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HYPERVITAMINEMIA B12 IN THE ELDERLY: A FORGOTTEN MARKER OF SERIOUS UNDERLYING DISEASES

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ABSTRACT

Hypervitaminemia B12, long neglected in clinical practice, is a biological anomaly whose pathological significance remains largely underestimated, particularly in the elderly. While medical attention has historically focused on vitamin B12 deficiency, several recent studies suggest that elevated levels of this vitamin may reveal serious underlying pathologies, such as solid neoplasia, haematological malignancies, chronic liver disease or renal failure. We report the case of a 91-year-old man hospitalized for asthenia, anorexia and altered general condition, in whom vitamin B12 assay revealed major hypervitaminemia (1318 pg/ml). The work-up revealed hepatic cirrhosis of alcoholic origin, complicated by hepatocellular carcinoma which was metastatic from the outset. This case illustrates the potential prognostic value of vitamin B12 dosage, particularly when coupled with C-reactive protein (BCI index), a high value (> 40,000) of which is associated with short-term mortality in patients with advanced cancer. Beyond hepatopathy, hypervitaminemia B12 is associated in the literature with increased haptocorrin release in myeloproliferative syndromes, excess transcobalamins in renal failure, or paradoxical elevation in certain inflammatory diseases. This biological marker, which is easy to obtain, could therefore become part of standardized geriatric assessment, particularly in oncogeriatrics, in order to guide diagnostic and prognostic strategy. The systematic inclusion of vitamin B12 assays in the general assessment of elderly patients, particularly in oncology settings, deserves to be reassessed.

KEYWORDS

Hypervitaminemia B12, elderly, B12 × CRP index (BCI), prognostic marker, neoplasia

LEARNING POINTS

- Hypervitaminemia B12 is an often overlooked but potentially significant marker of serious underlying pathologies—including solid neoplasms, liver disease, renal failure, and hematologic malignancies—especially in elderly patients.
- The B12 × C-reactive protein (CRP) index, easily obtainable from routine labs, may serve as a prognostic tool in oncology, with values over 40,000 being strongly associated with short-term mortality in advanced cancers.
- Routine screening for vitamin B12 levels in geriatric assessments should consider both deficiency and excess, with hypervitaminemia prompting systematic diagnostic evaluation to uncover latent or advanced disease.

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INTRODUCTION/BACKGROUND

High serum cobalamin (vitamin B12) has long been a misunderstood and underestimated anomaly, being considered as irrelevant from a diagnostic and clinical standpoint. Both fundamental and clinical research efforts were indeed concentrated, for a long time, on cobalamin deficiency[1]. Hypervitaminemia B12 is a biological anomaly that is largely underestimated because it is poorly understood. To date, there is no consensus as to what should be done in the event of an elevated vitamin B12 level. Research efforts have focused mainly on vitamin B12 deficiency, linked either to the syndrome of non-dissociation of vitamin B12 from its carrier proteins, or to Biermer's disease. According to the literature, vitamin B12 is an early marker of mostly serious pathologies, and systematic investigation of B12 hypervitaminemia is decisive for prognosis[1]. We report a case illustrating this issue.

CASE DESCRIPTION

A 91-year-old male presented with fatigue and loss of appetite for over 15 days. Repeated falls and shortness of breath were noted by those around him. The elderly patient's medical history included arterial hypertension treated with triple anti-hypertensive therapy (sartan, calcium channel blocker, thiazide diuretic), non-insulin-dependent diabetes mellitus on sitagliptin, chronic post

