Case Report

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Severe Hyperuricemia as a Presenting Feature of Megaloblastic Anemia

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ABSTRACT

Hyperuricemia is commonly associated with hematological malignancies and high cell-turnover states. In megaloblastic anemia, ineffective erythropoiesis can increase purine breakdown, but severe hyperuricemia as an initial presentation—especially in children—is rare and may mimic malignancy. A 10-year-old girl with Down syndrome presented with failure to thrive, severe pancytopenia, hepatosplenomegaly, and marked hyperuricemia, raising strong suspicion of acute leukemia. Bone marrow examination revealed megaloblastic hematopoiesis without excess blasts. Treatment with vitamin B12 and folate led to rapid hematological recovery and normalization of uric acid levels. Megaloblastic anemia should be considered in children presenting with severe hyperuricemia and cytopenias, even when malignancy is suspected. Early diagnosis allows prompt, curative therapy and avoids unnecessary aggressive interventions.

Introduction

Hyperuricemia, defined as an elevation of serum uric acid beyond the age- and sex-adjusted reference range, is a well-recognized biochemical abnormality in hematological malignancies, particularly acute leukemias and high-grade lymphomas. In these settings, accelerated cellular proliferation and turnover, either spontaneous or treatment-induced, result in excessive nucleic acid breakdown with consequent overproduction of uric acid. When severe, this process may culminate in tumor lysis syndrome, characterized by hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia, and may lead to acute kidney injury and life-threatening metabolic disturbances [1,2].

Beyond malignancy, hyperuricemia is also observed in non-neoplastic hematological conditions associated with increased cell turnover, including hemolytic anemias and ineffective erythropoiesis. Megaloblastic anemia, caused predominantly by deficiencies of vitamin B12 or folate, is characterized by defective DNA synthesis resulting in nuclear–cytoplasmic asynchrony and apoptosis of hematopoietic precursors within the bone marrow. This phenomenon, termed ineffective hematopoiesis, leads to cytopenias despite a hypercellular marrow and is accompanied

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by biochemical evidence of increased cell breakdown [3,4].

Although mild and transient elevations of serum uric acid have been described in megaloblastic anemia, severe hyperuricemia as a presenting feature is rare and sparsely reported in the pediatric literature. Such presentations may pose a significant diagnostic challenge, particularly in children with cancer-predisposition syndromes such as Down syndrome, where cytopenias, hepatosplenomegaly, and metabolic abnormalities immediately raise concern for leukemia [5]. Misinterpretation may result in unnecessary anxiety, invasive diagnostic procedures, and exposure to potentially harmful therapies.

A 10-year-old girl, born to non-consanguineous parents and diagnosed with Down syndrome at birth, presented with long-standing failure to thrive and progressive pallor since early childhood. Over the week preceding admission, she developed worsening fatigue, breathlessness on minimal exertion, and intermittent abdominal pain. There was no history of fever, bleeding manifestations, bone pain, or weight loss. The child had experienced recurrent respiratory tract infections over the previous two years and had required three packed red blood cell transfusions during the last five months for severe anemia.

Dietary assessment revealed poor oral intake for approximately one year, with a preference for juices and semisolid cereals and minimal consumption of animal-source foods, raising suspicion of nutritional deficiencies. There was no history of exposure to medications known to affect uric acid metabolism, including diuretics, antitubercular drugs, or anticonvulsants. Family history was unremarkable for hematological disorders or inherited metabolic diseases.

On examination, the child appeared pale, cachectic, and lethargic, with generalized hypotonia consistent with Down syndrome. She was tachycardic with a heart rate of 136 beats per minute and hypotensive, with a blood pressure of 70/56 mmHg, below the 3rd percentile for age and height. Hepatomegaly (liver palpable 4 cm below the costal margin) and splenomegaly (spleen palpable 3 cm below the costal margin) were noted. A grade 3/6 ejection systolic murmur was audible over the precordium, consistent with an anemia-related flow murmur. There was no lymphadenopathy, skin rash, or joint involvement.

Initial laboratory evaluation demonstrated severe macrocytic anemia (hemoglobin 1.9 g/dL; mean corpuscular volume 119 fL), thrombocytopenia (12,600/µL), and leukocytosis (17,600/µL) with an absolute neutrophil count of 3,980/µL. Reticulocyte count was inappropriately low for the degree of anemia. Renal function was preserved (blood urea 26 mg/dL; serum creatinine 0.7 mg/dL), but marked hyperuricemia was noted (serum uric acid 13 mg/dL; reference range 2–8 mg/dL). Serum electrolytes were initially within normal limits.

Peripheral blood smear examination revealed marked anisopoikilocytosis with macrocytes and ovalocytes, frequent hypersegmented neutrophils, and 16 nucleated red blood cells per 100 white blood cells, suggesting ineffective erythropoiesis (Figure 1).

