Internal MedicineToday
Gonabad University of Medical Sciences
June 2023. Vol 29. Issue 3

Case Report

Severe Vitamin B12 Deficiency Resulting in Severe Pancytopenia: A Case Report

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Citation Bakhtiari A, Tavakolizadeh M. [Severe Vitamin B12 Deficiency Resulting in Severe Pancytopenia: A Case Report]. Internal Medicine Today. 2023; 29(3): 156-162.

:https://doi.org/10.32592/imtj.2023.29.3.156

Received: 30 Sep 2024
Accepted: 01 Mar 2025
Available Online: 28 Mar 2025

Key words:
B12 deficiency,
Case report,
Pancytopenia,
Severe

ABSTRACT

Aims This case report aims to highlight a rare presentation of severe vitamin B12 deficiency resulting in severe pancytopenia in an elderly male patient, occurring in only 5% of patients with known B12 deficiency. Additionally, it discusses the hematological changes associated with B12 deficiency and how they can sometimes mimic hematological malignancies.

Case Patient The patient was an 86-year-old man from a rural area with a history of generalized weakness and jaundice. He had no significant past medical history besides prior pneumonia and cataract surgery. He presented with symptoms of anorexia, dizziness, and nausea but no fever. He was not a smoker, drinker, or drug user. The patient was living with his children and seemed to be economically disadvantaged.

Findings Initial examination revealed icteric sclera, pale conjunctiva, and 1+ edema in both lower limbs. Initial lab tests indicated increasing MCV, and peripheral blood smear showed hypersegmented neutrophils, macroovalocytes, anisocytosis, as well as possible RBC agglutination and schistocytes. The patient was diagnosed with megaloblastic anemia and started on high-dose vitamin B12 and folate. The patient's condition deteriorated, with a drop in platelet and WBC counts and the presence of schistocytes, leading to a bone marrow biopsy, which suggested MDS or AML-M6; however, further tests indicated a nutritional deficiency. The patient improved significantly with high-dose B12 and folate treatment, and blood counts normalized.

Conclusion The present case demonstrates that severe vitamin B12 deficiency can manifest as severe pancytopenia and that it can be mistaken for acute leukemia or other hematological malignancies.

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طب داخلی روز
فصلنامه دانشگاه علوم پزشکی و خدمات درمانی گناباد

مقاله موردی

پانسیتوپنی شدید به دنبال کمبود شدید ویتامین B12: گزارش موردی

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تاریخ دریافت: ۱۴۰۳/۰۷/۰۹
تاریخ پذیرش: ۱۴۰۳/۱۲/۱۱
تاریخ انتشار ۱۴۰۴/۰۱/۰۸

چکیده

هدف این گزارش موردی با هدف برجسته کردن تظاهرات نادر کمبود شدید ویتامین B12 که منجر به پان سیتوپنی شدید در یک بیمار مرد مسن می‌شود، می باشد. که تنها در ۵٪ از بیماران مبتلا به کمبود شناخته شده B12 رخ می دهد. علاوه بر این، تغییرات هماتولوژیک مرتبط با کمبود B12 و اینکه چگونه آنها گاهی اوقات می توانند بدخیمی های خونی را تقلید کنند، بحث می کند.

مشخصات بیمار: بیمار مردی ۸۶ ساله روستایی و دارای سابقه ضعف عمومی و زردی بود. او به غیر از پنومونی و جراحی آب مروارید قبلی، سابقه پزشکی قابل توجهی در گذشته نداشت. او با علائم بی اشتهایی، سرگیجه و حالت تهوع مراجعه کرد، اما تب نداشت. او سیگاری، الکل یا مصرف کننده مواد مخدر نبود. بیمار با فرزندان خود زندگی می کرد و به نظر می رسید از نظر اقتصادی ضعیف باشد.

یافته‌ها: در معاینه اولیه، صلبیه ایکتریک، ملتحمه رنگ پریده و ادم +1 در هر دو اندام تحتانی مشاهده شد. آزمایش‌های آزمایشگاهی اولیه نشان‌دهنده افزایش MCV بود و اسمیر خون محیطی نوتروفیل‌های بیش‌سگمانته، ماکرواوالوسیت‌ها، آنیزوسیتوز و آگلوتیناسیون RBCو شیستوسیت‌های احتمالی را نشان داد. بیمار مبتلا به کم خونی مگالوبلاستیک تشخیص داده شد و با دوز بالای ویتامین B12 و فولات مورد درمان قرار گرفت. وضعیت بیمار بدتر شد، با کاهش تعداد پلاکت ها وWBC ، و وجود شیستوسیت ها، که منجر به بیوپسی مغز استخوان شد. بیوپسی مغز استخوان MDS یا AML-M6 را پیشنهاد کرد، اما آزمایشات بیشتر کمبود تغذیه را نشان داد. بیمار با دوز بالای B12 و درمان فولات به طور قابل توجهی بهبود یافت و شمارش خون عادی شد.

