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FOLATE DEFICIENCY-INDUCED PSEUDO-THROMBOTIC MICROANGIOPATHY

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ABSTRACT

Pseudo-thrombotic microangiopathy is commonly linked with cyanocobalamin (vitamin B12) deficiency, but its association with folate deficiency is rare. This report details a case involving a 60-year-old man with a background of chronic alcohol use who presented with pancytopenia and schistocytes on his blood smear. Bone marrow aspiration showed erythroblastic hyperplasia with megaloblastic changes indicative of folate deficiency. Both cyanocobalamin and methylmalonic acid levels were normal, and there was no evidence of thrombotic thrombocytopenic purpura. Notably, the patient's haemoglobin and platelet counts improved after folate supplementation.

KEYWORDS

Folate deficiency, pseudo-thrombotic microangiopathy, macrocytic anaemia, thrombopenia, high homocysteine levels

LEARNING POINTS

- Pseudo-thrombotic microangiopathy related to folate deficiency is extremely rare and is defined by the presence of non-immune haemolytic anaemia, thrombocytopenia, and schistocytes observed in peripheral blood smears.
- The pathophysiology of pseudo-thrombotic microangiopathy associated with folate deficiency remains incompletely understood. Folate deficiency elevates homocysteine levels, which in turn cause endothelial dysfunction and activate platelets, thereby promoting micro thrombosis and intravascular haemolysis. Additionally, homocysteine has been suggested to act as a haemolytic toxin by generating free radicals within erythrocytes, potentially leading to intramedullary haemolysis.
- This case demonstrates that although the clinical presentation of folate deficiency-induced pseudo-thrombotic microangiopathy can be severe and may occasionally necessitate intensive care admission, prompt improvement was achieved following folate supplementation.

INTRODUCTION

Vitamin B9 (folate) is an essential nutrient critical for deoxyribonucleic acid (DNA) synthesis and homocysteine metabolism. Folate deficiency is well-known to cause macrocytic anaemia[1,2] and can result in neurodevelopmental abnormalities in the foetus during

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pregnancy[3]. Vitamin B12 (cyanocobalamin) is a water-soluble vitamin also required for DNA synthesis and homocysteine metabolism. Deficiency of B12 primarily affects rapidly dividing cells and typically leads to macrocytic anaemia, and in some cases, pseudo-thrombotic microangiopathy (pseudo-TMA) with intramedullary haemolysis[4].

Pseudo-TMA associated with folate deficiency is exceedingly rare, with only some scares cases previously reported in the literature[5-7]. Pseudo-TMA is characterized by non-immune haemolytic anaemia, thrombocytopenia, and schistocytes on peripheral blood smears. Folate deficiency may increase homocysteine levels, causing endothelial dysfunction, hypo-proliferative bone marrow, and structurally compromised erythrocyte membranes, which can ultimately lead to intramedullary haemolysis.

This report presents a case of pseudo-TMA secondary to folate deficiency in a male patient whose medical history was only remarkable for chronic alcohol use.

CASE DESCRIPTION

A 60-year-old man with a history of tobacco use and chronic alcohol intake (approximately 200 g of pure ethanol daily) was admitted to the emergency department during the winter season. He had experienced 3 weeks of progressive deterioration during alcohol withdrawal, characterized by confusion and diarrhoea, and was unable to walk, according to his brother.

On examination, the patient was confused (Glasgow Coma Score: 14/15) but showed no focal neurological deficit. He was tachycardic (140 bpm) with a blood pressure of 107/60 mmHg. Marbling and oedema were present in the lower limbs, but there was no respiratory distress.

Laboratory tests revealed pancytopenia and macrocytic anaemia (haemoglobin 3.8 g/dl; mean corpuscular volume, MCV, 123.2 fl), with reticulocytes at 5 g/l, platelets at 16 g/l, and leukocytes at 2.64 g/l. Peripheral blood smear indicated 1.2% schistocytes and hyper segmented neutrophils. Markers of haemolysis included elevated lactate dehydrogenase (568 IU/l), low haptoglobin (0.32 g/l), and normal orosomucoid (0.75 g/l). Troponin levels remained between 100-130 ng/l. The Coombs test was weakly positive for IgG on two occasions. Coagulation studies suggested disseminated intravascular coagulation with low prothrombin time activity (21%), factor V activity (62%), prolonged activated partial thromboplastin time ratio (1.30), moderate elevation of fibrin monomers (8.6 µg/ml), and a fibrinogen level of 2.1 g/l.

