BMJ Case Reports

Unusual association of diseases/symptoms

Severe folate-deficiency pancytopenia

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Summary

Folate-deficiency anaemia occurs in about 4 per 100 000 people, although severe cases causing moderate pancytopenia are rarer. We present the case of a significant folate deficiency in a 50-year-old alcoholic with a background of mild liver impairment and recurrent nasal and rectal bleeding. Her blood tests showed profound macrocytic anaemia with haemoglobin 2.6 g/dl, leucopoenia with white cell count 3.2 $\times$ 10^9/litre and thrombocytopenia with platelets 17 $\times$ 10^9/litre. Serum folate was 0.8 ng/ml (normal 2.5–13.5 ng/ml) confirming severe deficiency.

Despite these life-threatening results, the patient was stable, alert and was keen to avoid admission. Medical management of the anaemia included slow transfusion of red cells and one unit of platelets in view of haemorrhagic symptoms, two injections of vitamin B12 while awaiting assays and oral folic acid. A rapid improvement in the leucopoenia and thrombocytopenia resulted and no additional complications were encountered.

BACKGROUND

A few cases with pancytopenia secondary to folate deficiency in known chronic alcoholics with liver disease were reported 20 years ago but this case is unusually severe. This patient's marked macrocytosis and blood film appearances pointed to a vitamin B12 or folate deficiency and treatment was initiated while awaiting these assays; thereby, shortening the period of neutropenia and thrombocytopenia.

CASE PRESENTATION

A 50-year-old woman known to abuse alcohol was brought to accident and emergency (A&E) by her partner. He reported her as being unable to communicate for the last few days, being very confused with 'bruising all over' and bleeding from her nose and back passage. He explained that in the last 6 months she was having frequent nasal bleeding that later was followed by rectal bleeding. Simultaneously, she became easily fatigued, dyspnoeic on minimal exertion and confused.

Her background included an alcohol-induced neuropathy, asthma and sciatica. There was no previous history of bleeding disorders. She was not taking any medications, had around 50–100 units of alcohol a week and smoked 40 cigarettes a day.

When she was seen on A&E she was communicating with noticeable delay although was oriented in place, time and person. Her temperature was elevated 38.3 degrees with blood pressure 100/68, pulse 99 beats per min and respiratory rate 18 per minute.

She looked very pale and slightly jaundiced. She had a soft ejection systolic murmur at apex and normal breath sounds. Her abdomen was soft but not tender. Per rectal investigation showed no blood, piles or fissures.

INVESTIGATIONS

ECG was in normal sinus rhythm 90 beats per minute with ST segment depression in lateral leads. Chest X-ray (CXR) was normal. Dipstick urine was normal.

Her admission and repeated routine blood tests were followed (see table 1).

Blood film showed moderate macrocytosis and hypersegmented neutrophils on background marked anisocytosis with polychromasia. Her haematinics showed a significantly low serum folate level (0.8 µg/litre) with normal vitamin B12 (241 ng/litre) and iron levels (serum iron 48.4 µmol/litre and ferritin 422.0 µg/litre). Culture screen with two lots of blood cultures and urine culture were negative for bacterial growth. Abdominal ultrasound revealed enlarged liver with a slightly irregular, nodular outline and increased heterogeneous hepatic reflectivity suggestive of fatty infiltration and possibly fibrotic change but no splenomegaly.

TREATMENT

The patient was transfused 6 units of blood and received one unit of platelets as there level dropped later to 8 $\times$ 10^9/litre. She was started on regular folic acid, had two injections of B12 vitamin (1 mg hydroxocobalamin) and had a course of oral antibiotics.

OUTCOME AND FOLLOW-UP

Over the next 9 days our patient felt more energetic and her full blood count improved. It had returned to normal when checked by her general practitioner 6 weeks later.

DISCUSSION

This patient's severe anaemia was clearly a cause for alarm. Her history indicated that this had been slowly progressive but with a recent acute exacerbation. Transfusion was deemed necessary, although the risk of causing volume overload was recognised and so we proceeded with caution. Given the history of blood loss, and a platelet count falling into single figures, a single unit platelet transfusion was also necessary. This produced a satisfactory platelet increment, which further improved as the patient's folate deficiency was corrected.