نتیجه‌گیری: این مورد نشان می‌دهد که کمبود شدید ویتامین B12 می‌تواند به صورت پان سیتوپنی شدید ظاهر شود و می‌تواند با لوسمی حاد یا سایر بدخیمی‌های هماتولوژیک اشتباه گرفته شود.

کلیدواژه‌ها:
کمبود ویتامینB12
پانسیتوپنی
شدید
گزارش مورد

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Introduction

Pancytopenia is defined as a decrease in all three blood cell lines and could manifest with symptoms resulting from anemia, leukopenia or thrombocytopenia; patients may be asymptomatic [1]. The causes of this condition are numerous and varied [2]. The incidence of various disorders causing pancytopenia varies due to geographical distribution and genetic disturbances. The management and prognosis of pancytopenia depend on the underlying pathology [3]. The first step in the management of pancytopenia involves identifying the underlying cause and providing supportive care until the pancytopenia is resolved. A complete history and physical examination usually help in narrowing down the cause, which could then lead to further specific diagnostic studies [1]. Among the various causes, Folate and vitamin B12 deficiencies can cause megaloblastic anemia. Though anemia and thrombocytopenia are common features, they could present with pancytopenia as well [4]. Hematologic consequences include macrocytosis, hypersegmented neutrophils, leukopenia, thrombocytopenia, and pancytopenia (in rare conditions); this is seen in only 5% of patients with a known B12 deficiency [5]. Low vitamin B12 serum levels are common, especially in older people. Vitamin B12 is obtained through animal products consumed in the diet. Vitamin B12 deficiency is usually a response to insufficient intake or gastrointestinal disorders. Due to the low requirements in humans (2.4 mg/day), clinical or subclinical deficits may be delayed.

This case report aimed to highlight a rare presentation of severe vitamin B12 deficiency resulting in severe pancytopenia in an elderly male patient, which occurs in only 5% of patients with known B12 deficiency. It also emphasizes the importance of considering vitamin B12 deficiency in the differential diagnosis of pancytopenia, especially in older adults, and the need for prompt treatment. Additionally, it discusses the hematological changes associated with B12 deficiency and how they can sometimes mimic hematological malignancies.

Case Report

The patient was an 86-year-old man living in Gisour village of Gonabad City in Iran. He went to Bohlool Hospital's emergency room in July of this year with symptoms of generalized weakness and jaundice. Before this, the patient could perform personal tasks and live with his children. He appeared to be economically weak. According to the patient's son, jaundice developed during the last week, but the weakness had been progressive for the last few months. He had no history of similar symptoms before. He experienced anorexia but did not mention any other simultaneous digestive, respiratory, or urinary symptoms. He did not have a fever, and there were no changes in his urine or stool color. He had not traveled recently, and the family had no similar symptoms. His drug history was negative, and he had no previous chronic diseases. He had been hospitalized twice in previous years due to pneumonia and for cataract surgery. He did not use cigarettes, alcohol, or opium.

During the examination, he was alert and oriented to time and place. The sclera was icteric, and the conjunctiva was pale. The force of all four limbs was normal. He mentioned dizziness and nausea after standing up, and there seemed to be an imbalance. Lung and heart auscultation were normal. The abdomen was soft and without tenderness and guarding. He did not have organomegaly. There was no lymphadenopathy in the neck, axilla, or groin. There was 1+ edema in both lower limbs without any difference in size. In addition, there were no skin lesions.

During the initial visit to the emergency room, the following items were recorded.

BP=100/60 (TILT=Negative), PR=88, T=36.5, SPO_2=96 (without O_2 therapy)

According to the patient's history and examination, initial tests were requested in the emergency room and the documents of previous admissions were checked in the hospital information system (HIS). The noteworthy point in the previous documents was that the MCV was increasing in the tests [Table 1].

According to the results of the initial tests, a peripheral blood smear (PBS) was drawn in the emergency room and reviewed by a hematologist. The findings included hypersegmented neutrophils, macroovalocytes, anisocytosis, and a probability of RBC agglutination, with schistocytes reported at 4-5% [Figure 1].

