ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue V May 2025

A Case Report of Combined Severe Vitamin B_{12}, Folate and Iron Deficiency Anaemia in a 44-Year-Old Lady: Unusual Presentations with Haemolysis, Microcytosis and Pancytopenia

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DOI: https://doi.org/10.51244/IJRSI.2025.12050050

Received: 17 May 2025; Accepted: 22 May 2025; Published: 02 June 2025

ABSTRACT

A 44-year-old female with history of inadequate consumption of food of animal origin, presented with worsening symptoms of anaemia with a past medical history of passing dark tarry stools, heavy menses and multiple blood transfusions during her pregnancies. She is a nonsmoker, does not consume alcohol, no illicit drug use. Physical examination revealed jaundice, petechiae & ecchymoses and pallor without organomegaly or lymphadenopathy. Her initial haemoglobin was 2.1 g/dL with a mean corpuscular volume of 57.3 fL, an elevated red blood cell distribution width of 27.5%, platelet count of 25.2×10^3/µL and total WBC 2.7×10^3/µL. Peripheral blood smear revealed pancytopenia with anisocytosis, poikilocytosis, microcytosis, occasional large cells, elliptocytes, fragments and absence of hyper segmented neutrophils. Her liver & renal function tests were normal except for elevated total bilirubin of 42.5 µmol/L. Further investigations revealed elevated serum lactate dehydrogenase (LDH) of 467 U/L, serum ferritin 1787.7, elevated C-Reactive Protein (CRP), very low serum folate of 0.7 ng/ml & serum vitamin B_{12} <83 pg/ml, negative H. Pylori stool antigen occult blood, negative coombs test (both direct and indirect). The patient was diagnosed with haemolytic anaemia secondary to vitamin B_{12} deficiency, with concomitant folate and iron deficiency anaemia based on morphology.

We present this case as a reminder that severe vitamin B_{12} and/or folate deficiency may present with findings mimicking acute leukaemia and unusual microcytosis. Haematological findings resolved completely following appropriate replacement therapy.

Keywords: Iron deficiency, vitamin B_{12} deficiency, folate deficiency, pancytopenia

INTRODUCTION

When talking of combined-deficiency anaemia the focus of attention is often on concurrent deficiencies of vitamin B_{12} and folate. However, simultaneous deficiencies of vitamin B_{12} and iron may be a more common cause of combined-deficiency anaemia. Combined deficiencies of all the 3 substrates have rarely been reported to occur. Red blood cell morphologic characteristics in this setting may be variable reflecting the relative degree of deficiency of each of these substrates (1).

Masked megaloblastic anaemia is characterized by vitamin B_{12} and/or folate deficiency and normocytic or microcytic anaemia. Macrocytosis, the hallmark of vitamin B_{12}/folate deficiency anaemia, is frequently absent. This is why clinicians have to be aware of coexisting conditions that can mask the macrocytosis expression of megaloblastic anaemia, especially iron deficiency (1).

Here a patient with combined vitamin B_{12}, folate and iron deficiency anaemia with microcytic, hypochromic indices and the absence of hypersegmented neutrophils was treated under limited resource setting. This case and the literature review emphasize the need to consider combined-deficiency states in all cases of anaemia and especially pancytopenia as it may present with findings mimicking acute leukaemia.

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Case Presentation

A 44-year-old female presented to our facility as a referral case with a 2 weeks history of symptoms of anaemia, characterized by progressive generalized body weakness, heartbeats awareness, headache and dizziness. Her past medical history was consistent of passing dark tarry stools, heavy menses and multiple blood transfusions during her pregnancies due to anaemia. There was no history of difficulty in breathing, air hunger at night, lower limbs swelling, no fever, excessive night sweats or significant weight loss, and no bleeding tendencies except for noticeable subcutaneous bleeding. She also denied having abdominal pain or distension, vomiting, diarrhoea or constipation. She does not have any known comorbidities and she is a nonsmoker, does not consume alcohol, no illicit drug use. On general examination during admission, the patient was alert, afebrile, oriented to time, people and place, and not in any distress, she looked thin, pale, not jaundiced and scattered petechiae and fading ecchymoses, no lymphadenopathy. However, she developed jaundice on day 3 of admission. Her vital signs were blood pressure 116/73 mmHg, pulse 100/min, temperature 37C, respiratory rate 18 min, oxygen saturation 100% on room air, height 165 cm, and weight 56 kg. Systemic examination revealed normal cardiopulmonary system, her abdomen was soft and nontender, with no organomegaly, and neurological exam was unremarkable.

