






Case Report

An Association of Pure Red Cell Aplasia with Histiocytosis-Lymphadenopathy Plus Syndrome: A Rare Case Report

Histiyositoz-Lenfadenopati Plus Sendromu ile Saf Kırmızı Hücre Aplazisi Birlikteliği: Nadir Bir Olgu Sunumu

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ABSTRACT

Histiocytosis-lymphadenopathy plus syndrome (HLPS) is a rare autosomal recessive disease caused by a mutation in the SLCA29A3 gene. It is a group of disorders that includes H syndrome, pigmented hypertrichosis with insulin-dependent diabetes mellitus (PHID), Faisalabad histiocytosis and familial Rosai-Dorfman disease (RDD). The association of PRCA with HLPS is extremely rare and largely unknown. We report a rare case of a 5-year-old girl who presented with severe transfusion dependent anemia, subsequently confirmed to be PRCA and only after extensive workup could be diagnosed with HLP syndrome. Pure Red Cell Aplasia (PRCA) is a rare hematological disorder characterized by the absence or near absence of erythroid precursors in the bone marrow, leading to anemia due to a significant reduction in the production of red blood cells. Histiocytosis-lymphadenopathy plus syndrome is an autosomal recessive disorder associated with autoinflammatory features. A diagnosis of PRCA associated with HLPS requires a comprehensive diagnostic approach to rule out other potential causes of anemia and histiocytic proliferation. This case report presents a rare instance of PRCA associated with HLPS, exploring the diagnostic challenges.

Keywords: HLPS, PRCA, Anemia, autoimmune

ÖZET

Histiyositoz-lenfadenopati plus sendromu (HLPS), SLCA29A3 genindeki mutasyondan kaynaklanan nadir görülen otozomal resesif bir hastalıktır. H sendromu, insüline bağımlı diabetes mellitus ile birlikte seyreden pigmente hipertrikoz (PHID), Faisalabad histiyositozu ve ailesel Rosai-Dorfman hastalığı (RDD) gibi bir grup bozukluğu kapsamaktadır. PRCA ile HLPS birlikteliği son derece nadir olup büyük ölçüde bilinmemektedir. Bu yazıda, ağır transfüzyon bağımlı anemi ile başvuran, sonrasında PRCA tanısı doğrulanan ve ancak kapsamlı bir araştırmanın ardından HLP sendromu olarak tanı konulabilen beş yaşında bir kız çocuğuna ait nadir bir olgu sunulmaktadır. Saf kırmızı hücre aplazisi (PRCA), kemik iliğinde eritroid öncüllerinin yokluğu ya da neredeyse tamamen yokluğuyla karakterize, kırmızı kan hücresi üretiminin belirgin şekilde azalmasına bağlı anemiye yol açan nadir bir hematolojik bozukluktur. Histiyositoz-lenfadenopati plus sendromu ise otoinflatuvar özellikler gösteren otozomal resesif bir bozukluktur. HLPS ile ilişkili PRCA tanısı, aneminin ve histiyositik proliferasyonun diğer olası nedenlerini dışlamaya yönelik kapsamlı bir tanısal yaklaşım gerektirmektedir. Bu olgu sunumu, PRCA ile HLPS birlikteliğinin nadir bir örneğini ve beraberindeki tanısal güçlükleri ele almaktadır.

Keywords: HLPS, PRCA, Anemi, otoimmün

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INTRODUCTION

Histiocytosis-lymphadenopathy plus syndrome (HLPS) is a rare autosomal recessive disease caused by a mutation in the *SLCA29A3* gene. It is a group of disorders that includes H syndrome, pigmented hypertrichosis with insulin-dependent diabetes mellitus (PHID), Faisalabad histiocytosis and familial Rosai-Dorfman disease (RDD) [1].

Pure red cell aplasia (PRCA) is a rare hematologic disorder characterized by a selective reduction or complete absence of erythroid precursors in the bone marrow (with erythroblast <5%), leading to severe normocytic normochromic anemia with associated reticulocytopenia [2].

