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Persistently Elevated Vitamin B12: A Missed Diagnostic Opportunity?

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Background: Vitamin B12 testing is primarily performed to identify deficiency; however, persistently elevated serum vitamin B12 levels in patients not receiving supplementation are uncommon and may indicate underlying pathology. Emerging evidence suggests that unexplained hypercobalaminemia is associated with solid and haematological malignancies, although its diagnostic significance remains underrecognized. This study describes a patient with persistently elevated vitamin B12 levels that prompted further investigation and was associated with the diagnosis of a gastrointestinal stromal tumour (GIST).

Methods: We conducted a retrospective analysis of the clinical records of a 69-year-old female presenting with persistently elevated serum vitamin B12 levels (19,717 pg/mL; reference range: 173–700 pg/mL) despite no history of vitamin B12 supplementation. Clinical assessment, laboratory investigations, imaging, endoscopic findings, histopathology, treatment, and follow-up data were reviewed. Relevant literature was examined to place the findings within the context of current evidence.

Results: The patient had a history of type 2 diabetes, autoimmune thyroid disease, and mild iron deficiency anaemia. Gastroenterological evaluation identified a gastrointestinal stromal tumour (GIST), confirmed by positive immunohistochemical staining for CD117, CD34, and CD56. Following tumour resection and partial gastrectomy, vitamin B12 abnormalities persisted alongside hyperhomocysteinemia, despite normal liver and kidney function. The patient subsequently received adjuvant imatinib therapy. Current literature suggests that persistent hypercobalaminemia is associated with an increased risk of several solid malignancies and may reflect tumour-related alterations in vitamin B12 transport proteins or metabolism.

Conclusion: Persistent elevation of serum vitamin B12 in the absence of supplementation should not be dismissed as an incidental laboratory finding. This case highlights the importance

of considering occult malignancy in the differential diagnosis of unexplained hypercobalaminemia and supports further investigation into the role of vitamin B12 as a potential biomarker for earlier cancer detection.

KEYWORDS: Vitamin B12, Hypercobalaminemia, Gastrointestinal Stromal Tumour, Cancer Biomarker, Diagnostic Challenge

INTRODUCTION

Vitamin B12 (cobalamin) is essential for nervous system function, DNA synthesis, and red blood cell formation. Elevated serum B12 levels are uncommon and often overlooked in routine diagnostics. Persistent elevation, particularly above 1000 pg/mL, has been associated with solid cancers, liver disease, autoimmune disorders, and, rarely, macro-vitamin B12 complexes (Allen, 2012; Andrès et al., 2013; Obeid, 2022)thus causing uncertainties regarding safety of vitamin B12. We conducted a systematic literature search and a scoping review of human studies published in PubMed between January 2005 and March 2022, to investigate the association between vitamin B12 (concentrations of B12 biomarkers, intake, and genetic determinants. The mechanism of B12 elevation in malignancies remains unclear but may involve increased binding proteins or tumour-related metabolic changes.

In clinical practice, unexplained high B12 levels should prompt evaluation for underlying pathology, including malignancy (Arendt et al., 2016). We present a case of a 69-year-old woman with persistent, unexplained B12 elevation, ultimately diagnosed with gastrointestinal stromal tumour (GIST). This case highlights the importance of considering elevated B12 as a potential diagnostic clue for malignancies.

Case Report

A 69-year-old female attended Khozrevanidze Clinic in Batumi with no acute symptoms but a history of persistently elevated serum Vitamin B12 levels (19,717 pg/ml; reference range: 173–700 pg/ml) despite not taking supplements. She had a background of type 2 diabetes mellitus, managed with metformin (2000 mg daily), autoimmune thyroid disease with euthyroid status, and mild iron deficiency anaemia. On examination, her height was 165 cm, weight 84 kg (BMI 30.85).

Following consultations with gastroenterology and hematology teams, she underwent upper gastrointestinal endoscopy, which revealed a mass lesion. Histopathology confirmed a gastrointestinal stromal tumour (GIST) (D37.1) associated with gastritis and oesophagitis. Immunohistochemistry was positive for CD117, CD34, and CD56. The patient underwent successful tumour resection and partial gastrectomy.

Post-operative laboratory investigations (refer to Table 1) showed deranged complete blood count parameters consistent with iron deficiency anaemia, while kidney and liver function tests and electrolytes remained within normal limits. Hyperhomocysteinemia (D68.8) persisted following surgery.