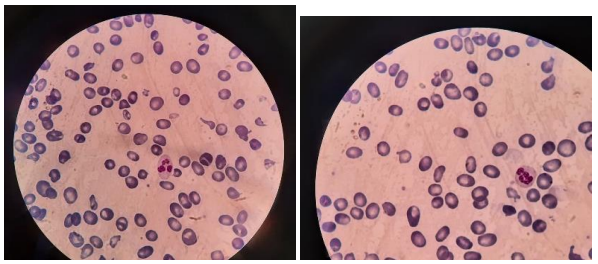
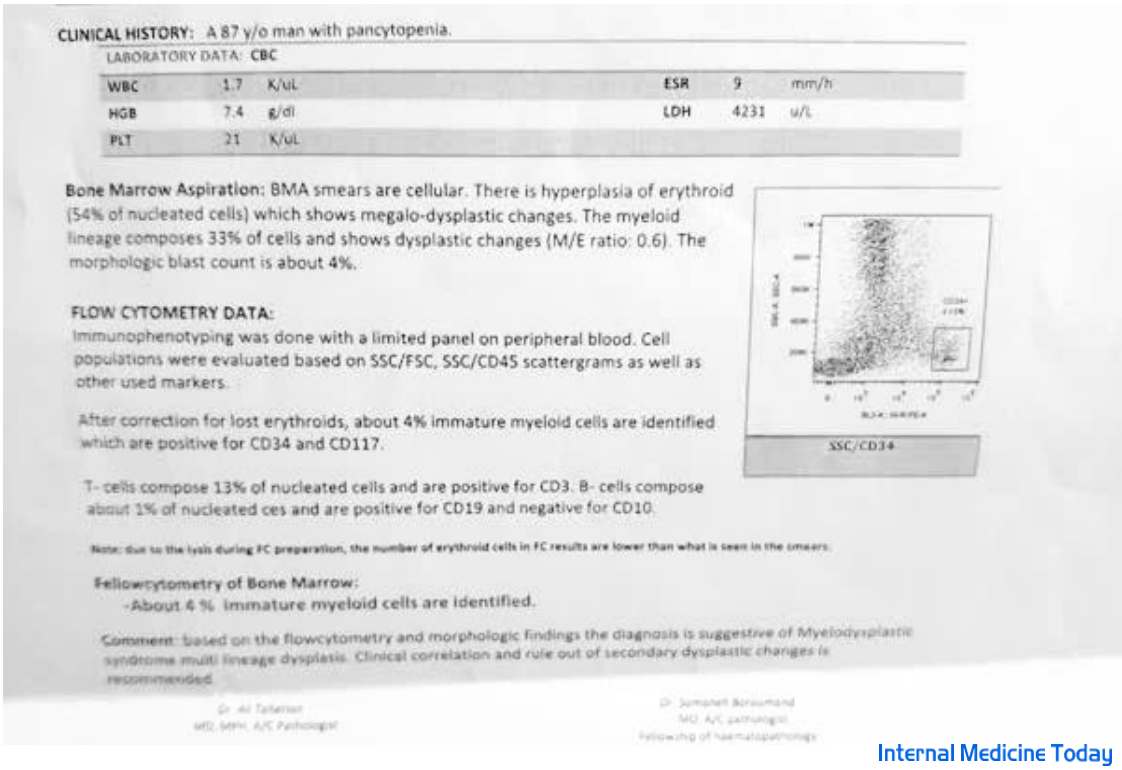


Figure 1. Peripheral blood smear (PBS)

According to the PBS, megaloblastic anemia was raised as the primary diagnosis, and a request for vitamin B12 and folate serum levels was sent. Treatment was initiated with a high dose of vitamin B12 (1000 micrograms daily) and folate (5 mg daily). Additional requested tests were sent to rule out other differential diagnoses.

Considering the changes in the patient's tests in the hospital, drop of platelets to 14000 and WBC to less than 1000, as well as the presence of this amount of schistocytes in the peripheral blood smear, which the usual course of megaloblastic anemia could not justify, the patient underwent BMA/B on the fifth day of hospitalization to rule out other concurrent diagnoses and biopsy was seen and a hypercellular bone marrow was reported, suggesting the possibility of MDS or AML-M6. Flow cytometry and cytogenetics were sent, and the answer was followed up. The requested CD markers were negative and 4% dysplasia was reported, and the diagnosis of MDS-MLD was raised; the pathologist recommended to rule out nutritional deficiencies as a differential diagnosis [Figure 2].


CLINICAL HISTORY: A 87 y/o man with pancytopenia.

