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A Rare Case of Unexpected High Plasma Vitamin B12 levels: A Case Report

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Abstract

High blood levels of vitamin B12 are often attributed to over-supplementation; however, elevated B12 levels can occur without supplementation, raising concerns about underlying serious conditions. This case report presents a 30-year-old female referred due to high serum cobalamin levels initially discovered during an evaluation for joint pain. Despite no vitamin B12 supplementation, her B12 levels rose from 2000 pg/mL to 7000 pg/mL over three months. Comprehensive testing, including liver and renal function tests, CBC, LDH, peripheral smear, thyroid function tests, homocysteine, methylmalonic acid levels, and imaging studies, revealed no abnormalities.

Active holotranscobalamin was elevated, but there were no signs of malignancy or other serious conditions. The patient remained clinically stable throughout a six-month follow-up. This case highlights the importance of a structured approach in evaluating elevated serum cobalamin levels and considering macro-vitamin B12 in the differential diagnosis. Further research is needed to understand the clinical significance of macro-vitamin B12 and its impact on B12 level interpretation.

Keywords: Macro-vitamin B12, Transcobalamins, Elevated serum cobalamin.

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1. Introduction

High blood levels of vitamin B12 are frequently attributed to over-supplementation with vitamin B12 or multivitamins. However, elevated B12 levels can also occur without any supplementation. The main causes of high serum cobalamin often involve serious conditions, where early diagnosis is crucial for a better prognosis. These conditions typically include solid tumors, hematologic malignancies, and diseases of the liver and kidneys. The importance of vitamin B12 testing as an early diagnostic tool for these diseases is significant.

A structured approach is necessary to identify when to investigate high serum cobalamin levels and to determine the appropriate clinical strategy upon finding elevated levels. While low serum cobalamin levels do not always indicate a deficiency, an unusually high level serves as a warning that necessitates ruling out several serious underlying conditions. High serum cobalamin is a common yet often overlooked abnormality, which can signal functional and qualitative vitamin B12 deficiencies.

Checking methylmalonic acid and homocysteine levels is essential to confirm genuinely high vitamin B12 levels and to further investigate the underlying causes. Most cases of hypercobalaminemia are related to quantitative abnormalities in transcobalamins. The primary conditions to consider when encountering high serum cobalamin levels include solid tumors, myeloproliferative disorders, liver metastases, liver diseases, and kidney failure.

2. Main Results

A 30-year-old female, a housewife married with two children aged 4 and 2 years, was referred by an orthopedic doctor due to elevated vitamin B12 levels. She initially presented with a history of multiple joint pain and body aches of two weeks' duration, particularly in the small joints of both hands, without morning stiffness. She denied any fever, rash, mouth ulcers, diarrhea, or weight loss. She reported no recent travel. Her medical history included iron deficiency anemia and vitamin D deficiency during both pregnancies, for which she received iron supplements and vitamin D. There was no family history of rheumatic disorders.

On physical examination, her vital signs were stable. Oral examination revealed no ulcers, and her tongue had normal papillae. The thyroid was not palpable, and there were no palpable lymph nodes in the neck, axilla, or inguinal areas. Her chest was clear on auscultation, cardiovascular examination revealed normal heart sounds, her abdomen was soft and non-tender with no visceromegaly, and gut sounds were audible. Her central nervous system examination was intact, and the locomotor examination showed no signs of arthritis.

Review of her medical records indicated a vitamin B12 level of 2000 pg/mL three months prior, at which time she was referred to a hematologist. Comprehensive testing including CBC, liver function tests, renal function tests, iron studies, LDH, reticulocyte counts, peripheral smear, chest X-ray, and abdominal ultrasound were all normal.

On her current visit, her vitamin B12 level had risen to 7000 pg/mL. She confirmed she was not taking any vitamin B12 supplements, only iron and vitamin D. Repeat testing included CBC, CRP, ESR, LDH, peripheral smear, reticulocyte counts, liver and renal function tests, thyroid function tests, calcium, magnesium, bone tests, chest X-ray, and abdominal ultrasound, all of which were normal. Active holotranscobalamin was elevated at 256 pmol/L, and homocysteine and methylmalonic acid levels were 109 μmol/L.

She was referred to an oncologist for further evaluation to rule out any hematological malignancy or occult tumor. A thorough workup including bone marrow examination, flow cytometry, and CT scans of the neck, chest, and abdomen revealed no abnormalities. Throughout this six-month workup, the patient remained clinically stable.