Initial investigations included haemoglobin (HB) of 2.1 g/dL with a mean corpuscular volume (MCV) of 57.3 fL, mean corpuscular haemoglobin (MCH) 14.5 pg, mean corpuscular haemoglobin concentration (MCHC) 25.3 g/dL and elevated red blood cell distribution width (RDW) of 27.5%, platelet count of 25.2×10^3/µL and total white blood cell count (WBC) 2.7×10^3/µL. Her liver & renal function tests were normal except for elevated total bilirubin of 42.5 µmol/L. Peripheral blood film was predominant with microcytosis with a few large cells noted as well as tear drop cells and elliptocytes. A couple of fragmented red blood cells were also noted, reduced WBC which appeared normal and low platelets count with no platelets clumps. Further investigations revealed elevated serum lactate dehydrogenase (LDH) of 467 U/L, serum ferritin 1787.7, elevated C-Reactive Protein (CRP), low serum folate of 0.7 ng/ml as well as low serum vitamin B_{12} < 83 pg/ml, negative H. Pylori stool antigen negative stool occult blood and negative coombs test (both direct and indirect). However, investigations such as reticulocytes count, methylmalonic acid and homocysteine level couldn't be done due to lack of these tests at our setting. The patient was diagnosed with hemolytic anemia secondary to vitamin B_{12} deficiency, with concomitant folate and iron deficiency anaemia based on morphological finding of red blood cells despite elevated serum ferritin levels that could be explained by ongoing inflammatory process as evidenced by elevated CRP.

Repeat Full Blood Count (FBC) revealed improvement of WBC and HB level with red cell indices but worsening of platelet count before start of therapy as seen on table 1 below. Once diagnosed, the patient was started on vitamin B_{12} supplement, 1000 mcg intramuscular injection on alternate days, folic acid 5 mg daily, and ferrous sulfate 200 mg three times daily on hospital day 3. She also received 2 units of packed red cell transfusion prior to diagnosis. The patient was discharged on hospital day 14 with a plan of doing intrinsic factor antibody and antiparietal cell antibody to further elucidate the cause of vitamin B_{12} deficiency.

Table 1: Serial Full Blood Count results showing the trend of blood cells and other parameters

Parameter	**5th March, 2024**	**9th March, 2024**	**12th March, 2024**	**15th March, 2024**	**At 1 month**	**Reference range**
WBC (/uL)	2.7 10e3	2.5	4.5	14.7	11.5	3.70 - 10.1
NEU (/uL)	1.4 10e3	1,5	4.0	11.0	6.4	1.63 - 6.96
LYM (/uL)	1.2 10e3	0.8	0.2	2.1	3.2	1.09 - 2.99
HB (g/dL)	2.1	2.0	3.2	3.9	12.1	12.9 - 15.9
MCV (fL)	57.3	57,2	62.7	69.9	79.6	81.1 - 96.0

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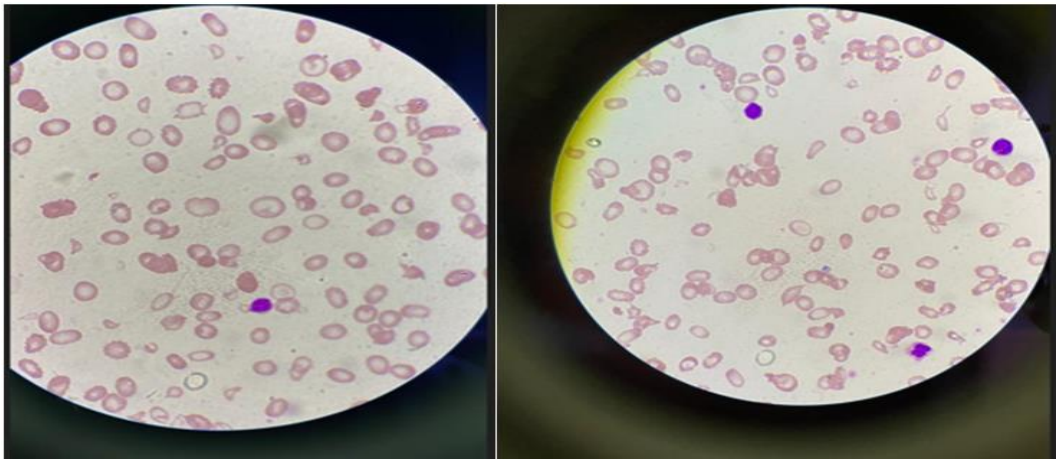
MCH (pg)	14.5	15.7	18.3	19.5	29.8	27.0 - 31.2
MCHC (g/dL)	25.3	27.4	29.1	27.9	31,7	31.8 - 35.4
RDW (%)	27.4	26.8	29.2	37.5	14.9	11.5 - 14.5
PLT (/uL)	25.2 10e3	2.5	6.8	134.8	163	155.0 - 366.0

Figure 1: Peripheral blood smear



Following vitamin $B_{12,}$ folate and iron replacement therapy, the patient reported increased well-being, including appetite and weight gain, and her icterus resolved. In the follow-up laboratory examinations, leucocyte and platelet counts in addition to serum bilirubin and lactate dehydrogenase levels normalised. At the end of 1 month, laboratory findings, including haemoglobin level, were all within the normal range.