The association of PRCA with HLPS is extremely rare and largely unknown. Thus, it presents as a challenging diagnostic and therapeutic dilemma. Diagnosis of HLPS is made on molecular studies based on detection of mutation in *SLC29A3* gene.

We report a rare case of a 5-year-old girl who presented with severe transfusion dependent anemia, subsequently confirmed to be PRCA and only after extensive workup could be diagnosed with HLP syndrome.

CASE REPORT

A 5-year-old girl child presented to the paediatric department with signs of hepatitis and history of evening rise of temperature which was intermittently relieved with medication, along with night sweats, progressive weakness, weight loss and cough for 3 months. On clinical examination, there was no organomegaly or lymphadenopathy. The patient also

had severe anemia, requiring multiple blood transfusions over several months.

Initial laboratory investigations revealed elevated liver enzymes, consistent with hepatitis and a hemoglobin level of 4.9 g/dL, indicating severe anemia with normal leukocyte and platelet counts. The patient had a positive Mantoux test three months earlier and had been started on anti-tubercular therapy (ATT), which included isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE). Given the clinical suspicion of isoniazid-induced hepatitis and possible drug-induced PRCA, isoniazid was discontinued, resulting in normalization of liver function tests. However, the anemia did not improve following the cessation of the drug. With the clinical suspicion of anemia of chronic disease, childhood myelodysplastic syndromes and early vitamin b12 or folate deficiency and PRCA, further investigations were performed.

Bone marrow examination revealed marked paucity of erythroid series (<5%) with maturation arrest at early normoblast stage. Some of the early erythroblasts exhibited dysplastic features. Myeloid series showed relative hyperplasia and sequential maturation with M:E ratio of 24:1. Megakaryocytes were normal in number as well as in morphology. There was no evidence of malignancy or other infiltrative disorders was noted (Figure 1). Thereafter, bone marrow biopsy sections were studied and revealed findings similar to bone marrow aspiration. Biopsy was mildly hypocellular for age with a marked paucity of erythroid series cells. Myeloid series cells and megakaryocytes were normal in morphology. Few scattered mitotic figures were identified. Additionally, many histiocytes were seen in the sections among the hematopoietic cells (Figure 2). A diagnosis of PRCA was made based on bone marrow examination.