Table 1 Results of routine blood tests

Blood test	Admission	9 days later	GP follow-up in 6 weeks	Normal range
Haemoglobin	26 g/l	83 g/l	129 g/l	130–180 g/l
White cell count	3.2×10^9/l	6.0×10^9/l	6.8×10^9/l	$4.0\text{-}11.0 \times 10^9$/l
Platelets	17×10^9/l	62×10^9/l	268×10^9/l	$150\text{–}400 \times 10^9$/l
Red blood count	0.56×10^{12}/l	2.50×10^{12}/l	4.33×10^{12}/l	$3.8\text{–}5.8 \times 10^{12}$/l
Haematocrit	0.075	0.261	0.408	0.37–0.47
Mean corp volume	133.9 fl	104.4 fl	94.2 fl	80–100 fl
Mean corp haemoglobin	46.4 pg	33.2 pg	29.8 pg	27.0–32.0 pg
Red cell dist width	17.5 %	30.1 %	14.4 %	11.8–14.8%
Neutrophils	1.90×10^9/l	3.50×10^9/l	3.1×10^9/l	$2\text{–}7.5\ 10^9$/l
Lymphocytes	1.20×10^9/l	1.30×10^9/l	2.5×10^9/l	$1.5\text{–}4 \times 10^9$/l
Monocytes	0.00×10^9/l	0.90×10^9/l	0.9×10^9/l	$0.2\text{–}1 \times 10^9$/l
Eosinophils	0.10×10^9/l	0.20×10^9/l	0.30×10^9/l	$0\text{–}0.4 \times 10^9$/l
Basophils	0.00×10^9/l	0.00×10^9/l		$0\text{–}0.2 \times 10^9$/l
Reticulocytes	11.3×10^9/l	**392.80×10^9/l**		**$10\text{–}100 \times 10^9$/l**
Thyroid-stimulating hormone		0.91 mU/l		0.38–4.70 mU/l
International normalized ratio	1.5	1.1		0.8–1.2
Adenosine-5′-triphosphate ratio	0.84	0.90		0.85–1.1
Fibrinogen	2.8 g/l	3.6 g/l		1.5–4.5 g/l
Vitamin B12	241 pg/mL			145–914 pg/mL
Serum folate	**0.8 ng/mL**			**2.5–13.5 ng/mL**
Serum ferritin	422 ng/mL			11–307 ng/mL
Serum iron	48.4 μmol/l			6.6–30.4 μmol/l
Bilirubin	30 μmol/l	16 μmol/l		3–22 μmol/l
Alkaline phosphatase	147 U/l	142 U/l		30–126 U/l
Alanine transaminase	28 U/l	22 U/l		9–52 U/l
Albumin	27 g/l	32 g/l		35–50 g/l
Corrected calcium	2.25 mmol/l	–		2.1–2.55 mmol/l
C reactive protein	33 mg/l	24 mg/l		0–5 mg/l

It was decided to start treatment with both vitamin B12 and folic acid because of the risks of exacerbating a neuropathy by supplying excess folate to a patient who might have been vitamin B12 deficient. Once the nutritional status was clarified, further vitamin B12 supplementation was not required.[1]

Folic acid deficiency is most frequently seen in alcoholics with a poor dietary intake. It is related to a number of factors. First, an inadequate ingestion of folate-containing foods, especially with a history of renal and liver failure, anorexia and restriction of foods rich in protein, potassium and phosphate, contribute to decreased folate intake.[2 3 5 6] Second, there is implicated impaired metabolism leading to inability to utilise absorbed folate: very active alcohol dehydrogenase binds up folate and, thus, interferes with folate utilisation. Third, alcoholics have an increased excretion/loss of folic acid with urine and, especially, bile. In addition, an increased excretion of folate can occur subsequent to vitamin B12 deficiency.[2 5 7]

There are also morphological changes in intestinal mucosal cells due to alcohol and folate deficiency but the significance is uncertain. Alcohol itself does not cause folate malabsorption in normal subjects in the absence of a low serum folate. Internal folic acid metabolism is also affected by ethanol. The gradual fall in serum folate seen in normal subjects on folate-deficient diets is greatly accelerated on ingestion of alcohol and is associated with megaloblastic marrow changes within 10 days. These reverse on stopping the alcohol and it has been suggested that there is a reversible sequestration of folate within hepatocytes and acute interruption of the enterohepatic circulation of methyltetrahydrofolate.[4-8]

Learning points

- Chronic alcoholics with liver disease are more prone to have folate deficiency and are more at risk of life-threatening pancytopenia as they would not seek medical advice in the first instance.
- They should be on lifelong folic acid supplements, which could be discontinued when the patient stops drinking alcohol.

Competing interests None.

Patient consent Obtained.

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