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Case Report

Severe Megaloblastic Anaemia Secondary to Coeliac Disease Mimicking Multiple Life-Threatening Disorders: A Case Report

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Abstract

Background: Megaloblastic anaemia can present with severe clinical and biochemical derangements that mimic other life-threatening conditions, including sepsis, acute leukaemia, and hemophagocytic lymphohistiocytosis (HLH). Identifying the underlying aetiology requires a high index of suspicion, especially in resource-limited or peripheral settings.

Case Presentation: A 26-year-old female patient with epilepsy on multiple antiepileptic drugs presented with exertional breathlessness, fever, and high-output heart failure. Investigations revealed macrocytic anaemia, bicytopenia, elevated lactate dehydrogenase levels, and high ferritin levels. A pruritic rash on her extensor elbows and a history of wheat intolerance led to the clinical suspicion of celiac disease, which was later confirmed by positive tissue transglutaminase antibodies. She was initiated on intramuscular vitamin B12, oral folate, and a strict gluten-free diet, resulting in rapid haematological and clinical recovery.

Conclusions: This case highlights the "megaloblastic mimics." Severe B12 and folate deficiencies can masquerade as cytopenia, haemochromatosis, sepsis, or HLH due to ineffective erythropoiesis. Correctly interpreting the reticulocyte production index and recognising pathognomonic skin findings, such as dermatitis herpetiformis, are crucial for avoiding misdiagnosis.

Keywords: Coeliac disease, dermatitis herpetiformis, megaloblastic anaemia, ineffective erythropoiesis

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Introduction

Megaloblastic anaemia, commonly resulting from vitamin B12 or folate deficiency, typically presents with insidious fatigue and macrocytosis. However, in severe cases, ineffective erythropoiesis can lead to intramedullary haemolysis, triggering a cascade of biochemical abnormalities [1]. These derangements can mimic acute, life-threatening pathologies, such as sepsis, acute leukaemia, and hemophagocytic lymphohistiocytosis (HLH) [2]. Furthermore, identifying the root cause of megaloblastosis is critical. Celiac disease is an autoimmune enteropathy triggered by gluten exposure that can occasionally present with atypical extraintestinal manifestations with characteristic dermatological findings [3]. This report presents a case of megaloblastic anaemia secondary to celiac disease with dermatitis herpetiformis. We aim to highlight diagnostic pitfalls and offer 'clinical pearls' for

navigating megaloblastic mimics, particularly in resource-limited settings.

Case Report

A 26-year-old woman presented to the medical ward with complaints of exertional breathlessness, fatigue, and swollen ankles. The patient also had a history of fever. Her past medical history was significant for epilepsy and a global learning disability after neonatal meningitis, for which she was on three antiepileptic medications: oxcarbazepine, topiramate, and clobazam. Upon revisiting her history with her mother later during the admission, it was revealed that the patient actively disliked wheat, bread, and roti, claiming that these foods made her feel "uncomfortable".

Physical examination revealed high-output heart failure. She had severe pallor accompanied by lemon-tinged icterus. Cardiovascular examination demonstrated a pulse rate of 118 beats per minute with a collapsing character and a blood pressure of 130/56 mmHg. Jugular venous pressure was elevated. Precordial examination revealed a thrusting, shifted cardiac apex and a gallop rhythm with an S4 and a systolic murmur. She also had bilateral pitting ankle oedema. A crucial dermatological finding was the pruritic skin rash localised to both extensor elbows (Figure 1). The mother confirmed that the rash appeared "from time to time" and was intensely pruritic. Initial laboratory investigations are shown in Table 1.



Figure 1: The extensor surface of the right elbow. Black arrowheads point to the pruritic rash.

The initial blood investigations revealed a severe anaemia with mild thrombocytopenia. The immediate diagnostic challenge was differentiating between primary marrow failure (potentially induced by her antiepileptic medication: oxcarbazepine) and severe haemolysis. The raw reticulocyte count was 3.7%; however, the calculated Reticulocyte Production Index (RPI) was suppressed at 0.5%, indicating a production defect rather than peripheral destruction. Peripheral blood film analysis revealed ovalocytosis with hypersegmented neutrophils, a hallmark of megaloblastic anaemia.

