Diagnosis and Management of Severe Aplastic Anaemia in a Paediatric Patient: A Case Report

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Abstract

Aplastic anaemia (AA) is a rare but severe haematologic condition that causes haematopoietic failure. This results in a decreased or absent number of haematopoietic precursor cells in the bone marrow. AA can occur at any age and affects both genders and all races equally. Here, we report a case of a 14-year-old boy who presented to the emergency department with multiple bruises over his body. Upon laboratory testing, he was discovered to have pancytopenia and a significant hypocellular marrow. The patient was treated with immunosuppressive therapy (IST) and planned for a bone marrow transplant after finding a suitable donor.

Keywords
Aplastic anaemia, pancytopenia, hypocellular marrow, immunosuppressive therapy (IST), bone marrow transplantation (BMT)

Introduction

Aplastic anaemia (AA) is a disorder of haematopoesis characterized by pancytopenia and a hypocellular marrow without any apparent underlying neoplastic process. By definition, there is no presence of abnormal infiltration (such as leukemic or cancerous cells) or increase in reticulin in the bone marrow. AA exhibits a biphasic age distribution with a peak prevalence in those aged between 20 and 30 and over 60¹. It can be inherited or acquired. Several inherited AAs have been described, among which the most common are Fanconi anaemia, Dyskeratosis Congenita, Diamond Blackfan anaemia, and Schwachman-Diamond syndrome². Acquired AA can be causes by a variety factor including radiation exposure, autoimmune disease, drugs (such as chloramphenicol), and chemicals (such as benzene).

Aplastic anaemia presents with signs and symptoms related to pancytopenia. Fatigue, pallor, and shortness of breath are associated with anaemia. Neutropenia correlates with an increased susceptibility to infections, and bleeding results from thrombocytopenia can manifest as petechiae, ecchymoses, or
gastrointestinal bleeding. In cases of aplastic anaemia, there is no enlargement of the lymph nodes, liver, or spleen. A diagnosis other than aplastic anaemia should be considered if enlargement is detected.

Severe aplastic anaemia (SAA) differs from its usual presentation of aplastic anaemia in terms of the severity and intensity of the condition. In SAA, this condition reaches a critical point where the bone marrow's ability to produce blood cells becomes severely impaired. The patient can present with more severe and life-threatening manifestations, including profound cytopenia that cause severe anaemia, a higher risk of serious infection, and uncontrolled bleeding. These will put them at a higher morbidity and mortality risk due to the severe depletion of blood cells. Here we present a case of severe aplastic anaemia in a 14-year-old boy.

Case Report
A 14-year-old boy was admitted to the hospital with a complaint of multiple bruises over his body, intermittent shortness of breath, and reduced effort tolerance for the past month. Upon physical examination, he was afebrile, with a blood pressure of 130/80 mmHg and a pulse rate of 98 beats per minute. Several bruises were found on his legs and thighs. His respiratory and cardiovascular system examinations were unremarkable. There was no palpable lymphadenopathy or hepatosplenomegaly and no physical abnormalities appointing towards inherited marrow failure syndrome IBMFSs.

Initial complete blood count revealed pancytopenia (Table 1). The reticulocyte count was 1%, normal lactate dehydrogenase (LDH), and negative Coomb test pointing toward hypo proliferative marrow rather than haemolysis. The liver function test, renal function test, and coagulation test were normal.

Peripheral blood smear showed pancytopenia with red blood cell anisopoikilocytosis, normal morphology of white blood cells (WBC), and platelets. The bone marrow aspiration showed markedly hypocellular fragments and trails, with no abnormal cells seen (see Figures 1 and 2). Bone marrow trephine biopsy revealed markedly hypocellular marrow with about 10% cells and 90% fats (Figure 3). There was no evidence of bone marrow infiltration by acute leukaemia, lymphoma, or non-hematopoietic cells. Flow cytometry study did not show presence of paroxysmal nocturnal haemoglobinuria (PNH) clone or acute leukaemia. Karyotyping also showed no abnormalities.

Further test results were negative for infection and connective tissue disease. He was diagnosed with severe aplastic anaemia according to Camitta criteria, 1976. The patient was started on triple immune suppression therapy: anti-thymocyte globulin (ATG), cyclosporine (CsA), and prednisone. He was planned for Hematopoietic Stem Cell Transplant (HSTC) later after finding a suitable donor.

Table 1: Blood results

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value (Normal range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>5.2 (13.0 - 17.0 g/dL)</td>
</tr>
<tr>
<td>Total white blood cell count</td>
<td>3.9 (4 - 10 x 10⁹/L)</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>0.46 (2 - 7 x 10⁹/L)</td>
</tr>
<tr>
<td>Platelet</td>
<td>2.0 (150-410 x 10⁹/L)</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>1% (0.5 - 2.5%)</td>
</tr>
<tr>
<td>B12</td>
<td>149 (133-675 pg/mL)</td>
</tr>
<tr>
<td>Folate</td>
<td>16 (&gt; 15 nmol/L)</td>
</tr>
<tr>
<td>Coomb test</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-HIV</td>
<td>Not reactive</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Not reactive</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Not reactive</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Not reactive</td>
</tr>
</tbody>
</table>
Figure 1: BMA showed hypocellular marrow fragments.

