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A 17-YEAR-OLD ADOLESCENT GIRL WITH PANCYTOPENIA: DIAGNOSTIC CHALLENGES IN DIFFERENTIATING REFRACTORY IMMUNE THROMBOCYTOPENIA FROM SEVERE APLASTIC ANEMIA

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Abstract

This needs to be determined since the medical problem involves an adolescent patient with pancytopenia, which may arise from immune-mediated cytopenias or bone marrow failure syndrome. We report the case of a 17-year-old previously healthy adolescent girl who arrived at the hospital with severe menstrual bleeding, petechiae, and bruising; she needed blood transfusions to treat her pancytopenia. The doctors treated her first for ~~refractory immune thrombocytopenia (ITP), a provisional diagnosis of ITP using corticosteroids and eltrombopag, but she did not achieve any enduring results. The bone marrow biopsy showed hypocellularity at 35–40%, megakaryocytic hypoplasia, trilineage suppression, and MF-2 grade reticulin fibrosis, confirming severe aplastic anemia (SAA). The medical practitioners administered supportive care through blood transfusion, in addition to eltrombopag medication. The medical practitioners then started evaluating her eligibility for Hematopoietic Stem Cell Transplantation (HSCT). Moreover, this case highlights that pancytopenia with bleeding symptoms requires prompt bone marrow examination to distinguish ITP from SAA, as treatment approaches differ fundamentally.

BACKGROUND

Pancytopenia among adolescents is an emergency diagnosis [1]. Bleeding accompanied by thrombocytopenia may cause immune thrombocytopenia (ITP) to be suspected initially; however, since pancytopenia has been detected, other conditions like aplastic anemia need to be ruled out [2]. Severe aplastic anemia disease occurs due to the attack of immune system cells on hematopoietic stem cells, hence inhibiting their capacity for multiplication in the bone marrow [3]. Severe aplastic anemia (SAA) refers to an immunemediated bone marrow failure disorder that results from the cytotoxic T cell-mediated destruction of hematopoietic stem cells, causing pancytopenia and hypocellular marrow [3,4]. SAA is caused by the activation of type 1 cytotoxic T cells and Th1 cytokines like IFN-γ and TNF-a which trigger cell death of hematopoietic stem and progenitor cells [5,6]. The two methods used to treat SAA completely differ from each other. ITP management focuses on reversing platelet destruction through corticosteroids or thrombopoietin receptor agonists, whereas SAA requires immunosuppression or Hematopoietic Stem Cell Transplantation (HSCT) to restore trilineage hematopoiesis [7,8]. The primary treatment for young patients with matched donors involves HSCT while immunosuppressive therapy (IST) with horse antithymocyte globulin (hATG),

cyclosporine A (CsA), and eltrombopag provides better treatment results when transplantation cannot occur at that moment [9–11].

CASE PRESENTATION

A 17-year-old previously healthy adolescent girl presented with a 4-month history of progressively worsening menorrhagia, generalized fatigue, and easy bruising. Menstrual bleeding was described as heavy, requiring 6–8 fully soaked sanitary pads per day with passage of clots, lasting 8–10 days per cycle. She also reported spontaneous petechiae over the lower limbs, intermittent gum bleeding during brushing, and multiple ecchymotic patches without preceding trauma. She developed exertional dyspnoea, dizziness, and severe lethargy during the last month, interfering with her ability to perform everyday tasks and attend school. The patient showed no signs of weight loss, night sweats, joint pain, drug usage (except prescribed medications), radiation exposure, or family history of blood disorders. She experienced two undocumented low-grade fever episodes during the last two weeks without any recorded infections. The patient showed no symptoms indicating an autoimmune disease.

The patient needed multiple admissions to another medical center during the last three months because of severe thrombocytopenia and symptomatic anemia, requiring packed red blood cell and single-donor platelet transfusions. The doctors established a **provisional** diagnosis of ITP because the patient showed severe bleeding symptoms together with thrombocytopenia. The patient received oral corticosteroids, which provided only slight relief. The patient developed "refractory ITP" because of ongoing thrombocytopenia, and she began treatment with eltrombopag 50 mg daily. Due to ongoing thrombocytopenia despite corticosteroids, she was labeled as having "refractory ITP" (provisionally) and started on eltrombopag 50 mg daily. However, the presence of pancytopenia (not isolated thrombocytopenia) should have prompted earlier diagnostic reconsideration [12].

Examination at our center revealed a pale complexion, exhaustion, multiple petechiae on both lower legs, scattered ecchymoses across her arms, and mild gingival bleeding. There was no lymphadenopathy or hepatosplenomegaly. No clinical signs of chronic liver disease or collagen vascular disease could be detected. There were stable vital signs and no fever present.