Given the presence of trisomy 21, pancytopenia, hepatosplenomegaly, leukocytosis, and hyperuricemia, acute leukemia was strongly suspected.

Bone marrow aspiration demonstrated a hypercellular marrow with marked megaloblastic changes affecting erythroid and myeloid precursors, without an increase in blast percentage. Trephine biopsy confirmed panmyelosis with increased reticulin fibrosis, consistent with severe ineffective hematopoiesis rather than malignant infiltration. Cytogenetic and flow cytometric analyses did not reveal evidence of leukemia.

The child was managed with intramuscular cyanocobalamin at a dose of 500 µg daily for five consecutive days, followed by oral cyanocobalamin 500 µg daily and folic acid 5 mg daily for six weeks. Allopurinol (100 mg/m² per dose, three times daily) was administered for one week to address hyperuricemia. In view of cardiac decompensation secondary to profound anemia, a packed red cell transfusion (5 mL/kg) was given cautiously, and intravenous fluids were restricted to two-thirds maintenance to prevent fluid overload.

During treatment, the child developed hypokalemia (nadir 2.4 mEq/L), which was corrected with parenteral potassium supplementation [6]. A progressive rise in hemoglobin and platelet counts was observed, accompanied by normalization of serum uric acid levels. By day 15, hemoglobin had increased to 7.7 g/dL, mean corpuscular volume had decreased to 106 fL, and platelet count had risen to 56,000/µL. Complete normalization of the hemogram was achieved within one month.

Further evaluation revealed primary hypothyroidism, for which levothyroxine therapy was initiated.

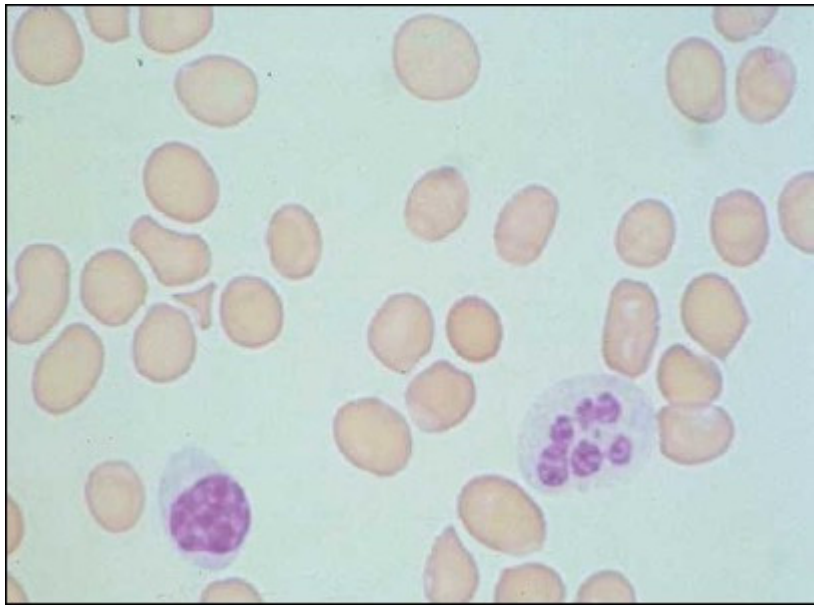

Fig. 1. Peripheral blood smear with hypersegmented neutrophils Peripheral blood smear demonstrating marked macrocytosis with macroovalocytes, pronounced anisopoikilocytosis, and multiple hypersegmented neutrophils. Occasional nucleated red blood cells are noted, consistent with ineffective erythropoiesis seen in severe megaloblastic anemia (original magnification ×100).

Screening for celiac disease was negative, and cardiological assessment did not reveal structural abnormalities. The child remains on follow-up with sustained hematological remission.

Discussion

This case illustrates an uncommon but clinically important presentation of megaloblastic anemia with severe hyperuricemia, mimicking a hematological malignancy. Hyperuricemia reflects an imbalance between uric acid production and excretion and is most often associated with conditions involving rapid cellular turnover. In malignant disorders, particularly leukemias and lymphomas, accelerated proliferation and lysis of tumor cells release large quantities of purine nucleotides, which are metabolized to uric acid. When renal excretion is overwhelmed, uric acid accumulates, predisposing to crystal-induced nephropathy and acute kidney injury.

In megaloblastic anemia, defective DNA synthesis due to vitamin B12 or folate deficiency results in nuclear maturation arrest and apoptosis of hematopoietic precursors within the bone marrow [7]. Although the marrow is hypercellular, the effective output of mature blood cells is reduced, leading to cytopenias. The extensive intramedullary destruction of nucleated cells increases purine turnover and uric acid production, providing a plausible mechanism for hyperuricemia in this setting. However, clinically significant hyperuricemia is rarely reported, likely because most patients are diagnosed before ineffective hematopoiesis becomes extreme.