The patient also had cytolysis, with markedly raised hepatic enzymes and gamma-glutamyl transferase. Bilirubin was increased to 40 µmol/l, mainly conjugated. Renal function was preserved, with creatinine at 92 µmol/l and urea at 17.5 mmol/l. C-reactive protein was 19.1 mg/l. Blood gases showed respiratory alkalosis (pH 7.56), hyperlactatemia (10.5 mmol/l), and bicarbonate of 19 mmol/l.

Due to the severity of his condition, he was admitted to intensive care. Although upper gastrointestinal bleeding was suspected, gastroscopy was not initially performed due to the absence of hematemesis or melaena. Computed tomography imaging showed no evidence of active bleeding. Echocardiography showed preserved left ventricular ejection fraction but features of dilated cardiomyopathy,

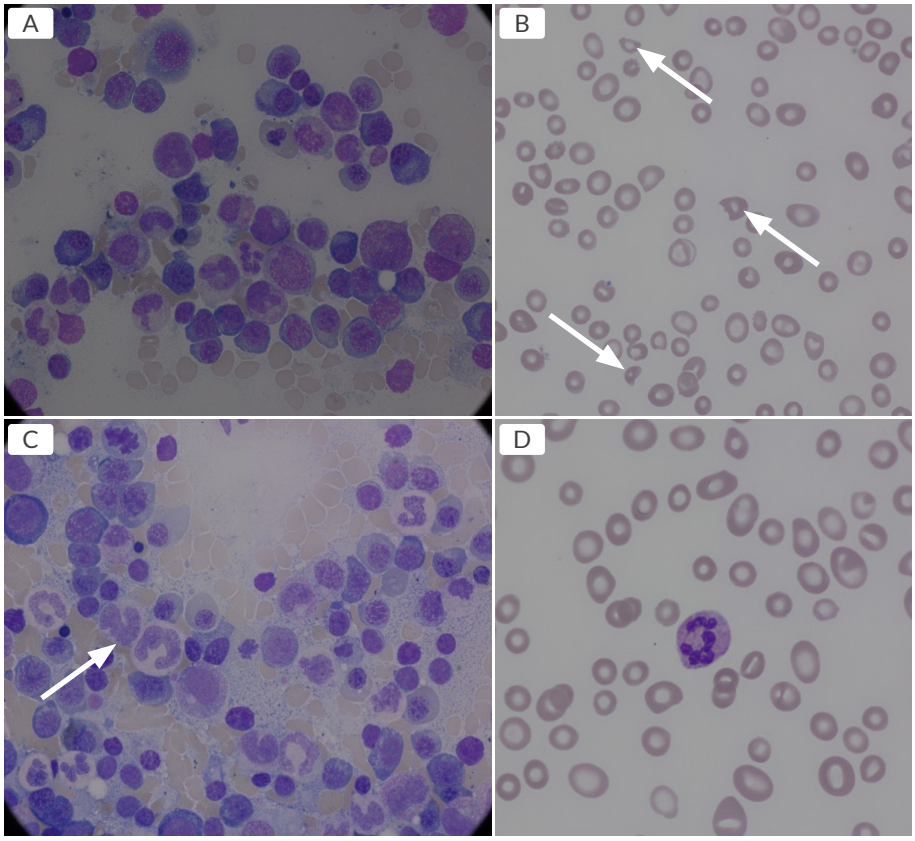


Figure 1. Image of bone marrow aspiration revealing hyperplastic erythroblastic bone with schizocytes and hypersegmented neutrophils. A) Hyperplastic erythroblastic bone marrow; B) Schistocytes; C) Metamyelocyte with ribbon-like nucleus; D) Hypersegmented neutrophils.

likely due to chronic alcohol abuse.

Significant folate deficiency (<1.4 mmol/l) and a marked high homocysteine serum level (105 µmoll) were detected, which improved to 26.1 µmol/l following supplementation. Vitamin B12 deficiency was excluded (serum B12: 313 pmol/l; methylmalonic acid: 0.5 µmol/l).

ADAMTS13 activity (25%; reference >65%) indicated partial deficiency (15 to 50%)[8], a finding of uncertain clinical significance. Severe deficiency (<10%) is diagnostic for thrombotic thrombocytopenic purpura (TTP); partial reductions may result from impaired synthesis or secretion due to endothelial dysfunction[9]. In this case, the low reticulocyte count and raised MCV did not support thrombotic microangiopathy, and TTP was considered unlikely.