On lab results, there were signs of pancytopenia with low hemoglobin level of 5.3 g/dL, absolute neutrophil count 0.41 $\times 10^9$/L, and consistently low platelet levels less than 20-30 $\times 10^9$/L on multiple labs (Table 1). MCV level increased to 104 fL. Peripheral blood smear showed anisopoikilocytosis, dimorphic red blood cells, some macrocytic cells, and large platelets, but no blasts.

Reasons for performing bone marrow aspiration and biopsy were persistent cytopenia involving all three lineages and the requirement for transfusions. Bone marrow examination revealed bone marrow cellularity of 35-40% (which is low for age), few megakaryocytes, and low hematopoietic cellularity. However, trilineage hematopoiesis was seen, albeit decreased. Blast percentage was 3%. Reticulin staining showed MF-2 grade fibrosis (diffuse reticulin network with intersections). No dysplastic changes met criteria for myelodysplastic syndrome. Cytogenetics was normal. The findings confirmed acquired severe aplastic anemia.

INVESTIGATIONS

The following tables summarize the key hematological and bone marrow findings.

Table 1 presents serial peripheral blood counts demonstrating progressive pancytopenia.

Parameter	18-Jan-2025	07-Jul-2025	09-Jul-2025	Normal Range
Hemoglobin (g/dL)	9.1	8.2	5.3	12.0 - 16.0
WBC ($x10^9$/L)	2.6	3.71	5.9	5.0 - 10.0
ANC ($x10^9$/L)	0.6	1.45	0.41	2.0 - 7.0
Platelets ($x10^9$/L)	16	34	_	150 - 450
MCV (fL)	81.0	92.5	104.0	76.5 - 96.0
Blood Film: Anisopoikilocytosis, dimorphic picture, large platelets, Macrocytes, hypersegmented neutrophils.				

Table 2 summarizes the bone marrow biopsy findings, showing hypocellularity and megakaryocytic hypoplasia.

Table 2. Bone Marrow Findings

Feature	Finding
Cellularity	Hypocellular (35–40%) for age
Hematopoiesis	Trilineage present with subtle dyserythropoietic features
Megakaryocytes	Markedly reduced
Blasts	3% (within normal limits)
Reticulin Fibrosis	Grade MF-2 (diffuse increase with extensive intersections)
Iron Stores	Grade +2; no ringed sideroblasts
Other	Prominent lymphocytes and plasma cells (23% and 9%, respectively)

Table 3 shows other relevant investigations, including coagulation profile and ultrasound findings.

Table 3. Other Key Investigations

Test	Result
Coagulation Profile (PT/INR)	Normal (PT: 10.5s, Control: 11.0s, INR: 1.00)
Ultrasound Abdomen	Mild right hydronephrosis; otherwise, normal (no hepatosplenomegaly)
Blood Culture (AKUH)	Preliminary: *Staphylococcus species (not aureus)*; deemed a likely contaminant
Dengue NS1	Negative
Vitamin B12	868 pg/mL (Normal)

DIFFERENTIAL DIAGNOSIS

The initial clinical suspicion was provisional refractory ITP, given the bleeding manifestations and severe thrombocytopenia. The finding of prominent lymphocytes and plasma cells in the marrow added support to an immune-mediated process. However, the persistence of trilineage cytopenia, transfusion dependence, and the hypocellular bone marrow were pathognomonic for acquired aplastic anemia. The bone marrow findings ruled out myelodysplastic syndrome (no significant dysplasia or blast excess) and acute leukaemia. Malaria was not confirmed. Mild hydronephrosis was incidental.

TREATMENT

The management was multifaceted:

- **Supportive Care:** Regular transfusions of single-donor platelets and packed red cells.
- **Disease-Specific Therapy:** Corticosteroids initially for suspected ITP; due to refractoriness, eltrombopag (Elbonix 50 mg daily) was started. Current American Society of Hematology (ASH) 2026 guidelines recommend eltrombopag in combination with IST (hATG and CsA) for treatment-naïve SAA [4,9]. Our patient was already on eltrombopag monotherapy from prior ITP management; this was continued while evaluating definitive therapy, but the standard of care would be combination therapy [4,9].
- **Adjunct Therapy:** Folic acid supplementation.
- **Definitive Therapy Evaluation:** HSCT was identified as the preferred curative treatment. A search for a suitable Human leukocyte antigen (HLA) matched donor was initiated. For patients without a matched donor, IST plus eltrombopag is a reasonable alternative [4,12]. The decision requires individualized assessment of donor availability, infection risk, and response to IST [13].

OUTCOME AND FOLLOW-UP

The patient showed a partial response to the treatment with eltrombopag due to an improvement in platelets, but remained dependent on transfusions. The patient was discharged for further monitoring under strict outpatient haematology control to evaluate her response to therapy and plan HSCT when an optimal donor is found.