The presence of Down syndrome added substantial diagnostic complexity in this case. Children with trisomy 21 are at increased risk of acute lymphoblastic leukemia and acute megakaryoblastic leukemia, as well as transient abnormal myelopoiesis in infancy [5]. Consequently, cytopenias and organomegaly in this population appropriately prompt evaluation for malignancy. Although hyperuricemia has been reported in individuals with Down syndrome, this association is generally attributed to dietary and metabolic factors rather than intrinsic hematological abnormalities. In the present case, secondary causes of hyperuricemia—including renal dysfunction, drug exposure, dehydration, inherited purine metabolism disorders, and endocrine abnormalities—were systematically excluded.

Hepatosplenomegaly in megaloblastic anemia is thought to arise from compensatory extramedullary haematopoiesis and increased clearance of abnormal erythroid precursors. Increased reticulin fibrosis observed in the bone marrow may reflect chronic ineffective haematopoiesis and has been described in severe vitamin B12 deficiency, where sustained intramedullary apoptosis and cytokine-mediated stromal activation contribute to secondary myelofibrotic changes [8]. These alterations are typically reversible following correction of the underlying deficiency and should not be

misinterpreted as primary myeloproliferative or infiltrative marrow disorders.

From a diagnostic perspective, this constellation of hepatosplenomegaly, pancytopenia, marrow hypercellularity, and biochemical evidence of increased cell turnover can closely resemble acute leukemia or other malignant hematological conditions, particularly in children with trisomy 21. In such settings, careful morphological assessment of the peripheral blood smear and bone marrow remains pivotal. The presence of macro-ovalocytes, hypersegmented neutrophils, and a paucity of true blasts strongly favours megaloblastic anemia, even when leucocytosis or nucleated red cells raise concern for malignancy.

From a diagnostic perspective, this constellation of hepatosplenomegaly, pancytopenia, marrow hypercellularity, and biochemical evidence of increased cell turnover can closely resemble acute leukemia or other malignant hematological conditions, particularly in children with trisomy 21. In such settings, careful morphological assessment of the peripheral blood smear and bone marrow remains pivotal. The presence of macro-ovalocytes, hypersegmented neutrophils, and a paucity of true blasts strongly favours megaloblastic anemia, even when leucocytosis or nucleated red cells raise concern for malignancy.

The marked hyperuricemia observed in this patient is best explained by accelerated purine turnover secondary to extensive intramedullary cell death rather than tumor cell lysis [9]. Unlike tumor lysis syndrome, hyperuricemia in megaloblastic anemia is not accompanied by hyperphosphatemia or hypocalcemia and rarely results in acute kidney injury. Consequently, urate-lowering therapy is usually required only transiently, with definitive resolution achieved through vitamin repletion and restoration of effective haematopoiesis.

Recognition of this mechanism has important therapeutic implications. Misclassification as a malignant process may expose patients to unnecessary intensive hydration, rasburicase, cytotoxic therapy, or prolonged hospitalization. In contrast, prompt initiation of vitamin B12 and folate replacement leads to rapid hematological recovery, normalization of metabolic abnormalities, and regression of organomegaly. The brisk response observed in this case further supports the diagnosis and underscores the reversibility of even severe presentations [10].

Finally, this case highlights the need for heightened clinical awareness of nutritional deficiencies in vulnerable pediatric populations, including children with developmental disabilities and restricted dietary intake. In resource-limited settings, delayed recognition of megaloblastic anemia may allow ineffective erythropoiesis to progress to extreme biochemical and clinical manifestations. Incorporating early nutritional assessment and peripheral smear evaluation into the diagnostic algorithm for children presenting with pancytopenia and hyperuricemia can facilitate timely diagnosis, avert unnecessary investigations, and improve outcomes.

Conclusion

Severe hyperuricemia is an uncommon but important manifestation of megaloblastic anemia and may closely mimic hematological malignancy, particularly in children presenting with pancytopenia and organomegaly. This diagnostic challenge is further amplified in patients with Down syndrome, in whom the threshold for suspecting leukemia is appropriately low. Recognition of the characteristic hematological features of megaloblastic anemia, together with an understanding of the pathophysiological basis of hyperuricemia due to ineffective erythropoiesis, is essential to avoid misdiagnosis.

This case underscores that even profound metabolic derangements and marrow fibrosis can be reversible with timely vitamin B12 and folate replacement. Early identification and appropriate treatment not only result in rapid hematological and biochemical recovery but also prevent unnecessary invasive procedures, exposure to aggressive therapies, and associated morbidity. Awareness of this rare presentation reinforces the need to include nutritional deficiencies in the differential diagnosis of hyperuricemia with cytopenias in pediatric practice, ensuring accurate diagnosis and optimal patient outcomes.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

Author contribution

MM, SS, and NR were involved in the diagnosis and care of the patient, as well as the preparation of the manuscript and its revisions.

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Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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