Journal of the Postgraduate Institute of Medicine 2023; 10(1): E203 1-5

http://doi.org/10.4038/jpgim.8379

Case Report

Two unusual presentations of vitamin B12 deficiency

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Key words: **B12 deficiency, haemolysis, leucoerythroblastosis, hyperpigmentation**

Abstract

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Received: 26 Mar 2022, accepted revised version: 02 Sep 2022, Published: 16 Jan 2023

Competing Interests: Authors have declared that no competing interests exist

Introduction

Vitamin B12, a water-soluble vitamin, is important in DNA synthesis. Inadequate intake of animal foods and pernicious anaemia (loss of intrinsic factor due to autoimmune atrophic gastritis) are known to be the most common causes of severe deficiency worldwide [1]. Although most of the patients with deficiency have only mild haematological findings, a very few present with symptomatic pancytopaenia, severe anaemia (haemoglobin <6 g/dL) leucoerythroblastic blood picture with haemolysis and organomegaly, mimicking haematological malignancy, as in patient A.

Cutaneous manifestations, including poor wound healing and hair changes, could also be presenting complaints, as in patient B. In this case series, we present two cases with uncommon clinical manifestations of vitamin B12 deficiency and a marked clinical response with B12 replacement.

Case Presentations

Patient A

A 30-year-old vegan male presented with dizziness, lethargy and exertional dyspnoea of two weeks duration and significant weight loss. He was pale and icteric with splenomegaly. Investigations (Table 1) showed severe anaemia with indirect hyperbilirubinemia. The direct agglutination test was negative excluding autoimmune haemolytic anaemia. The blood picture revealed leucoerythroblasts with mixed deficiency anaemia and hyper-segmented neutrophils. Ultrasonography confirmed splenomegaly of 11.5 cm in the absence of hepatomegaly and lymphadenopathy.

Bone marrow aspiration, performed to exclude the presence of an acute leukaemia, showed a markedly hypercellular marrow with megaloblastic and normoblastic

maturation with occasional hyper segmented forms seen in megakaryopoiesis. Although it was suggestive of vitamin B12/ folate deficiency, levels were not performed due to the limitation of resources.

Table 1: Summary of the investigations (Patient A).

Investigation	Before Treatment	Two months after treatment
White Blood Count (4.5-11 x 10^9/L)	3.7X 10^9/L	
Neutrophils% (40-60%)	66%	
Lymphocytes% (20-40%)	26%	
Haemoglobin (14-17g/dL)	4g/dL	11g/dL
Mean Corpuscular Volume (80-100fL)	95fL	88fL
Mean Cell Haemoglobin (28-34pg)	32pg	32pg
Platelets (150000-45000/mm^3)	102000/mm^3	180000/mm^3
Erythrocyte sedimentation rate (<15mm/hour)	50mm/1st hour	
C reactive protein (8-10mg/L)	5.9mg/L	
Nucleated red cells 0/100 WBC	10/100WBC	
Retic count (0.5-2.5%)	5.9%	1.3%
Retic Index (0.5-2.5%)	1.6	0.8
Total bilirubin (1.7-20 micromole/L)	40	16
Direct bilirubin (<5.1 micromole/L)	11.4	5
Indirect bilirubin (3.4-12 micromole/L)	31	11
Lactate Dehydrogenase level (140-280 U/L)	5200 U/L	820 U/L

Normal ranges are included within brackets

Patient B

A 38-year-old male, vegan for 10 years, presented with a non-healing wound in the right leg, lethargy and exertional dyspnoea of one month's duration. He was pale, icteric and had thin brown coloured hair (Figure 1 & 2).

Figure 1: Brown coloured thin hair

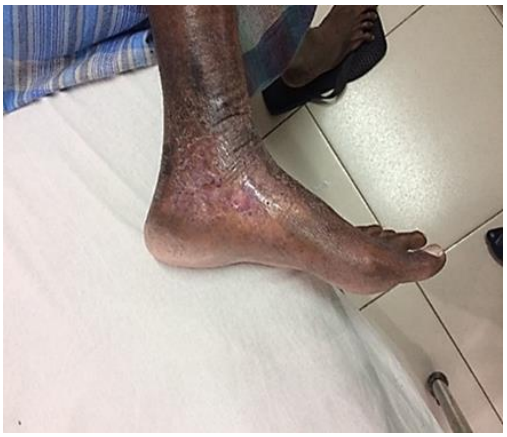

Figure 2: Non-healing ulcer of the leg

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There was a mild splenomegaly and bilateral lower limb symmetrical sensory type polyneuropathy up to the knee. The full blood count showed pancytopaenia with a macrocytic anaemia. He had an indirect hyperbilirubinemia. The serum LDH was high with a value of 630U/L, while the direct agglutination test was negative. The reticulocyte count was 4% (Table 2). Ultrasound scan of the abdomen showed a prominent splenomegaly (11.5cm). Bone marrow aspiration revealed severe megaloblastic anaemia with a markedly hypercellular marrow with megaloblastic and normoblastic maturation and occasional hyper-segmented forms.