The unifying diagnosis for macrocytic anaemia with bicytopenia, a pruritic extensor rash (suspected dermatitis herpetiformis), and wheat intolerance was celiac disease. The definitive key investigations for this diagnosis are an Upper Gastrointestinal Endoscopy (UGIE) with duodenal biopsy and a skin biopsy for immunohistochemistry. However, a skin biopsy for immunofluorescence testing was unavailable due to resource constraints in our peripheral setting, and the UGIE was deferred as the patient's mother declined consent for the invasive procedure. Consequently, the diagnosis was advanced by sending serum IgA tissue transglutaminase (tTG) levels. Additionally, we performed a contrast-enhanced CT scan of the brain to exclude celiac disease, epilepsy, and cerebral calcification (CEC) syndrome, given the history of epilepsy; however, the imaging results were normal.

Pending confirmatory laboratory results for vitamin deficiencies and celiac serology, a therapeutic trial was initiated. Blood samples were drawn for vitamin B12 and folate levels, and the patient was started on intramuscular vitamin B12 1000 □ g every other day for six doses and oral folate 5 mg daily. The patient was also advised to maintain a strict gluten-free diet.

The patient showed dramatic clinical and haematological improvement. Clinically, her exertional breathlessness and signs of high-output heart failure, including the tachycardia, gallop rhythm, and peripheral oedema, completely resolved as her anaemia improved. Furthermore, the intensely pruritic rash on her extensor elbows (dermatitis herpetiformis) faded significantly and ceased itching following her adherence to the strict gluten-free diet. At a one-week follow-up post-discharge, her haemoglobin level more than doubled to 8.1 g/dL. Her RPI indicated a marrow response, which increased to 6.8%. The LDH elevation resolved, dropping to 979 U/L, and her platelet count normalised to 273 x 109/L.

Table 1: Initial blood investigations with reference values

Investigation	Result	Normal range
White blood cell count	4.76 x 10^9/L	4-11 x 10^9/L
Haemoglobin	3.5 g/dL	11.5-15.5 g/dL
Mean corpuscular volume	107.2 fL	80-96 fL
Platelet count	127 x 10^9/L	150-400 x 10^9/L
Erythrocyte sedimentation rate	120 mm/h	0-20 mm/h
C-reactive protein	21 mg/L	<5 mg/L
Serum creatinine	0.68 mg/dL	0.6-1.5 mg/dL
Total bilirubin	1.4 mg/dL (with a higher indirect fraction)	0.3-1.5 mg/dL
Aspartate aminotransferase	56 U/L	<40 U/L
Alanine aminotransferase	22 U/L	<40 U/L
Alkaline phosphatase	79 U/L	39-117 U/L
Lactate dehydrogenase	6065 U/L	240-480 U/L
Ferritin	900 µg/L	15-200 µg/L
Transferrin saturation	93%	16-50%
Triglyceride	301 mg/dL	<150 mg/dL

Assays performed before treatment revealed a severe deficiency: folate was 3.2 ng/mL (3.2-26.8), and Vitamin B12 was low at 130 pg/mL (183-822 pg/mL). The serum IgA tTG result was positive at 112 AU/ml (>8 AU/ml), confirming the diagnosis of celiac disease. Repeat iron studies performed at 1month post-discharge confirmed the resolution of the apparent iron overload, demonstrating a markedly improved ferritin level of 182 µg/L (15-200 µg/L) and a transferrin saturation of 24%. This normalisation reflected proper iron utilisation following the restoration of effective haematopoiesis. The patient was continued on intramuscular vitamin B12 1000 □ g every 3 months and oral folic acid 5 mg daily (Figure 2).

Discussion

This case serves as a vital pedagogical tool for clinicians, highlighting how severe megaloblastic anaemia can present as a multisystem disorder. The following clinical pearls outline the diagnostic traps and mimics encountered in this case study.

1. The "optical illusion" of the normal reticulocyte count. In severe anaemia, a raw reticulocyte count can be misleading. This patient had a seemingly adequate reticulocyte percentage (3.7 %). However, because the total number of mature red blood cells is reduced, the reticulocyte percentage appears falsely elevated. To accurately assess bone marrow function, the RPI must be calculated, which corrects for both the patient's haematocrit and the premature release of reticulocytes (maturation factor)[4]. This patient's RPI was 0.5%, correctly identifying ineffective erythropoiesis rather than peripheral haemolysis.