Figure 2: BMA showed hypocellular cell trails.
Figure 3: Bone marrow trephine biopsy showed hypocellular marrow with 10% cellularity.

Discussion

We describe an interesting case of idiopathic severe aplastic anaemia in a 14-year-old boy. To diagnoses AA there must be at least two of the following: haemoglobin concentration <100g/l, platelet count <50 x10⁹/L, and neutrophil count <1.5x10⁹/L. The modified Camitta criteria are used to assess the severity in which severe AA is defined as marrow cellularity <25%, plus at least 2 of: (i) neutrophils <0.5 x10⁹/L, (ii) platelets <20 x10⁹/L and (iii) reticulocytes count <20 x10⁹/L.

The first step in understanding the pathogenesis of AA is to divide it into inherited and acquired cases. Inherited marrow failure syndrome IBMFSs are disorder affecting important cellular functions such as DNA repair, telomere preservation, and ribosome biogenesis. While in acquired AA, the aetiologies include exposure to benzenes, radiation, infections (such as Epstein Barr Virus (EBV), Human Immunodeficiency Virus (HIV), parvovirus, and hepatitis), autoimmune disorders (such as Paroxysmal Nocturnal Hemoglobinuria (PNH) and Systemic Lupus Erythematosus (SLE)), and medications (such as alkylating agents, chloramphenicol, and anti-epileptics). More commonly AA is idiopathic, and mounting evidence indicates that immune dysregulation is the underlying cause.

Many conditions are present in children with pancytopenia, some of which may also feature a hypocellular marrow and extensive investigations are mandatory to exclude them. The comprehensive clinical course, family history, exposure to medications, toxins, infectious agents, physical abnormalities, and laboratory tests should be carefully evaluated. Meticulous investigations are required to confirm the diagnosis and: (i) exclude other causes of pancytopenia and hypocellular bone marrow, (ii) exclude inherited marrow failure syndrome IBMFSs, (iii) screen for an underlying cause, and (iv) document co-existing abnormal cytogenetic, and PNH clones. An appropriate evaluation of AA should include a complete blood count, reticulocytes count, peripheral smear, a bone marrow aspiration/biopsy, infective screening such as human immunodeficiency virus (HIV) / hepatitis serologies, vitamin B12/folate levels, flow cytometry to detect PNH or acute leukaemia and cytogenetic studies.
A complete blood count, reticulocyte count, and peripheral blood smear is to confirm existing cytopenia and to rule out the signs of dysplasia. Trephine biopsy is crucial in the diagnosis of aplastic anaemia because of the frequent difficulty in obtaining an adequate aspirate with the result being a ‘dry tap’. The bone marrow is usually hypocellular with a marked reduction of haemopoietic cells. A patchy pattern of erythropoiesis and megakaryopoiesis is typically absent in AA⁹. Myeloid cells are mainly replaced by fat but there is a variable inflammatory infiltrate composed of lymphocytes, plasma cells, macrophages, mast cells, and sometimes eosinophils. There is usually little if any increase in reticulin fibres. Infective screening is used to detect any infection that causes AA, and Vitamin B12 and folate level deficiency should be corrected before a final diagnosis of AA is confirmed. Flow cytometry is used to detect PNH clones that can occur in 50% of patients with AA. Majority of AA patients have normal cytogenetics, but some of these alterations are neither harmful nor suggestive of MDS (in the absence of dysplasia). These include, among others, trisomy 8, del13q, and loss of heterozygosity of the short arm of chromosome 6⁹.

In our case, the patient's medical history revealed no prior medication use and no known history of radiation or chemotherapy exposure, ruling out these common causes. Additionally, the absence of any viral infections or autoimmune disorders, normal serum vitamin B12/folate levels, no PNH clone or acute leukaemia or lymphoma detected in flow cytometry analysis and normal cytogenetic studies further complicated the diagnostic process. Despite the challenges posed by the idiopathic nature of his condition, the patient displayed remarkable stability and responded favourably to the tailored treatment plan.

Management of aplastic anaemia is directed at the underlying cause. Remove the offending agent(s), if possible. Initial management consists largely of supportive care with blood transfusions, platelet concentrates, and treatment and prevention of infection¹⁰. All blood products should be leucodepleted, to reduce the risk of alloimmunization, and irradiated, to prevent grafting of live donor lymphocyte.

Once a diagnosis is established, bone marrow transplantation (BMT) and full-dose immunosuppressive therapy (IST) using eltrombopag, anti-thymocytes (ATG), cyclosporin A and prednisone are the treatment of choices for AA patients in children and adults. Numerous studies have demonstrated that BMT is highly successful when an HLA-matched sibling is available (matched related donor, MRD), with 5-year survival rates of 90% and higher, making BMT the recommended first-line therapy in this setting¹¹.

**Conclusion**

This case report highlights the complexity and diagnostic difficulties associated with severe aplastic anaemia, serving as a valuable contribution to the existing literature and emphasizing the importance of early diagnosis and targeted management in paediatric patients to reduce the risks of morbidity and mortality.

**Declaration**

Author(s) declares that no conflict of interest.

**References**


10. Bacigalupo A. How I Treat How I treat acquired aplastic anemia. Published online 2017. doi:10.1182/blood-2016-08