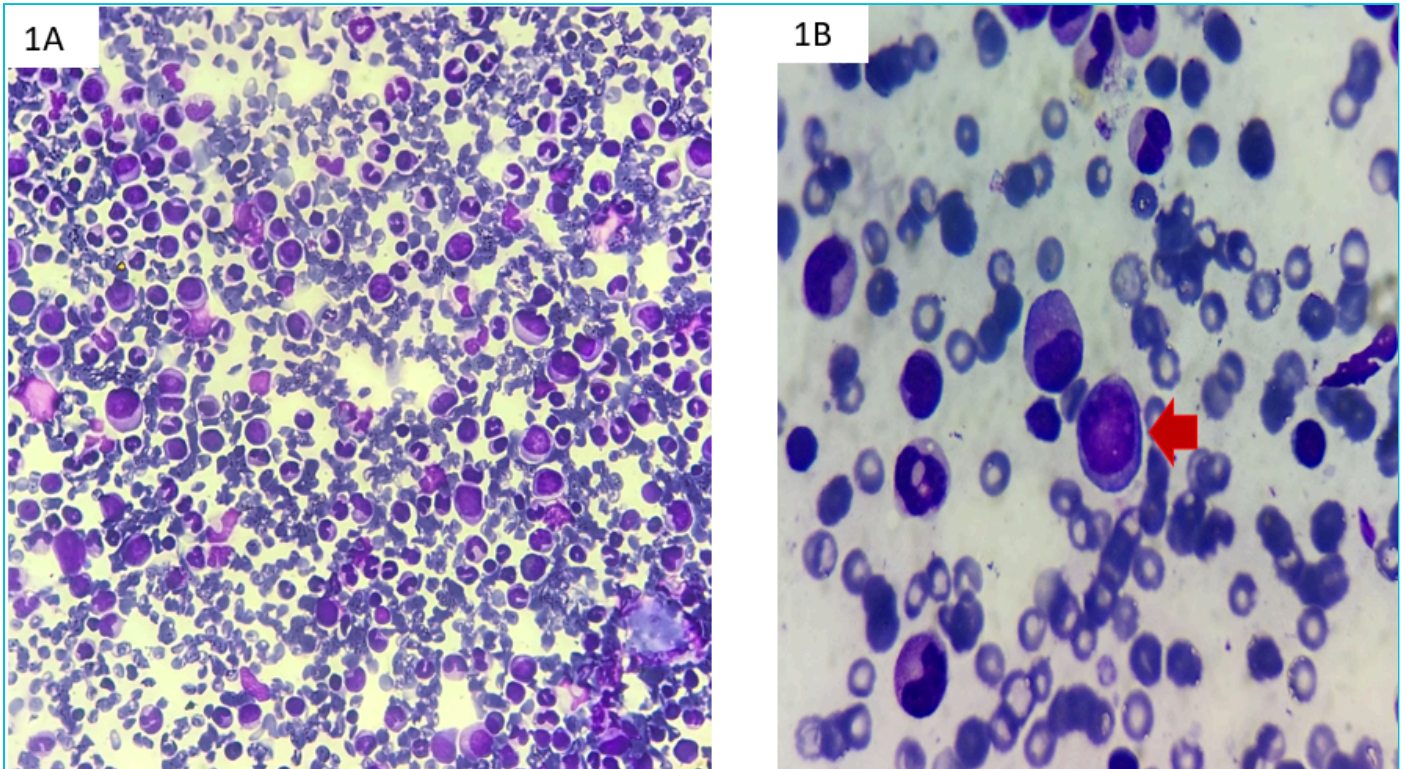


Figure 1. Bone marrow aspiration. A) Smears show predominantly myeloid series cells normal in morphology with occasional erythroid cells. B) Pronormoblast (red arrow)