2. The iron paradox: "starving" but "overloaded". Severe megaloblastic anaemia frequently presents with a biochemical profile mimicking haemochromatosis. This patient presented with a ferritin level of 900 µg/L and transferrin saturation of 93%. This paradox occurs in ineffective erythropoiesis, where red blood cell precursors undergo apoptosis within the bone marrow (intramedullary haemolysis) before maturing. The iron destined for haemoglobin synthesis is subsequently released back into the marrow and circulation, leading to elevated serum iron levels, high transferrin saturation, and a secondary surge in ferritin[5]. In this patient, the apparent iron overload was corrected with effective haematopoiesis.

3. The sepsis mimic. As seen in our patient (low-grade fever, ESR of 120 mm/h, CRP of 21 mg/L, and ferritin of 900 µg/L), severe B12 and folate deficiency can present with low-grade fever, elevated inflammatory markers, and elevated ferritin levels [6]. This constellation of findings frequently triggers an automatic reflex to initiate broad-spectrum antibiotics for presumed sepsis. However, fever and inflammatory responses are likely cytokine-mediated reactions to massive intramedullary destruction of erythroblasts.

4.The HLH trap: Hemophagocytic lymphohistiocytosis is a life-threatening hyperinflammatory syndrome. Our patient presented with multiple red flags for HLH: fever, bicytopenia, an LDH level in the 6000s, ferritin level of 900 µg/L, and high triglyceride levels (301 mg/dL).

However, a key clinical distinction was that the patient was relatively "not that unwell" compared to the systemic toxicity typically seen in true HLH, and other

biochemical abnormalities could be explained by ineffective erythropoiesis alone [6]. Elevated triglyceride levels could be due to the long-term use of antiepileptic drugs [7].