After discussion with both a hematologist and an oncologist, the impression was that the elevated vitamin B12 levels could be due to a functional abnormality of vitamin B12 or be idiopathic in nature. High blood concentrations of vitamin B12 are often caused by over-supplementation; however, there are instances in which high vitamin B12 levels are seen in the absence of supplements. Macro-vitamin B12 is an underrated cause of supra-physiological cobalamin plasma levels and should be considered in the differential diagnosis.

3. Discussion

The mechanisms that might link these conditions with elevated serum vitamin B12 levels are incompletely understood and may be related to release from damaged cells into the circulation (liver disease), reduced clearance (renal failure, liver disease), increased serum levels of transcobalamin II or other transcobalamins, or increased haptocorrin [1]. There is no evidence that elevated vitamin B12 levels play any role in the pathogenesis of these conditions, and the finding is likely to simply be a marker of hepatic dysfunction or other systemic processes. If an elevated vitamin B12 level is detected in an individual who has not recently received a vitamin B12 injection or taken a vitamin B12 supplement, it may be appropriate to review the medical history, examination, and laboratory testing to determine if one of these systemic conditions is present [2]. We obtain a complete blood count (CBC) with differential, complete metabolic panel, and pursue further testing if abnormalities are found.

A low total plasma vitamin B12 supports a clinical suspicion of B12 deficiency, while the interpretation of an unexpectedly normal/high level is marred by controversies. Macro-B12 is most often defined as the fraction of B12 that can be removed by precipitation with polyethylene glycol (PEG), a nonspecific procedure that also removes protein polymers and antibody-bound analytes. Plasma B12 includes B12 attached to transcobalamin and haptocorrin, and an increased concentration of one or both proteins almost always causes an elevation of B12. The total plasma B12 is measured by automated competitive binding assays, often incorrectly referred to as immunoassays, since the binding protein is intrinsic factor

and not an antibody. An unexpectedly high level of B12 may be further explored using immunological measurements of haptocorrin and transcobalamin (optionally combined with, e.g., size-exclusion chromatography). Nonspecific methods, such as PEG precipitation, are likely to give misleading results and cannot be recommended. Currently, the need for evaluation of a high B12 of unknown etiology is limited since other tests (such as measurements of methylmalonic acid) may better guide the diagnosis of B12 deficiency [1].

Vitamin B12 (cobalamin, B12) deficiency may result in irreversible neurological damage. Therefore, an early diagnosis is mandatory, most often guided by the measurement of total B12 in a blood sample [2]. Measurements of other biomarkers, such as the "active" part of B12 (holoTC or "active B12"), or the metabolic marker methylmalonic acid (MMA) and, to some extent, homocysteine (Hcy), are considered superior to total B12 in their diagnostic utility. Yet, the measurement of total plasma B12 remains the first-line analysis when suspecting B12 deficiency. This is due to the easy availability of the assay and its low cost, as compared to the assessment of other analytes [3].

A low level of plasma total B12 suggests the presence of a deficient state, while the interpretation of a higher level may be a challenge. Does an unexpectedly high level reflect the absence of B12 deficiency, or should the clinician be aware of other possibilities? Numerous case studies, as well as more extensive works on cohorts of patients, have addressed this issue, giving somewhat conflicting conclusions. Some authors argue that a high level of total plasma B12 (observed without any clear reason) has limited clinical implications [4]. Others suggest a high level of B12 is misleading and is caused by analytical flaws or the presence of an ill-defined inert "macro-B12" that can be removed by precipitation with polyethylene glycol (PEG). Some papers go so far as to suggest an algorithm involving PEG precipitation applied to all samples with an increased level of B12 [5]. Much of these controversies are caused by an incomplete understanding of the nature of B12 and its binding proteins in blood plasma, as well as the analytical procedures employed for its analysis.

Plasma B12 (total B12) covers various forms of the vitamin bound to two binding proteins, haptocorrin (HC) and transcobalamin (TC) [6]. In healthy individuals, the concentration of total B12 is around 200–600 pmol/L (Stabler and Allen). The upper ligand "X" (bound to the Co-ion) differs in various molecular forms of the vitamin: the coenzymes methyl-B12 and deoxyadenosyl- B12, as well as their ubiquitous precursors, e.g., hydroxo-B12 and cyano-B12, are abundant in foods and vitamin pills, respectively. All four forms are present in blood plasma and bind with comparable affinities to the B12 binding proteins [7]. In addition, plasma contains inactive B12 derivatives (the so-called analogs) without a known biological function in humans [8].

