Section: General Medicine

Original Research Article

BEYOND ANEMIA: MULTISYSTEM MANIFESTATIONS OF SEVERE VITAMIN B12 DEFICIENCY IN A YOUNG MALE

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ABSTRACT

A 19-year-old male presented with progressive generalized weakness and jaundice for two weeks. He was found to have pancytopenia, macrocytic anemia, indirect hyperbilirubinemia, and markedly low serum vitamin B12 levels. Dermatologic examination revealed hyperpigmented knuckles, a classical but often overlooked sign of severe B12 deficiency. Following parenteral vitamin B12 therapy, the patient exhibited rapid hematologic improvement, including a reticulocyte response and normalization of bilirubin levels. This case highlights the importance of early recognition of multisystem manifestations of vitamin B12 deficiency to avoid misdiagnosis and unnecessary invasive testing.

Keywords: Vitamin B12 Deficiency; Pancytopenia; Macrocytic Anemia; Hyperbilirubinemia; Knuckle Hyperpigmentation; Methylcobalamin.

INTRODUCTION

Vitamin B12 deficiency is a common yet frequently underdiagnosed condition that can produce a wide spectrum of systemic manifestations. Beyond megaloblastic anemia, severe deficiency may mimic hemolytic anemia, infiltrative marrow disease, or systemic inflammatory disorders. Dermatologic features such as hyperpigmented knuckles, though underrecognized, provide important diagnostic clues. Early management is critical, as timely parenteral replacement can reverse most hematological and systemic abnormalities.[1-5]

CASE PRESENTATION

A 19-year-old male presented with generalized fatigue and yellowish discoloration of the eyes and skin for two weeks. He denied fever, abdominal pain, dark urine, high-risk behavior, or chronic illnesses. No medication history was reported.

Clinical Examination

- Pallor ++
- Icterus ++
- Pulse 120/min, BP 110/58 mmHg, RR 24/min, afebrile
- Mild hepatosplenomegaly
- Cardiovascular, respiratory, and neurological examinations: Normal

Investigations

Comparison Table: Admission vs. Discharge Investigations

Parameter	On Admission	At Discharge
Hemoglobin (g/dL)	5.80	7.20
TLC (/cumm)	3050	4980
Neutrophils (%)	62%	44%
Lymphocytes (%)	34%	49%
PCV (%)	17.5	21.7
MCV (fL)	130.40	117.70
Platelet Count (/mm³)	60,000	1,26,000
ESR (mm/hr)	120	—
Total Bilirubin (mg/dL)	4.93	1.80
Direct Bilirubin (mg/dL)	0.65	0.34
Indirect Bilirubin (mg/dL)	4.28	1.46
SGOT (U/L)	127	27
SGPT (U/L)	65	30
Alkaline Phosphatase (U/L)	41	44
Vitamin B12 (pg/mL)	159	950
Ferritin (ng/mL)	349	123
Reticulocyte Count (%)	0.8%	6% (after therapy)
LDH (U/L)	4356	—
Coombs Test	Negative	—
Viral Markers	HIV, HBsAg, HCV – Non-reactive ,	HAV IgM, HIV, HBsAg, HCV – Non-reactive

Peripheral Smear

RBCs: Macrocytes, dimorphic picture, few nucleated RBCs.

WBCs: Leukopenia, relative lymphocytosis (48%), activated lymphocytes, no blasts.

Platelets: Reduced (~38,000/µL).

Impression: Macrocytic (Dimorphic) anemia with leukopenia and thrombocytopenia.

Imaging

- Ultrasound abdomen: Mild splenomegaly (12.5 cm), normal liver echotexture.

Dermatologic Finding

- Hyperpigmentation of knuckles—a known but underreported manifestation of chronic B12 deficiency.

Differential Diagnosis

- Hemolytic anemia (excluded: low reticulocyte count, negative Coombs test)
- Leukemia or marrow infiltration (less likely due to classic B12 pattern)
- Aplastic anemia
- Chronic liver disease (LFT pattern inconsistent)
- Folate deficiency (not supported by clinical picture)

Treatment

- Intravenous methylcobalamin 1000 mcg daily × 7 days
- Oral folic acid 5 mg daily
- One unit packed red blood cell transfusion

Outcome and Follow-Up

By day 7, the patient reported symptomatic improvement. Reticulocyte count increased to 6%, indicating marrow recovery. Hemoglobin improved to 7.2 g/dL, bilirubin declined significantly, and LDH decreased. The patient was discharged on: - Methylcobalamin 1000 mcg weekly × 6 weeks, then monthly × 6 months

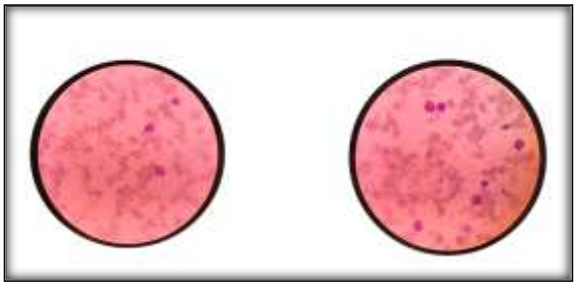
- Folic acid 5 mg daily × 1 month

He remains under follow-up with continued hematologic improvement.