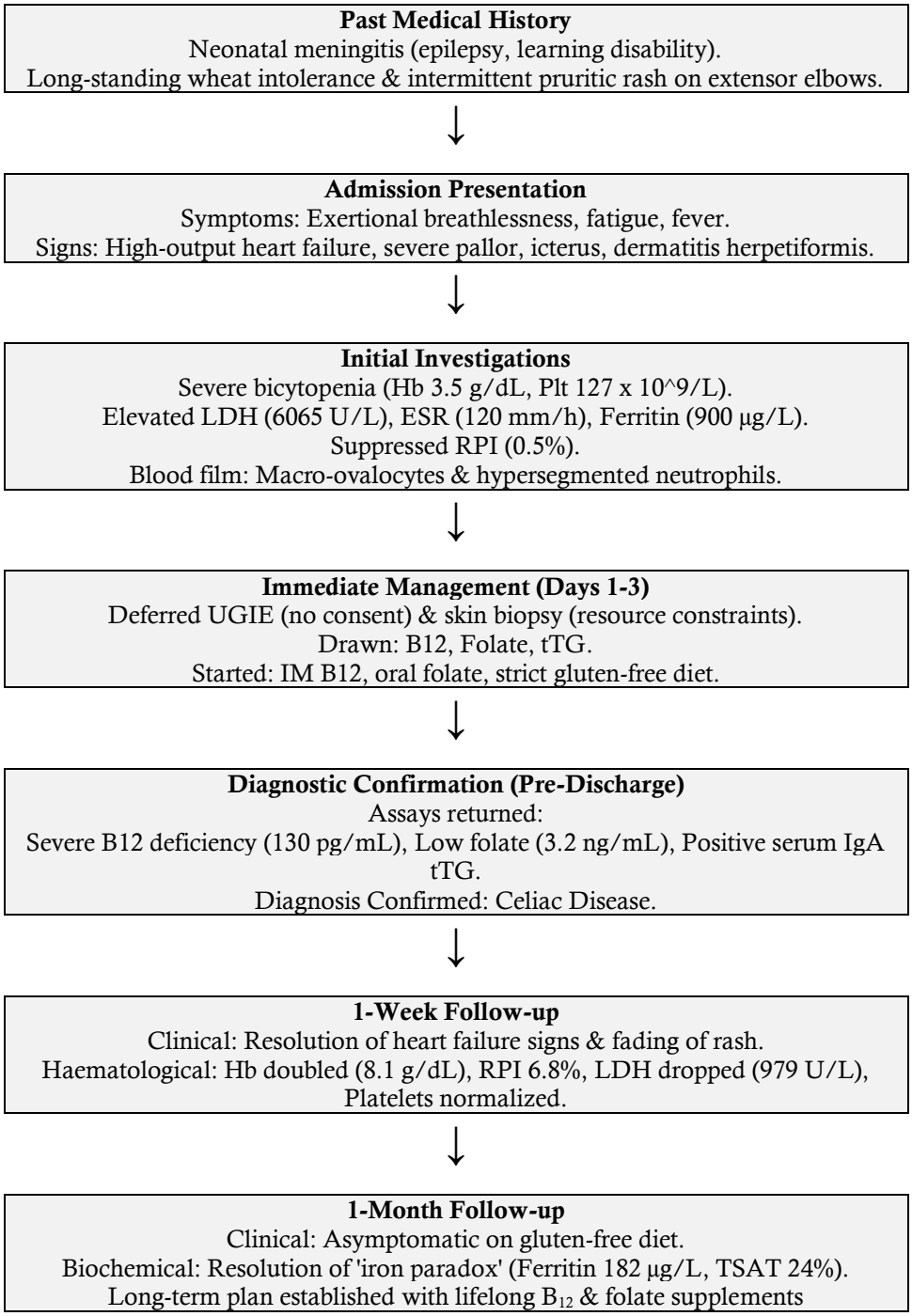


Figure 2: Timeline of the patient's clinical course, diagnostic workup, and response to treatment.

5. The ESR trap: inflammation vs artefact. The patient had an ESR of 120 mm/h. While this can indicate severe inflammation, it is crucial to remember the rheological principles underlying the ESR test. The test measures the rate at which red blood cells fall in a column of plasma at room temperature. In severe anaemia, the decreased number of red blood cells allows them to fall much faster through the plasma, resulting in an artificially extreme ESR elevation that does not necessarily correlate with the degree of true systemic inflammation [8]. However, this extreme elevation is likely multifactorial. Beyond the rheological artefact of profound anaemia, true systemic inflammation driven by severe small bowel enteropathy, or the potential presence of co-existing autoimmune diseases—which share a well-documented epidemiological overlap with celiac disease—must also

be considered as significant contributing factors to this high ESR.

Finally, this case underscores the importance of a thorough clinical evaluation. The subtle, intermittent, pruritic rash on the extensor elbows was the clinical linchpin. Dermatitis herpetiformis is the cutaneous manifestation of celiac disease, and recognising it allowed for the unifying diagnosis of the patient's severe anaemia and wheat intolerance.

A primary limitation in our diagnostic pathway was the absence of histological confirmation. Current guidelines, including those from the American College of Gastroenterology, establish duodenal biopsy as the reference standard for diagnosing celiac disease in adults [9]. In our case, this definitive investigation via Upper Gastrointestinal Endoscopy (UGIE) could not be performed because the patient's mother declined consent for the invasive procedure. Furthermore, confirming dermatitis herpetiformis via a skin biopsy with immunofluorescence was precluded by the severe resource limitations of our peripheral healthcare setting. Given these logistical and consent-related limitations, the diagnosis was made on strong clinical grounds, relying on the convergence of positive serology, the pathognomonic clinical presentation, and the patient's rapid, sustained clino-haematological recovery following a strict gluten-free diet and vitamin replacement.

Patient's perspective

(As narrated by the patient's mother)

"We were terrified when my daughter became so weak, swollen, and breathless. Because of her learning disability, it is sometimes hard for her to explain how she feels, but seeing her heart racing and her having no energy was very frightening. She had always disliked eating bread or wheat, but we never imagined it was actually a serious disease making her sick. When the doctors diagnosed her and started the vitamin injections, the change was like a miracle. Within just a few days, her breathing went back to normal, her swelling disappeared, and her energy returned. Even the terrible, itchy rash she had suffered from on her elbows for a long time finally faded away. We are so incredibly happy and relieved to have her back to her usual self, and we are now strictly and successfully managing her gluten-free diet at home."

Conclusion

Megaloblastic anaemia is a common haematological disorder, but its severe forms can present with biochemical abnormalities that can easily mislead clinicians toward diagnoses of sepsis, acute leukaemias, haemochromatosis, or HLH. Careful interpretation of the RPI, understanding the mechanics of intramedullary haemolysis, and vigilance for extra-haematological clues, such as specific dermatological signs, are essential for delivering life-saving and cost-effective targeted therapy in resource-poor settings.

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

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