Approximately 4/5 of circulating B12, as well as all of the analogs, are bound to HC. In healthy individuals, HC occurs at a concentration of 240–680 pmol/L [9].

HC is a glycoprotein produced in all exocrine glands and in white blood cells. Its half- life (approximately 17 days) is quite long [10]. The turnover of HC becomes

considerably faster if the content of sialic acid on its surface is low, as is the case with HC encapsulated in granulocytes. B12 and its analogs bound to HC are slowly cleared by the liver, where HC is degraded, and the attached ligands are excreted with the bile. The main part of the excreted B12 is reabsorbed after binding to intrinsic factor (IF), a protein produced by the parietal cells in the stomach [11]. IF recognizes B12 and facilitates its intestinal uptake via interaction with an IF-B12-specific receptor. At the same time, IF has a low affinity for the analogs, which are expected to pass to the large intestine without any significant adsorption.

B12 from dietary sources eventually enters the blood, peaking at approximately 7 hours after ingestion [12]. The incoming vitamin primarily binds to TC due to its high binding capacity (600–1200 pmol/L;, maintained by a steady production of TC in endothelial cells. TC has an affinity for B12, which is comparable to that of HC, but the binding of the analogs to TC is relatively weak. The produced TC-B12complex (often referred to as holoTC or "active B12") is promptly absorbed by human tissues ($t½ \approx 1$ hour;) and particularly by the liver [13]. The fast clearance of TC-B12 stipulates its low steady-state concentration (≈60–80 pM), which corresponds under normal conditions to 10–20% of total plasma B12 [14]. A low level of holoTC contrasts with the high concentration of the "inert" macro-B12. This uncertainty has led some laboratories to adopt additional testing methods, such as PEG precipitation, to distinguish between "true" B12 and macro-B12, although this approach is not universally accepted [15].

The existence of macro-B12, sometimes associated with increased total B12 levels, raises significant concerns. The term "macro-B12" typically refers to B12 bound to immunoglobulins, resulting in a large molecular complex that might be incorrectly measured by automated assays. However, evidence supporting the routine clinical significance of macro-B12 remains limited. While the presence of macro-B12 could theoretically lead to misinterpretation of a patient's B12 status, the exact prevalence and impact of macro-B12 are still not well defined.

The debate around the clinical implications of elevated plasma B12 continues. Some researchers emphasize that high B12 levels could be benign or secondary to other conditions, such as liver disease or cancer, rather than indicating a primary issue with B12 metabolism. For instance, liver dysfunction can result in the release of stored B12, leading to elevated serum levels. Similarly, certain malignancies, particularly those affecting the liver or blood, can cause increased production of B12 binding proteins, thus raising total B12 levels. These conditions highlight the need for a thorough clinical evaluation when high B12 levels are detected.

Given these complexities, the initial step in assessing an unexpectedly high B12 level should be a detailed patient history and physical examination, followed by appropriate laboratory tests. These might include liver function tests, renal function tests, and a complete blood count. If these initial tests do not identify a cause, more specific investigations may be warranted, such as measuring haptocorrin and transcobalamin levels, or performing imaging studies to check for possible neoplastic processes.

While a low plasma B12 level is a well-established marker of B12 deficiency, the interpretation of high plasma B12 is more nuanced and context-dependent. Elevated B12 levels can indicate a variety of underlying conditions, some of which may be serious. However, the clinical approach should be cautious, ensuring that a comprehensive evaluation is performed to determine the underlying cause of the abnormal laboratory result. Further research is needed to clarify the clinical significance of macro-B12 and to establish more precise guidelines for the assessment of elevated B12 levels.

4. Conclusion

This case underscores the complexity of interpreting elevated vitamin B12 levels, especially in the absence of supplementation. While high serum cobalamin often necessitates ruling out serious conditions such as malignancies and organ dysfunction, this patient's extensive workup revealed no underlying pathology. The findings suggest that functional abnormalities of vitamin B12 or idiopathic causes may be responsible. Clinicians should be aware of macro-vitamin B12 as a potential factor and maintain a comprehensive approach to diagnosing elevated B12 levels, ensuring thorough evaluation and appropriate follow-up.

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