Table 2: Summary of the investigations (Patient B)

	Before Treatment	Two months after treatment
White Blood Count (4.5-11 x 109/L)	1.78x10^9/L	
Neutrophils% (40-60%)	30%	
Lymphocytes% (20-40%)	66%	
Monocytes%	2%	
Haemoglobin(14-17g/dL)	6g/dl	12g/dl
Mean Corpuscular Volume(80-100fl)	105fl	90fl
Mean Cell Haemoglobin (28-34pg)	33pg	31pg
Platelets (150000-45000/mm^3)	97000/mm^3	160000/mm^3
Erythrocyte Sedimentation Rate(<15mm/hour)	4mm/1st hr	
C Reactive Protein(	4mg/L	
Retic count (0.5-2.5%)	4%	1.2%
Retic index (0.5-2.5%)	1.6	0.9
Total bilirubin (1.7-20 micromole/L)	60	17
Direct bilirubin (<5.1 micromole/L)	20	4
Indirect Bilirubin (3.4-12 micromole/L)	40 micromol/L	13 micromol/L
Lactate Dehydrogenase Level (140-280 U/L)	640U/L	280 U/L

Normal ranges are included within brackets.

Both patients were initially transfused with packed red cells to control the symptoms. They were commenced on replacement therapy (vitamin B12 intramuscularly, 1000 micrograms every other day for 6 doses with folic acid 5mg daily) for which there was marked clinical and haematological response in 2 months.

Discussion

Vitamin B12 (cyanocobalamin) is required as an essential cofactor for biochemical pathways involved in DNA/RNA synthesis and fatty acid metabolism [1] for regeneration of tetrahydrofolate and conversion of homocysteine to methionine [1]. Humans rely on dietary intake if B12, mainly ~~on~~ via animal-based foods, as they cannot synthesize vitamin B12 [1]. A typical, non-vegetarian diet contains adequate vitamin B12 but a vegan or strict

vegetarian diet typically does not contain sufficient amounts of vitamin B12, as plant foods lack adequate supply.

Rapidly proliferating haematopoietic precursor cells are highly sensitive to vitamin B12 deficiency, resulting in megaloblastic changes and ineffective erythropoiesis, thrombocytopenia and leucopoenia as in our first patient [2]. Most of vitamin B12 deficient patients have only mild haematological findings. However, in approximately 10% of patients, symptomatic pancytopaenia, severe anaemia and haemolytic anaemia have been reported. [2,3]

Our first patient had an uncommon presentation of vitamin B12 deficiency with pancytopenia and a leucoerythroblastic blood picture. There was evidence of haemolysis with elevated LDH and splenomegaly, bilirubinaemia and reticulocytosis. Intramedullary destruction of red blood cells in the setting of vitamin B12 deficiency is a well-recognized, but poorly understood, phenomenon [2,3] which is a cause for this ongoing haemolysis. Additionally, elevated homocysteine levels have been described as a possible aetiology for both intravascular and intramedullary haemolysis [4,5]. Homocysteine increases the risk of haemolysis in vitamin B12, and folate deficiency as demonstrated in-vitro [2,3,4]

Abnormal and fragile red cell precursors in megaloblastic anaemia break down leading to intramedullary haemolysis. This results in leucoerythroblastosis and a raised LDH [3,6]. So leucoerythroblastosis and haemolysis are proven, but uncommon, manifestations of vitamin B12 deficiency. However, haematological malignancies need to be excluded as in our patients. Splenomegaly and/or hepatomegaly have been reported in cases with severe B12 deficiency, although rare. Hyperplasia of the reticuloendothelial system (removal of defective erythrocytes), sequestration of macrocytes in the spleen and a prothrombotic state in the portal veins are speculated causes of splenomegaly [3,7]. Skin hyperpigmentation, vitiligo, hair changes (discoloured brittle hair with premature whitening) and recurrent angular stomatitis have been reported [8]. Hyperpigmentation, which may herald vitamin B12 deficiency, is generalized with accentuation in the flexures, palms and soles and is attributed to increased melanin synthesis [4,8,9]. Reduced type glutathione normally inhibits the rate limiting enzyme of melanin synthesis, tyrosinase. Due to cobalamin deficiency, the glutathione level is reduced causing impairment of the normal inhibition of melanin synthesis causing hyperpigmentation [9].

Poor wound healing in vitamin B12 deficiency is also a very uncommon presentation. Elevated homocysteine levels can lead to endothelial dysfunction [8,9]. The endothelium-derived signalling molecule nitric oxide, which regulates vascular function, causes microvascular failure [8]. Hair follicle bulbs contain rapidly dividing cells which are greatly affected in B12 deficiency causing hair loss and discoloration.

Conclusion

In this case series we have described two unusual presentations of vitamin B12 deficiency, one with pancytopenia and a leucoerythroblastic blood picture mimicking

acute leukemia and another with poor wound healing with discolored hair. We should be aware of these possible presentations, secondary to vitamin B12 deficiency, as appropriate treatment provides rapid resolution of the signs and symptoms.

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