DISCUSSION

This case emphasizes the difficulties encountered during the diagnosis of bleeding disorders and cytopenia in adolescents. ITP is characterized by an isolated decrease of platelets below 100 $\times 10^9$/L without any other cytopenias [1]. In case of persistent anemia and neutropenia, ITP must be reconsidered, and a bone marrow test should be conducted [1,2]. The key feature of ITP is the destruction of platelets due to immunity in the presence of normal megakaryocytes [1]. SAA is a bone marrow failure disease that manifests itself with hypocellular bone marrow along with the following parameters: Absolute neutrophil count (ANC) less than 0.5 $\times 10^9$/L, platelets less than 20 $\times 10^9$/L, reticulocytes less than 20 $\times 10^9$/L [3,4].

The initial misclassification as refractory ITP occurred because bleeding symptoms and severe thrombocytopenia dominated the presentation – a recognized diagnostic pitfall [5]. Acquired SAA results from immune-mediated destruction of hematopoietic stem cells by autoreactive cytotoxic T lymphocytes. Elevated levels of interferon-γ and tumor necrosis factor-α lead to stem cell apoptosis [6]. The presence of marrow lymphocytes in this case supports immune-mediated marrow suppression.

Reticulin fibrosis in aplastic anemia: Classic SAA is not primarily a fibrotic marrow disorder; however, mild to moderate reticulin fibrosis (MF-1 or MF-2) is observed in 15–30% of cases at diagnosis [7,8]. This fibrosis is typically reversible with successful immunosuppression and does not confer a worse prognosis when treated appropriately [7,8]. The pathophysiology is thought to involve cytokine-driven stromal activation (particularly transforming growth factor-β and platelet-derived growth factor) rather than primary clonal myeloproliferation [7]. Our patient's MF-2 fibrosis is consistent with this literature and does not contradict the diagnosis of SAA. Importantly, the presence of reticulin fibrosis should not deter clinicians from pursuing IST or HSCT, as it does not independently predict poor outcomes [7,8].

Eltrombopag use in SAA. The US Food and Drug Administration initially approved eltrombopag for refractory ITP as a thrombopoietin receptor agonist. Over the past decade, eltrombopag has become a standard component of SAA management. Landmark trials demonstrated that adding eltrombopag to standard IST (antithymocyte globulin plus cyclosporine) significantly improved overall and complete response rates [4,9]. The RACE trial (2022) confirmed that eltrombopag plus IST produced higher response rates at 6 months compared to IST alone [4]. Current ASH 2026 guidelines recommend eltrombopag in combination with IST, not as monotherapy, for treatment-naïve SAA [4,9]. Our patient received eltrombopag as

monotherapy due to the prior ITP diagnosis; this was continued while arranging definitive therapy, but the standard of care would be combination therapy.

Mechanistically, eltrombopag has dual effects in SAA: it directly stimulates hematopoietic stem and progenitor cells via c-MPL activation and also exerts immunomodulatory effects by reducing IFN-γ production and restoring regulatory T cell function [14,15]. These properties make it particularly valuable in the SAA setting. International guidelines establish matched sibling donor HSCT as first-line treatment for children and adolescents with SAA [4,12]. Long-term survival for pediatric matched-donor transplantation exceeds 85–90% [12]. For patients without matched sibling donors, matched unrelated donor HSCT is increasingly used, especially in those with severe cytopenias [13]. Recent data have also demonstrated excellent outcomes with haploidentical HSCT using post-transplant cyclophosphamide, with 3-year overall survival of 92% in upfront therapy [16]. However, the decision requires individualized assessment of donor availability, infection risk, and response to immunosuppressive therapy [12,13]. HSCT is not absolute but is preferred when a suitable donor is available.

The emergence of HLA loss as a mechanism of immune escape in AA has provided new insights into disease pathophysiology and potential for spontaneous remission. Somatic mutations leading to loss of HLA class I expression on hematopoietic stem cells allow these clones to evade T-cell attack [17,18]. In our patient, although formal HLA loss testing was not performed, the prominent lymphocytosis on bone marrow and rapid progression suggest an active immune process that could potentially be targeted by such escape mechanisms [19,20].

Clinical lessons. This case highlights the importance of the following three principles: (1) No pancytopenia can be considered as an ITP before proved otherwise; (2) All patients with multilineage cytopenia must undergo bone marrow biopsy; and (3) Referral to transplantation centers early in the course of a disease significantly enhances survival rate in severe cases of AA.

Limitations. This case report has several limitations. HLA loss analysis was not performed at diagnosis, which could have provided additional insight into the immune pathophysiology. Long-term follow-up data on clonal evolution and response to definitive therapy are pending. Nevertheless, this case highlights important diagnostic and therapeutic principles.

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Zeeshan Ahmed: Case management and drafting
Shahzad Bashir: Supervision and critical revision
Ghulam Muhammad: Literature review and drafting assistance

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