started 6 months prior to his presentation to our ER, when he went to private hospital for URTI symptoms. Incidentally, he was found to have low hemoglobin and platelets count. As per the family, no further intervention was done and he was discharged on Iron therapy.

The day before presenting to ER, the child was playing around when he had minor trauma which resulted in lips bleeding that didn't stop with compression. The family went to PHC and he was found to have low platelets count, so, referred to Pediatric Emergency Department (PED) in Riyadh, Saudi Arabia At King Fahad Medical City (KFMC) for investigation. Upon further history: There was a history of on and off bruising for the past 6 months. No hematuria, no hemoptysis, no hematochezia or epistaxis. There was a history of fatigability for 2 - 3 months and weight loss. His mother noticed a non-tender swelling in his left axilla for 6 months, with no change in size or any other lumps. No recent history of travel. No fever, rash or night sweat. He is Fully vaccinated for his age, medically free with no previous surgeries, not using any medications. The parents are second degree cousins. He has 4 other siblings (3 girls and1boy) who are healthy. No Family history of blood disorder, inherited disorders or malignancies.

At the time of presentation to the emergency room (ER), he was well looking, not dysmorphic, alert and conscious, pale but not jaundiced, well hydrated with no signs of distress.

On physical examination, he was hemodynamically stable, active, and afebrile. There were spots of blood in his mouth. Examination of the abdomen resulted in the presence of hepatomegaly (4 cm below the costal margin). Lymph nodes were palpable, firm and mobile, mainly in the left axillary region (2 x 3 cm), Submandibular lymph nodes and the left inguinal area, with no signs of inflammation. There was also a petechial rash on the face and lower limbs.

Initial CBC upon admission showed the following: WBC: 2,9*10^3 - ANC: 0.18*10^3 - Hg: 9.7 - PLT: 12*10^3. Peripheral blood smear showed few Tear Drop Cells but no blasts. Viral panel was unremarkable and immunoglobulin serum level showed high IgA. Bone marrow biopsy showed normal cellularity with no evidence of malignancy. Serum QuantiFERON was negative as well, and Tuberculosis was ruled out.

Double negative Test results showed Alpha beta TCR+DNT cells = 2.8% of Total CD3 cells; (Normal Range < 2%).

Anti-platelets antibodies were negative, as well as Anti-Neutrophils antibodies. ALPS Panel Genetic Study showed: two synonymous heterozygous variants c.351 C>T and c.447G>A were detected in exon 3 of AIRE gene, with uncertain clinical significance.

This AIRE gene encodes the AIRE protein, that in turn plays a role in the mechanism which eliminates self-reactive T cells, which would cause an autoimmune disease if defective, besides the defective apoptosis of the reactive T cells, resulting in the lymphoproliferation.

The patient received Random Platelets as initial management in the ER, but repeated CBC showed significant drop in Platelets count. Another Pack of Platelets was given to the child which showed minimal improvement with platelets of 8*10^3.

The child was admitted to the ward for investigation.

During his stay no major events happened. He was started on aphaeresis PLT transfusion with daily platelets count measurement, then IVIG was added when there was no response to transfusion, and the bone marrow was normally reactive.

Steroids and mycophenolate mofetil were added upon establishment of the diagnosis, on which he was discharged after showing a good response with a close follow up.

Discussion

The immune response to infectious agents results in the expansion of antigen-specific lymphocytes, some of which could become harmful to the host. The maintenance of proper homeostasis requires that lymphocyte expansion be appropriately balanced by lymphocyte elimination [1]. ALPS is a chronic, nonmalignant lympho-proliferative disorder caused by mutations in the genes that are involved in apoptosis. This impaired apoptosis leading to accumulation of lymphocytes causes manifestations of lymphadenopathy, auto-immune phenomena and high risk of developing malignant lymphomas. Most of the patients manifest between 6 months to 18 years. The most common autoimmune disorder is immune thrombocytopenic purpura and hemolytic anemia.

ALPS should be kept in mind as an important differential diagnosis when encountering a child with autoimmune hemolytic anemia, Evans syndrome, lymphadenopathy and spleno-hepatomegaly. So far there are no curative treatment modalities for this entity apart from bone marrow transplantation.

Initial line of treatment for most patients is either prednisolone alone or in combination with intravenous immunoglobulin [4-10].

Conclusion

Even though the clinical significance of the two synonymous heterozygous variants in the AIRE gene was previously uncertain, its co-incidence with the clinical and laboratory diagnostic criteria of ALPS in this case has made it significant apparently, which would be furtherly studied by the parental segregation analysis.

Ethical Considerations and IRB Approval

A written consent was obtained and signed by the legal guardians of both children for full disclosure while maintaining strict confidentiality in respect to the patient medical information and images under the approval of King Fahad Medical City (KFMC) research center ethical committee. Under the umbrella of KFMC Institutional Review Board (IRB), this case was approved.

Data Availability

The data that support the findings of the study are available from the corresponding author upon reasonable request.

Conflict of Interest

All authors have no example conflicts of interest to disclose.

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