Parameter	Results	Normal values
Sodium (mmol/l)	137	135-145
Potassium (mmol/l)	4.4	3.5-5
Creatinine (µmol/l)	124	<115 (variable depending on lab)
Creatinine clearance (estimated) (ml/min/1.73 m^2 of floor space)	48	>60
Haemoglobin (g/dl)	9.4	11.8-16.7
Mean corpuscular volume (fl)	94.3	82.2-96.3
Leukocytes (× 10^9/l)	5.60	4.1-10.5
Platelets (× 10^9/l)	213	172-398
Total bilirubin (µmol/l)	32	<17
GGT (IU/l)	162	<55
Alkaline phosphatases (IU/l)	442	30-120
AST (IU/l)	76	<35
ALT (IU/l)	37	<45
Prothrombin time (sec)	13.4	11-13.5
Albumin (g/l)	24	35-50
Pre-albumin (g/l)	<0.03	0.2-0.4
CRP (mg/l)	47	<10
Ferritin (ng/ml)	905	20-250
Vitamin B12 (pg/ml)	1318	191-485
Folate (ng/ml)	Normal	5-20
Alpha-fetoprotein (ng/ml)	4841	<10
Carcinoembryonic antigen (ng/ml)	Normal	<5
BCI (B12 × CRP index)	61946	> 40,000: poor prognosis

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; CRP, C-reactive protein; GGT, gamma-glutamyl transferase.

Table 1. Summary of biological data.

obstructive bronchitis and an episode of rectorrhagia on grade 2 haemorrhoidal pathology. On clinical examination, oedema of the lower limbs and abdominal palpation raised suspicion of ascites were noted. Cutaneous findings included mucocutaneous icterus. The laboratory work-up on admission *(Table 1)* revealed no hydroelectrolytic disorders; normal sodium (137 mmol/l); normal potassium (4.4 mmol/l), moderate renal failure with creatinine clearance 48 ml/min/1.73 m^2 (normal range: >60 ml/min/1.73 m^2), creatinine at 124 µmol/l, anaemia (haemoglobin at 9.4 g/dl normal range: 11.8-16.7 g/dl), normocytic with mean corpuscular volume at 94.3 fl (normal range: 82.2-96.3 fl), with a normal leukocyte count of 5.60 ×10^9/l, platelet count 213 ×10^9/l (normal range: 172-398 ×10^9/l). Liver function tests were, with subicteric cholestasis: total bilirubin 32 µmol/l (normal range: <17 µmol/l); gamma-glutamyl transferase 162 IU/l (normal range: <55 IU/l) and alkaline phosphatase 442 IU/l (normal range: 30-120 IU/l), moderate elevation of aspartate aminotransferase (AST) at 76 U/l and alanine aminotransferase (ALT) level was within normal range at 37 U/l; normal prothrombin time 13,4 seconds (normal range: 11 to 13.5 seconds). The patient was severely malnourished, with albumin at 24 mmol/l and prealbumin less than 0.03. A moderate biological inflammatory syndrome was noted, with a C-reactive protein (CRP) level of 47 mmol/l (normal range: <10 mmol/l). We completed the workup by measuring ferritin, which was elevated to 905 ng/ml (normal range: 20-250 ng/ml), and detected hypervitaminemia B12 at 1318 pg/ml (normal range 191-485 pg/ml) and a normal serum folate level. We completed the investigative work-up with a thoracic-abdominal-pelvic computed tomography (CT) scan, which revealed a large abdominal-pelvic effusion, a dysmorphic liver with lobulated contours, and a suspicious heterogeneous mass in the anterior part of the right lobe measuring 7.7 cm in height, 8.4 cm in thickness and 7.2 cm in transverse dimension, with compression of the portal vein. There was a mass in the posterior part of the right lobe of the liver measuring approximately 5 × 6.2 × 6.4 cm. Other nodular lesions less than 10 mm in diameter were seen in the right lobe. The extrahepatic bile ducts are dilated. The gallbladder is of normal size, with a thin wall containing stones. There were no pancreatic or adrenal abnormalities. Dense thickening of the anterior peritoneal fat was observed possibly related to peritoneal carcinosis. The patient thus presented with hepatic cirrhosis classified as Child-Pugh B9 MELD 8, complicated by probable hepatocellular carcinoma, which was metastatic from the outset and was the source of the patient's altered general condition and oedematous-ascitic decompensation regards aetiology, hepatitis A, B and C serologies came back negative. On questioning, the patient mentioned alcohol consumption of 2 bottles of wine a day. Oesophageal fibroscopy revealed grade 1 oesophageal varices, no gastric varices. The output of evacuation and exploratory paracentesis was 6.5 litres of exudate, with no biological signs of infection. We completed this work-up with an alpha fetoprotein assay increased to 4841 ng/ml. (normal laboratory value: <10 ng/ml) and normal carcinoembryonic antigen levels. From an oncogeriatric standpoint, the patient was classified as WHO 2, with progressive loss of autonomy. The B12 × CRP index (BCI) was calculated at 61,946. Following a multidisciplinary consultation, palliative care was decided upon.