Table 1: Post-operative blood test anomalies

Test	Result
RBC	Low
HGB	Low
HCT	Low
Monocyte	High
Eosinophils	High
MPV	Low
ESR	Low
Homocysteine	High
RBC: Red Blood Cells, HGB: Hemoglobin, HCT: Hematocrit, MPV: Mean Platelet Volume, ESR: Erythrocyte Sedimentation Rate	

She was started on imatinib (Gleevec) 400 mg daily as part of her follow-up management. Given her persistent post-operative hyperhomocysteinemia, she was also started on folic acid/vitamin B6/vitamin B12 complex once daily. This supplementation was initiated to treat her hyperhomocysteinemia.

DISCUSSION

Persistent elevation of serum Vitamin B12 can serve as an important diagnostic clue for serious underlying conditions, including hepatic and haematological malignancies (Serraj et al., 2011)it can be sometimes paradoxically accompanied by signs of deficiency reflecting a functional deficit in relation to qualitative abnormalities related to defects in tissue uptake and action of vitamin B12. Etiological profile of hypervitaminemias B12 has mostly serious disease entities and for which early diagnosis is crucial to the plan rather than prognostic. These entities are represented mainly by solid malignancies, hematological malignancies and liver diseases. This reflects the potential significance that may have the dosage of vitamin B12 as an early marker of diagnosis of these diseases. Codified approach is needed to determine the potential indications of the search for a hypervitaminemia B12 and practice what to do to pass before the discovery of a high serum level of cobalamin."","container-title":"Presse Medicale (Paris, France: 1983. In our patient, markedly elevated B12 was accompanied by hyperhomocysteinemia and prompted further investigation, which resulted in the diagnosis of a GIST. Although the exact mechanism remains unclear, proposed explanations include increased availability of B12 from tumour-produced biochemicals that support nucleic acid synthesis and cell proliferation, as well as haptocorrin release from granulocytic cells responding to tumour activity (Lacombe et al., 2021).

CD117 positivity, as seen in our patient, is a recognized immunohistochemical marker for GISTs (Sarlomo-Rikala et al., 1998). CD56 positivity, though more classically associated with neuroendocrine tumours, has also been reported in a subset of GISTs, which may reflect a degree of neuroendocrine differentiation within the tumour (Chen et al., 2020). Persistent plasma B12 ≥ 1000 pg/mL has been strongly associated with increased incidence of solid cancers (HR 5.90; 95% CI 2.79–12.45) compared to non-persistent elevation, suggesting that persistent B12 elevation may help identify patients who warrant further evaluation for occult malignancy (Lacombe et al., 2021).

Elevated B12 has been reported in association with several malignancies, including gastric, colon, breast, liver, lung, prostate, and childhood brain tumours (Jammal et al., 2013; Lin

et al., 2010; Cui et al., 2016; Simonsen et al., 2014; Fanidi et al., 2019; Luu et al., 2021; Price et al., 2016)2005 and 30th April, 2008 in the UMAG pole departments (emergency, internal medicine, acute geriatrics and medical intensive care. In liver cancers, high B12 levels have been linked to tumour progression, poorer survival, and correlations with tumour markers such as alpha-fetoprotein (Cui et al., 2016; Lin et al., 2010; Simonsen et al., 2014). Lung carcinomas have shown a positive association between B12 elevation and cancer risk, with stronger links in specific histological types and in men (Fanidi et al., 2019; Luu et al., 2021)including cancer risk. We aimed to elucidate the role of vitamin B12 in lung cancer etiology via direct measurements of pre-diagnostic circulating vitamin B12 concentrations in a nested case-control study, complemented with a Mendelian randomization (MR. Even modest increases in B12 have been associated with prostate cancer risk (Price et al., 2016).

Although the patient's serum B12 remained elevated, persistent hyperhomocysteinemia may suggest impaired intracellular utilization of vitamin B12 despite elevated circulating concentrations. This may have been influenced by partial gastrectomy and long-term metformin use, both of which can impair B12 absorption. However, these factors do not fully explain the markedly elevated pre-operative serum B12 level, which remains clinically significant and warrants consideration of malignancy, liver disease, haematological disease, autoimmune disease, and macro-vitamin B12 in the differential diagnosis (Ardeman & Chanarin, 1966; Infante et al., 2021).

This case adds to the limited literature on GISTs associated with persistent, unexplained B12 elevation. While B12 testing is primarily used to detect deficiency, sustained high levels without supplementation should prompt further investigation, particularly for malignancy. Early recognition may allow timely intervention and improve patient outcomes.

CONCLUSION

Persistent, unexplained elevation of serum vitamin B12 should prompt careful evaluation for underlying disease, including malignancy, liver disease, haematological disorders, autoimmune conditions, and macro-vitamin B12. In this case, markedly elevated B12 in the absence of supplementation prompted further investigation and was associated with the diagnosis of a gastrointestinal stromal tumour. This case highlights the importance of not dismissing unexplained hypercobalaminaemia as an incidental laboratory finding.

Conflict of Interest

The authors declare no conflict of interest.

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