LABORATORY DATA: CBC

WBC	1.7	K/uL	ESR	9	mm/h
HGB	7.4	g/dl	LDH	4231	u/L
PLT	21	K/uL			

Bone Marrow Aspiration: BMA smears are cellular. There is hyperplasia of erythroid (54% of nucleated cells) which shows megalo-dysplastic changes. The myeloid lineage composes 33% of cells and shows dysplastic changes (M/E ratio: 0.6). The morphologic blast count is about 4%.

FLOW CYTOMETRY DATA:

Immunophenotyping was done with a limited panel on peripheral blood. Cell populations were evaluated based on SSC/FSC, SSC/CD45 scattergrams as well as other used markers.

After correction for lost erythroids, about 4% immature myeloid cells are identified which are positive for CD34 and CD117.

SSC/CD34

T- cells compose 13% of nucleated cells and are positive for CD3. B- cells compose about 1% of nucleated ces and are positive for CD19 and negative for CD10.

Note: due to the lysis during FC preparation, the number of erythroid cells in FC results are lower than what is seen in the smears.

Fellowcytometry of Bone Marrow:

-About 4 % immature myeloid cells are identified.

Comment: based on the flowcytometry and morphologic findings the diagnosis is suggestive of Myelodysplastic syndrome multi lineage dysplasia. Clinical correlation and rule out of secondary dysplastic changes is recommended.

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Figure 2. Bone marrow aspiration and flow cytometry data.

According to the patient's bedside manner and the improvement of the tests in the following days (the seventh day from the start of treatment with high dose B12 and folate), the patient was discharged, and the patient's CBC was followed up one week and one month after discharge with the continuation of vitamin B12 and folate treatment, and it was normal.

Table 1. Laboratory findings during hospitalization and follow-up after discharge

	Admission	2 Days Later	4 Days Later	1 Week Later	2 Weeks Later	Normal
WBC	1500	1200	1000	2100	4300	4000-11000
RBC	1.15	2.08	1.92	2.38	2.9	Male: 4.5-6 Female:4-5.1
Hb	4.7	7.1	6.5	7.3	9.8	Male:14-17.5
HCT	14.6	22.3	20.3	24.8	30.4	Male: 40-50
MCV	127.0	107	105.7	104	103.6	80-96
MCH	40.9	34	33.9	31	33.5	27-33
MCHC	32.2	32	32.0	29	32.3	32-36
Neutrophils	45.8	50.4	41.8	46	60	
Lymphocyts	44.1	39.3	45.2	42	34	
Mix	10.1	10.3	13	12	6	
Platelet	21,000	19,000	14,000	62,000	175,000	150,000-450,000
RDW	24.2	26.7	25.7	22	22.7	
Lymphocyts	700	500	500	880	1460	
BUN	28	23	21	20		Male < 120 Year(s): 8-24
Creatinine	0.83	0.91	0.97	0.93		2 - 120 Year (s) 0.7-1.4

Na.	137.6	139	137	141		135-145
K	4	4.6	4.1	4.19		3.5-5
Bilirubin Total	2.3	1.9	1.74	1		
Bilirubin Direct	0.83	0.54	0.53	0.34		0.1-0.3
AST	63				26	<37
ALT	53				30	<41
ALP	115				116	Male: 90-360
LDH1	8086	2540	2320	1700	1400	
ESR	63				9	0-20
CRP	3					Negative<6
Ferritin	48					
Iron	145					
TIBC	305					
Folic acid	8.6					
VIT B12	56					
Indirect Combs		Negative				
Reticulocytes		0.5				
Direct Combs		Negative				
HCV Ab		Negative				
HIV Ab		Negative				
HBS Ag		Negative				
ANA		Negative				
COLD Agglutinin Titre			Negative			

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Discussion

Vitamin B12 (cobalamin CBL) is a water-soluble vitamin required to form hematopoietic cells (red blood cells, white blood cells, and platelets). It is involved in the process of synthesizing DNA and myelin sheath [6]. This vitamin is found in animal products, including fish, meat, poultry, eggs, and dairy. The most common causes of vitamin B12 deficiency include difficulty absorbing vitamin B12 from food, lack of intrinsic factors due to pernicious anemia, prior gastrointestinal surgery, prolonged use of certain medications, such as metformin and proton pump inhibitors, and dietary deficiency [7].

Malnutrition, often called insufficient nutrition, is a common condition with advancing age. Malnutrition is associated with unfavorable outcomes in older subjects [8]. The prevalence of anemia is also high in older people [6]. In addition, anemia in older individuals can be secondary to potentially inappropriate prescribing [9], low protein intake and albumin levels [10], and selective nutritional deficiency [11].