DISCUSSION

The association between hypervitaminemia B12 and solid neoplasia was first described and documented by Carmel et al. in 1975, with studies of vitamin B12 and its transporters in a population of 139 patients with cancer pathology clearly demonstrating an association between hypervitaminemia B12 and neoplasia[2].

The major cancers that were implicated were hepatocellular carcinoma and secondary hepatic tumours, breast cancer, colon cancer, stomach cancer and pancreatic tumours[1].

Studies confirm the significant link between B12 hypervitaminemia and liver disease. In an internal medicine study, 31% of patients with elevated B12 had non-neoplastic liver disease, with 80% of cases being chronic and 25% having reached the stage of cirrhosis[3]. Similarly, the BDOSE study found that alcoholism (with or without manifest hepatic abnormalities) and neoplasia was the most frequent causes of B12 hypervitaminemia[3]. Zulfiqar et al.[4] confirmed this fact. Factors with a significant link to hypervitaminemia B12 in univariate analysis were: acute renal failure (p=0.0002); liver diseases (p<0.0001) and solid neoplasia (p=0.0030). Hepatic metastases were on the threshold of significance (p=0.0622), and variables independently related to hypervitaminemia B12 were: acute renal failure (odds ratio, OR=6.3; 95% confidence interval, CI=2.7-8.1; p<0.0001); liver diseases (OR=5.4; 95% CI=3.1-6.9; p<0.0001); hematological disorders (OR=5.7; p=0.0017); and age ≥ 75 years (OR=3.7; 95% CI=1.9-4.8; p=0.0416). The pathophysiologic mechanism is an excess cobalamin release by the liver and the hepatic synthesis decrease of transcobalamin II, which is essential for tissue fixation of B12 vitamin[5].

From a prognostic point of view, the correlation found in some cases between the size of certain tumours, notably liver tumours, and elevation of vitamin B12 levels has led to the suggestion that hypervitaminemia is a possible tumour marker of poor prognosis. This is confirmed by the prospective series by Geissbuhler et al.[6]; the authors insist that vitamin B12 should be measured in patients with neoplasia, particularly in the elderly, as one of the factors in the decision to continue curative treatment and/or to carry out paraclinical examinations; this is in correlation with the standardized geriatric assessment. This was also found the study by Salles et al.[7], and in the study by Tal et al. who reported an increase in mortality associated with high vitamin B12 levels in a series 1,570 patients over 65 years of age hospitalized in a geriatric ward[8]. Geissbühler et al. had attributed prognostic value to vitamin B12 levels in patients with neoplasia[6]. The BCI is highly predictive of mortality in

palliative cancer. A value >40,000 is associated with 90% mortality at 3 months[6]. These results were confirmed in a study of a larger group of patients with advanced cancer[9]. A total of 329 patients with advanced palliative cancer were included, with a median age of 68.7 years. These patients were divided into 3 groups, according to their BCI (group 1: BCI <10,000; group 2: BCI between 10,000 and 40,000; group 3: BCI >40,000). According to the results of this prospective study, a high BCI (>40,000) predicts a low survival rate (median survival of 29 days) patients with advanced cancer. Consideration should be given to the future use of this index in the management strategy of patients with advanced tumour pathology[9-10].

CONCLUSION

Hypervitaminemia B12 remains an underestimated anomaly, to which serious pathological conditions are linked. Solid neoplasia, haemopathy, acute/chronic liver disease and renal failure are the main causes of elevated vitamin B12 levels. Vitamin B12 dosage in the geriatric population could be an additional marker in the diagnosis and prognosis of these conditions and could form an integral part standardized geriatric assessment in the field of oncogeriatrics.

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