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# MACRO-VITAMIN B12 AS CAUSE OF FALSELY ELEVATED COBALAMIN LEVELS

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## ABSTRACT

*Introduction:* High blood concentrations of vitamin B12 are often caused by over-supplementation. However, there are instances in which augmented vitamin B12 levels are seen in the absence of supplements. Macro-vitamin B12 is an underrated cause of supra-physiological cobalamin plasma levels.

*Case description:* A 70-year-old man was referred to an ambulatory internal medicine centre because of high vitamin B12 levels yet he denied taking supplements. An X-ray showed a tumour in the right upper lobe of the lung, which triggered further examinations. An MRI scan of the brain came back normal as well as a CT scan of the abdomen, and colonoscopy. The pulmonologist requested a PET-CT scan, which showed an isolated 18-FDG uptake in the area of the lung mass that was detected earlier. The patient underwent surgery with adjuvant cis-platinum and gemcitabine and is still making good progress. The vitamin B12 levels persisted after successful treatment of lung adenocarcinoma; determination of vitamin B12 after PEG (polyethylene glycol) precipitation showed normal concentrations.

*Discussion:* A high vitamin B12 plasma concentration in the absence of vitamin supplementation can be a daunting diagnostic problem for the internist, as there are several possible underlying causes. In this case the diagnosis of lung carcinoma was made, the patient was treated appropriately, yet this pathology had no correlation with the cobalamin levels.

*Conclusion:* A high vitamin B12 concentration can be the impetus of thorough medical inquiries. Internists should be careful not to forget macro-vitamin B12 as a possible source of falsely elevated vitamin B12 values.

## KEYWORDS

Macro-vitamin B12; vitamin B12; polyethylene glycol; cobalamin; assay interference

## LEARNING POINTS

- When encountering an otherwise unexplainable B12 hypervitaminosis, the diagnosis of macro-vitamin B12 should be taken into account to avoid unnecessary extensive medical examinations.
- PEG precipitation can distinguish between a 'real' high vitamin B12 and macro-vitamin B12.
- A high vitamin B12 concentration is no guarantee for adequate cobalamin storage. In case of suspicion, a vitamin B12 measurement after PEG precipitation should be considered.

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## INTRODUCTION

Vitamin B12 is a water-soluble vitamin; because molecules with vitamin B12 activity contain the mineral cobalt, they are referred to as cobalamins. There are two metabolically active forms of vitamin B12: methylcobalamin and 5-deoxyadenosylcobalamin. Vitamin B12 acts as a cofactor for two enzymes, methionine synthase and L-methylmalonyl-CoA mutase to catalyse homocysteine to methionine and to convert L-methylmalonyl-CoA to succinyl-CoA. Cobalamins are important for the process of erythropoiesis, myelination and DNA synthesis. High-serum vitamin B12 is quite common in clinical practice – prevalence is estimated to lie between 10 and 18%[1]. Besides supplementation, there are several possible causes for high vitamin B12 concentrations.

## CASE DESCRIPTION

A 70-year-old man was referred to an ambulatory internal medicine centre by his general practitioner (GP) because of high levels of vitamin B12 for which his doctor had no explanation. The patient had no complaints. He denied the use of any vitamin supplements in the prior months. This patient had a history of arterial hypertension and stenting of the iliac artery. He was taking nebivolol, amlodipine, low-dose acetylsalicylic acid, fenofibrate and allopurinol. The physical examination was unremarkable. Bloodwork done by his GP showed hypervitaminosis B12 on several occasions; no other biochemical abnormalities were present. As high vitamin B12 concentrations are sometimes associated with haematological malignancies and solid cancers, an extensive medical exploration was undertaken. Carcinoembryonic antigen (CEA) and neuron-specific enolase test results were normal. The patient underwent an X-ray of the chest, CT abdomen and colonoscopy, which revealed a mass in the upper lobe of the right lung. An MRI scan of the brain was negative for metastases, and an 18-FDG-PET-CT scan showed isolated 18-FDG uptake at the site of the lung mass. The patient underwent surgery with adjuvant chemotherapy of cisplatin and gemcitabine; he recovered and is making good progress. A few months after the treatment a new vitamin B12 measurement was carried out and demonstrated a persisting high vitamin B12 concentration; another measurement of vitamin B12 was taken after polyethylene glycol precipitation (PEG), and this time the lab result for vitamin B12 came back normal *(Table 1)*.

## DISCUSSION

High serum levels of vitamin B12 are often due to supplementation. However, in the absence of vitamin supplements clinicians often think of hepatic or renal impairment, or haematological or solid malignancies *(Table 2)*[2]. In this case there was a solid tumour; however, this was not causing the rise in cobalamin levels. Interfering antibodies can cause macro-vitamin B12. These are aggregates of immunoglobulin G (IgG) antibodies that form immune complexes with vitamin B12[3] and are biologically inactive; only the free fraction of vitamin B12 is of biochemical importance. The prevalence of such immune complexes is estimated to be 18%[4]. Awareness within the medical community is inadequate and in case of suspicion, a vitamin B12 measurement after PEG precipitation should be considered.

| | Before referral | After tumorectomy | After dilution | After PEG precipitation | Reference range |
|---|---|---|---|---|---|
| Vitamin B12 | > 2000 | > 2000 | 5357 | 384 | 197 - 771 ng/l |

*Table 1. Laboratory values of vitamin B12 before and after PEG precipitation.*

| | |
|---|---|
| Hepatic | Alcoholic liver disease<br>Liver cirrhosis<br>Acute hepatitis |
| Renal | Renal failure |
| Haematological | Chronic myeloid leukaemia<br>Acute leukaemia<br>Polycythaemia vera<br>Myelofibrosis |
| Solid tumours | Hepatocellular carcinoma<br>Liver metastasis<br>Breast carcinoma<br>Colon carcinoma |
| Interfering antibodies | Macro-vitamin B12 |

*Table 2. Causes of elevated vitamin B12 levels in the absence of vitamin supplements.*

## CONCLUSION

Macro-vitamin B12 is a relatively new medical entity that warrants greater attention. Physicians may not only risk misdiagnosis and conducting unnecessary tests but also may overlook actual B12 deficiencies by assuming normal vitamin B12 levels. More research is needed to fully comprehend the clinical significance of this under-recognised biochemical anomaly.

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