B12 deficiency is common among individuals over 60 due to the increased prevalence of pernicious anemia, atrophic gastritis, infection with Helicobacter pylori, and malnutrition [7]. Adverse outcomes of B12 deficiency can manifest as hematologic or neurologic consequences. A hallmark sign of B12 deficiency is megaloblastic anemia, classically found with oval macrocytes, usually with considerable anisocytosis and poikilocytosis, which are the main features. Some of the neutrophils are hypersegmented (more than five nuclear lobes). There may be leukopenia due to a reduction in granulocytes and lymphocytes, but this is usually >1.5 × 109/L; the platelet count may be moderately reduced, rarely to <40 × 109/L. The severity of all these changes parallels the degree of anemia [12 –17], a combination of these, or (rarely) pancytopenia and hemolysis. In the present case, along with schistocytes in the peripheral blood smear -MAHA-, there was a significantly high LDH serum level, with platelets decreasing to 14,000 and leukocytes decreasing to 1,000. Only two-thirds of B12 deficient patients may manifest hematological abnormalities [18]. Indeed, pancytopenia, in which all blood cell lines are decreased, is seen in only 5% of patients with a known B12 deficiency [18]. Hemolysis and increased levels of lactate dehydrogenase (LDH) and bilirubin in B12 deficiency most often occur within the bone marrow, often referred to as intramedullary hemolysis or ineffective erythropoiesis [6,18]. Extra medullary hemolysis has also been rarely reported secondary to a variety of factors, most often via antibody-mediated destruction, high levels of homocysteine leading to endothelial dysfunction and lysis, or due to mechanical destruction of poorly formed red blood cells as they traverse small capillaries beds [20]. These processes explain the elevation of LDH and bilirubin in patients with megaloblastic anemia, as they reflect the underlying hemolytic activity and ineffective erythropoiesis associated with the disease [21 ,22] . In megaloblastic anemia, the reticulocyte count can be variable. Typically, when the body experiences hemolysis or significant loss of red blood cells, it compensates by increasing reticulocyte production from the bone marrow. Ineffective erythropoiesis and reticulocyte crisis after treatment are other causes of increased reticulocyte in megaloblastic anemia [22,23].

In summary, increased LDH and bilirubin levels in megaloblastic anemia arise from hemolysis associated with ineffective erythropoiesis due to vitamin B12

deficiencies. The reticulocyte count serves as an indicator of bone marrow response but may not always reflect effective erythropoiesis due to the nature of megaloblasts produced during this condition.

The initial presentation with pancytopenia, splenomegaly, and leukoerythroblastosis was considerably concerning for an underlying malignancy. Severe megaloblastic anemia may be mistaken for acute leukemia [20]. In this patient, due to the progressive course of pancytopenia, despite the initiation of proper treatment with the possibility of leukemia, the patient underwent a bone marrow biopsy.

Neurological changes associated with B12 deficiency include sensory deficits, paresthesia, weakness, ataxia, and gait disturbance, while severe cases can cause spasticity and paraplegia [7].

Deficiency is based on the concordance of anamnestic, clinical, and cytological elements and the assay of associated biomarkers. The serum dosage of vitamins B12 and B9 should be included in the initial etiological assessment of pancytopenia due to non-specific clinical signs. Cobalamin and folate deficiency manifestations are relatively similar, reflecting their intricate co-enzymatic functions. In industrialized countries, provided the diet is balanced and in the absence of underlying disease, vitamin requirements are generally met, making nutritional deficiencies rare. Due to potential complications, the importance of early diagnosis and prompt vitamin supplementation must be emphasized [24].

Due to the significant complications and severe morbidity caused by the late treatment of the deficiency of these vitamins, it is necessary to start the treatment quickly and with a sufficient dose.

Conclusion

Oval macrocytes, usually with considerable anisocytosis and poikilocytosis, are the main features. Some of the neutrophils are hypersegmented (more than five nuclear lobes). There may be leukopenia due to a reduction in granulocytes and lymphocytes; however, this is usually >1.5 × 109/L; the platelet count may be moderately reduced, rarely to <40 × 109/L. The severity of all these changes parallels the degree of anemia.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Gonabad University of Medical Sciences, Iran (Code: IR.GMU.REC.1403.048).

Funding

The authors declare that they have no conflicts of interest to disclose.

Authors' contributions

Contributed to the design of the manuscript: AB; carried out the search based on the keywords: MT and AB; Contributed to the drafting of the manuscript and case report: MT and AB. All authors approved the last version of the manuscript.

Conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors extend their gratitude to the Clinical Research Development Unit of Bohlool Hospital at Gonabad University of Medical Sciences (Iran) for their invaluable support in the preparation of the present work.

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