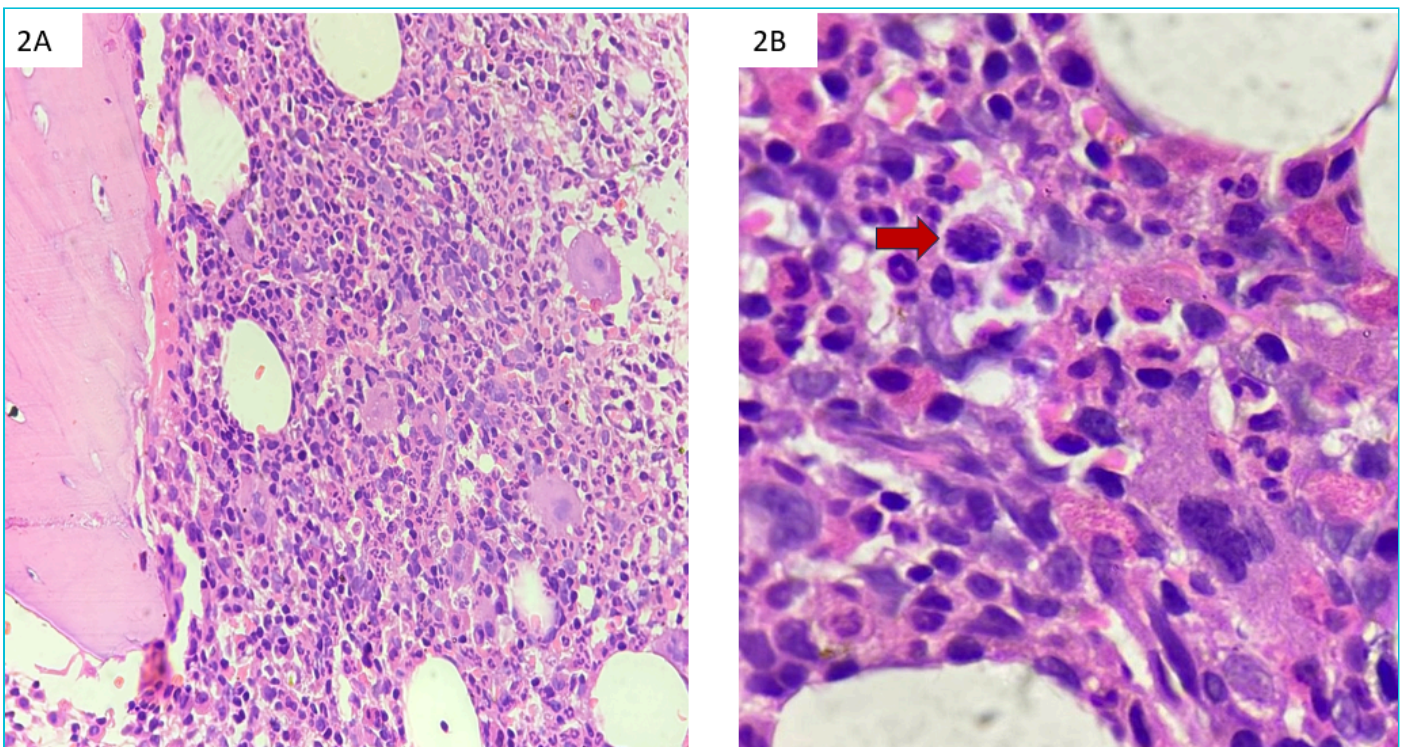


Figure 2. Bone marrow biopsy. A) Sections revealing predominantly myeloid series cells and megakaryocytes displaying normal morphology with very few erythroid series cells comprising of early forms only. B) Atypical mitosis (red arrow)

In further workup, viral serologies for parvo B19, EBV, HBV and HCV were negative. Renal function test was within normal limit. Iron studies as well as serum vit B12 and folate levels were within normal range. Autoimmune workup, including anti-nuclear antibody (ANA) and rheumatoid factor (RF) were negative. No evidence of any malignancy or organomegaly were noted on radiological examination. With all the possible secondary causes PRCA ruled out, for definitive diagnosis study was conducted to investigate the genetic causes of PRCA. This revealed a homozygous mutation in the *SLC29A3* gene (NM_018344.6, exon 4) (c.401G>A,p.Arg134His,[95x/98X] which is associated with HLPS. At the time of diagnosis, the patient did not exhibit other clinical features suggestive of HLPS, such as lymphadenopathy, skin changes, or organomegaly. The patient was closely followed after the diagnosis. One month later, the patient began developing hyperpigmentation, a known feature of HLPS. The patient was managed with monthly blood transfusions and prednisolone 10mg twice daily. Her Hb remained between 7-8g/dl. One year later, the child complained of increased frequency of urination and fever (101-103 degree Fahrenheit). The child was rushed to the hospital and was investigated. The ABG analysis showed metabolic acidosis and RBS was 350mg/dl. Patient was diagnosed with Diabetic ketoacidosis and admitted in ICU and started on intravenous insulin, intravenous fluids with KCL and antibiotics for urinary tract infection. The patient improved symptomatically in a week and was shifted to the ward and later discharged on prednisolone and injection glargine.

DISCUSSION

Pure Red Cell Aplasia (PRCA) is a rare hematological disorder characterized by the absence or near absence of erythroid precursors in the bone marrow, leading to anemia due to a significant reduction in the production of red blood cells. An essential aspect of understanding PRCA is distinguishing it from other types of anemia [3].

PRCA can be congenital, as in Diamond-blackfan anemia, or acquired, either as a primary autoimmune condition or secondary to other underlying conditions, including thymomas, viral infections (such as parvo B19), malignancies, and certain medications. Clinically, PRCA typically presents with symptoms of anemia, including fatigue, pallor, and shortness of breath, with

laboratory findings showing profound anemia and markedly low reticulocyte levels. At the same time, white blood cell and platelet counts often remain normal [4].