DISCUSSION

Iron, vitamin B_{12} and folate are required for essential metabolic functions. Deficiency states of these nutrients, either singly or in combination, are common clinical conditions. Clinically, they present with not only disordered haematopoiesis, but also widespread effects in other organs that can precede the appearance of haematological abnormalities. Investigation of suspected iron, vitamin B_{12} or folate deficiency should first be directed at establishing that the deficiency state exists, but this can be challenging because of the limitations of available biomarkers for evaluating tissue status. A careful assessment of clinical symptoms and signs is indispensable to guide appropriate requesting and interpretation of relevant laboratory tests(2)**.**

Inadequate consumption of animal foods and pernicious anaemia (loss of intrinsic factor due to autoimmune atrophic gastritis) are the most common causes of severe vitamin B_{12} deficiency worldwide in children and adults, respectively (3,4). Vitamin B_{12} deficiency may cause reversible megaloblastic anaemia and/or demyelinating central nervous system disease. For unclear reasons, the severity of megaloblastic anaemia in vitamin B_{12}-deficient individuals is inversely correlated with the degree of neurological dysfunction (3). This can be witnessed in this case as the patient did not present with any neurological symptoms while having severe deficiency.

Although most of the vitamin B_{12}-deficient cases have only mild haematological findings, in approximately 10% of patients, life-threatening conditions such as symptomatic pancytopenia, severe anaemia (defined as a haemoglobin level < 6g/dL and haemolytic anaemia have been reported (5,6). This patient had severe pancytopenia, features of haemolysis with severe anaemia requiring blood transfusion.

Commonly, vitamin B_{12} deficiency is associated with macrocytic anaemia (7). However, the patient's mean corpuscular volume (MCV) was low which was more suggestive of the presence of iron deficiency anaemia. Despite elevated serum ferritin levels the diagnosis of Iron deficiency anaemia based on morphological finding of red blood cells was made. This could be explained by ongoing inflammatory process as evidenced by elevated

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CRP. Ferritin is the intracellular storage form of iron. It is an acute phase reactant and a marker of acute and chronic inflammation. In inflammation, liver disease, and malignancy, ferritin levels can rise because ferritin is an acute phase protein (8). Increased RDW was consistent with poikilocytosis and anisocytosis picture in the peripheral blood smear.

In a study including 201 adults with well-documented vitamin B_{12} deficiency, approximately 10% of the patients were found to have life-threatening haematological manifestations. Among these were pancytopenia (5%), severe anaemia (defined as a haemoglobin level < 6 g/dL; 2.5%) and haemolytic anaemia (1.5%) (5). Our patient had severe microcytic anaemia, pancytopenia and findings of haemolysis (fragmented, misshapen cells in the peripheral smear mimicking microangiopathic haemolytic anaemia, indirect hyperbilirubinaemia and marked increase in LDH). Notably, reticulocytes count could not be performed due to lack of the test at our facility at the time. Concurrent haemolysis in patients with vitamin B_{12} deficiency is a well-recognised phenomenon and has been attributed mainly to intramedullary destruction of erythrocytes (ineffective erythropoiesis) (9,10).

Owing to the poor dietary history of our patient, it was thought inadequate dietary intake to be the cause of the combined deficiencies. However, the patient is 44 years of age, and pernicious anaemia has been reported as the most common cause of severe vitamin B_{12} deficiency in adults (3,10)This makes testing for anti-Intric Factor (IF) and antiparietal cell antibodies mandatory to rule out this possibility. Due to lack of these investigations at our facility and financial constraints on the patient's side this could not be achieved.

CONCLUSION

This case report described a patient with nutritional deficiencies who presented with unusual presentations. It displayed the complexity of diagnosing where clinicians should be familiar of these possible presentations and have a high index of suspicion, particularly in high-risk populations and in resource limited settings. Besides, appropriate treatment provides rapid resolution of the associated signs and symptoms.

Conflicts Of Interest

The author declare that there are no conflicts of interest regarding the publication of this case report.

Consent To Publish

Written informed consent to publish this case report was obtained from the patient.

Authors Contributions

JM was involved in patient care, drafting of the manuscript, literature review and critical revision of the manuscript for important intellectual content and approved the final manuscript.

FUNDING

No funding was sought for this case report.

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