RESULTS

Vitamin B12 deficiency is a complex hematologic and metabolic disorder with significant multisystem involvement. Its pathophysiology is rooted in impaired DNA synthesis, primarily due to the disruption of methylation reactions and the folate cycle. Methylcobalamin and adenosylcobalamin, the two active forms of vitamin B12, are essential cofactors for methionine synthase and methylmalonyl-CoA mutase. Their deficiency leads to the accumulation of methylmalonic acid (MMA) and homocysteine, which contribute to oxidative stress, myelin damage, and ineffective erythropoiesis.

Photograph of patient showing hyperpigmented knuckles



Peripheral smear showing macrocytic dimorphic anemia with nucleated RBCs.

Hematologic Pathophysiology

Ineffective erythropoiesis results from nuclear-cytoplasmic asynchrony in erythroid precursors, producing large, fragile, immature red cells that undergo apoptosis within the bone marrow. This accounts for the markedly elevated LDH (4356 U/L) and indirect hyperbilirubinemia, both of which are classic biochemical signatures of intramedullary hemolysis. The low reticulocyte count (0.8%) further supports this mechanism, differentiating it from peripheral hemolytic anemias where reticulocyte production is elevated.

The presence of leukopenia and thrombocytopenia, as in this case, reflects pan-lineage marrow failure and occasionally leads to misdiagnosis as aplastic anemia or acute leukemia. However, the absence of blasts, normal iron studies, and characteristic macrocytosis help distinguish B12 deficiency from these conditions.

Dermatologic and Mucocutaneous Involvement

Cutaneous hyperpigmentation—particularly knuckle pigmentation—is an underreported yet significant manifestation. The mechanism is hypothesized to involve defective DNA synthesis affecting melanin distribution and melanocyte regulation. Some studies suggest elevated ACTH-like activity in B12 deficiency may enhance pigmentation. Recognition of these subtle signs can facilitate early diagnosis without invasive procedures.

Neurological Considerations

Although this patient lacked neurological deficits, neuropsychiatric manifestations can range from peripheral neuropathy, ataxia, and loss of vibration sense to mood disturbances and cognitive dysfunction. Elevated homocysteine and methylmalonic acid contribute to neurotoxicity. The absence of neurological involvement in severe hematologic deficiency highlights the diverse spectrum of B12 presentation.

Gastrointestinal and Hepatic Manifestations

Indirect hyperbilirubinemia (4.28 mg/dL) and mildly elevated transaminases result from heightened erythroid turnover and hemolysis rather than intrinsic liver disease. The improvement in bilirubin levels after therapy (1.80 mg/dL on discharge) correlates with reduced ineffective erythropoiesis.

Differentiation From Other Causes of Pancytopenia: Given its presentation, this condition can be mistaken for: - Myelodysplastic syndrome (MDS) - Aplastic anemia - Acute leukemia - Hemolytic anemias - Infiltrative marrow disorders (lymphoma, tuberculosis)

Bone marrow biopsy is often avoided if classical biochemical and hematologic features of B12 deficiency are present, as seen in this case. Literature emphasizes that unnecessary biopsies often occur when simple laboratory markers like MCV, LDH, and bilirubin trends are not fully appreciated.

Therapeutic Response and Recovery Pattern

The hallmark of successful treatment is the reticulocyte crisis, typically occurring 4–7 days after parenteral therapy. The rise from 0.8% to 6% in this patient marks an appropriate marrow response. Hemoglobin improvement is slower and depends on iron availability, coexisting folate levels, and splenic function.

MCV reduction from 130.4 fL to 117.7 fL within days is another indicator of recovery, though normalization may take weeks.

Clinical Significance

This case reinforces the importance of screening for B12 deficiency in: - Young individuals with pancytopenia

- Patients with unexplained hyperbilirubinemia
- Macrocytosis with low reticulocyte count
- Dermatologic clues such as knuckle pigmentation

Early identification avoids misdiagnosis, prevents invasive procedures, and ensures rapid recovery with simple, inexpensive treatment.

Learning Points

Vitamin B12 deficiency continues to be a major reversible cause of hematologic failure globally. According to Stabler et al. (NEJM), up to 15% of cases of pancytopenia in young adults may be attributed to unrecognized cobalamin deficiency. Numerous studies, including O'Leary & Samman, have emphasized the multisystem involvement of severe deficiency, with dermatologic manifestations such as hyperpigmented knuckles gaining prominence in recent years. Case series from India report that B12-related pancytopenia often mimics leukemia or aplastic anemia due to high LDH levels (>3000 U/L), marked macrocytosis, and splenomegaly. Rapid response to parenteral B12 remains one of the strongest diagnostic indicators.

CONCLUSION

Severe vitamin B12 deficiency can mimic serious hematologic disorders but remains fully reversible with timely diagnosis and treatment. Recognizing its multisystem manifestations, including cutaneous signs, is crucial for early intervention and avoidance of unnecessary invasive investigations.

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