Histiocytosis-lymphadenopathy plus syndrome is an autosomal recessive disorder associated with autoinflammatory features. The clinical presentation can include cutaneous hyperpigmentation, hypertrichosis, and induration. Multiple systems can be involved.

HLPS is caused by homozygous or compound heterozygous mutations in the *SLC29A3* gene. This gene is located on chromosome 10q22 and encodes for human equilibrative nucleoside transporter 3 (hENT3). The hENT3 is a member of the equilibrative nucleoside transporter (ENT) family which consists of 475 amino acids and is localized in the endosomes, lysosomes, and mitochondria. This transporter is responsible for maintaining the cytoplasmic pool of nucleosides required for functioning of various cellular pathways. Nucleoside transportation is obstructed when *SLC29A3* is mutated leading to intracellular nucleosides accumulation [5]. Along with transport alterations, Kang N et al documented that possible loss of hENT3 functions in all H and pigmented hypertrichotic dermatosis with insulin-dependent diabetes syndromes is a result of either mistrafficking or altered stability of mutant hENT3 proteins [6]. However, the mechanism behind autoinflammation and development of PRCA is still poorly understood [1].

Mutations in the *SLC29A3* gene have been reported in many diseases, namely H syndrome, pigmented hypertrichotic dermatosis with insulin-dependent diabetes, Faisalabad histiocytosis, and Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) [5]. Hyperglycemia requiring insulin therapy is a documented feature of HLPS syndrome and presented in our patient within one year of the diagnosis.

Initially regarded as separate entities, HLPS and PRCA are now recognized as part of the same disease spectrum due to their overlapping clinical features and shared genetic basis. Some individuals may present with signs and symptoms typical of a specific condition, while others exhibit combinations of nonspecific features.

To date, no link between PRCA with HLPS has been documented in the literature. Our case is first case

demonstrating this connection to the best of our knowledge.

Literature search revealed several reports on PRCA arising after initiation of antitubercular treatment with isoniazid consistently identified as the cause. Discontinuation of isoniazid prompted a rapid improvement in these cases [7,8].

In our country tuberculosis is an important differential considered in unexplained fever cases (Pyrexia of unknown origin) given the high prevalence of tuberculosis. A positive Mantoux test in our patient thus prompted to initiate antitubercular therapy in the absence of evidence of any other disease.

However, in the present case, discontinuation of isoniazid did not ameliorate the anemia in the child. This compelled us to investigate further and studies were performed. Thereafter, SLC29A3 gene mutation was detected and a diagnosis of HLPS was rendered.

Cagdas D et al reported immunoglobulin therapy and low dose corticosteroids were helpful in resolution of pure red cell aplasia associated with HLPS (SLC29A3 gene defect) [1].

The patient was managed with steroids and blood transfusions and still developed another complication of the SLC29A3 mutation ie insulin dependent diabetes. Blood transfusions were useful only in providing symptomatic relief. This underscores the challenges in the management of this disease. The overall prognosis remains. In this case, none of the known causes of PRCA could be diagnosed, hence a whole genome sequencing was done to look for genetic causes which led to the diagnosis.

CONCLUSION

HLPS is a rare autoimmune genetic disorder and is very difficult to diagnose. PRCA is a rare cause of anemia and its association with HLPS is even rarer. Our patient presented with severe anemia, entirely dependent on blood transfusions for maintaining hemoglobin levels and was treated as tuberculosis initially. A diagnosis of PRCA in association with HLPS requires a comprehensive diagnostic approach to rule out other potential causes of anemia and histiocytic proliferation. This case report presents a rare instance of PRCA associated with HLPS, exploring the diagnostic challenges. Through this case, we aim to highlight the potential link between immune-mediated mechanisms

in both conditions and contribute to the limited literature on this unusual association.

This case report emphasizes the role of molecular studies and inclusion of rare entities like HLPS in differentials in the management of such patient.

Patient Consent Form / Hasta Onam Formu

The parents' of this patient consent was obtained for this study.

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

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