Serological tests for human immunodeficiency virus, hepatitis C virus, and hepatitis B virus were negative. Protein electrophoresis showed moderate hypoproteinaemia with beta–gamma bridging. Bone marrow aspiration revealed a hypercellular, erythroblastic marrow with moderate megakaryocytic cellularity, consistent with vitamin deficiency-induced megaloblastic anaemia and dysmyelopoiesis. Megakaryocytes displayed abnormal nuclear segmentation resembling a rosary pattern. The erythroid lineage showed pronounced hyperplasia, asynchronous maturation, frequent megaloblasts, irregular nuclear contours, multinucleation, nuclear fragmentation, and occasional mitotic figures. The granulocytic series exhibited dysplastic changes, including hyper segmentation of neutrophils, large metamyelocytes with ribboned nuclei, and disordered segmentation. No pathological infiltration was found. Numerous macrophages containing hemosiderin and cellular debris suggested increased intramedullary turnover *(Fig. 1)*.

The diagnosis was pseudo-thrombotic microangiopathy secondary to folate deficiency, with confusion and hepatic cytolysis attributed to severe anaemia. After transfusion with two units of packed red blood cells, the patient's mental status improved, hepatic cytolysis resolved, and hyperlactatemia normalized. Features of disseminated intravascular coagulation regressed following folate and vitamin K supplementation. No bleeding occurred during hospitalization, although two platelet transfusions were administered. Both anaemia and thrombocytopenia showed favourable improvement within 1 week of starting folate supplementation.

DISCUSSION

This case highlights that folate deficiency can be a cause of pseudo-TMA, a phenomenon typically associated with vitamin B12 deficiency. Clinical presentation can be severe, occasionally requiring intensive care admission. In our patient, rapid improvement followed blood transfusion and folate supplementation, leading to discharge after 1 week and continuation of folate therapy at home.

The pathophysiology of pseudo-TMA due to folate deficiency is not completely understood. Folate is involved in homocysteine to methionine conversion, so deficiency leads to raised homocysteine levels, as seen in this patient. Elevated homocysteine may cause endothelial dysfunction and platelet activation, promoting microthrombosis[10] and resulting in intravascular haemolysis. Homocysteine has also been proposed as a haemolytic toxin that generates free radicals within erythrocytes, potentially resulting

Features	Thrombotic microangiopathy	Pseudo-thrombotic microangiopathy
Pathophysiology	Formation of microthrombi in small vessels with endothelial injury and platelet-rich aggregate	Unclear - Elevated homocysteine may induce intramedullary haemolysis, and endothelial dysfunction/platelet activation, promoting intravascular haemolysis
Schistocytes	Prominent schistocytosis on peripheral blood smear	Schistocytes may be present but are usually fewer and sometimes less prominent
Reticulocyte response	Appropriate regenerative response with increased reticulocyte count	Inadequate or low reticulocyte response, reflecting ineffective erythropoiesis
Mean corpuscular volume (MCV)	Normal or slightly increased	Overt macrocytosis (high MCV)
Lactate dehydrogenase (LDH)	Elevated due to peripheral haemolysis	Very markedly elevated on average, often higher than in true TMA
ADAMST 13 activity	Often sorely decreased in true thrombotic thrombocytopenic purpura	Within normal range (partial deficiency in DIC, autoimmune cytopenia or secondary TMA following DIC, sepsis or HELLP syndrome)
Course under appropriate therapy	Improvement with plasma exchange and/or specific therapy, variable renal and neurologic prognosis	Rapid correction after vitamin supplementation, overall favourable prognosis

Table 1. *Distinguishing pseudo-thrombotic microangiopathy due to folate deficiency from true thrombotic microangiopathy?*

Abbreviations: TMA, thrombotic microangiopathy; DIC, disseminated intravascular coagulation; HELLP, haemolysis, elevated liver enzymes, and low platelet count.

in intramedullary haemolysis[11], although conclusive evidence is lacking. It can be helpful to distinguish between non-immune haemolytic anaemia associated with folate deficiency, in which haemolysis primarily occurs within the bone marrow, and pseudo-thrombotic microangiopathy due to folate deficiency, where haemolysis is predominantly intravascular.

The metabolic pathways of cobalamin and folate are closely related, as both are essential for homocysteine metabolism. Therefore, deficiencies in either nutrient lead to similar increases in homocysteine, suggesting a common mechanism for both types of pseudo-TMA.

While pseudo-TMA linked to vitamin B12 deficiency is well-documented, reports of folate deficiency-induced pseudo-TMA remain rare. A study in healthy adults found that folate and B12 deficiencies had comparable effects on homocysteine levels, with folate deficiency being more prevalent[12]. This case demonstrates that folate deficiency-induced pseudo-TMA may occur in individuals without a significant medical history apart from chronic alcohol consumption. Low folate levels typically reflect nutritional deficiency, particularly in the context of poor diet or alcoholism, as in this case.

The rare previous reports of folate-induced haemolytic anaemia[5,6,8] often noted underlying gastric disorders, undernutrition drug addiction or chronic alcohol use, with gastrointestinal disease potentially further impairing folate absorption.

A notably low reticulocyte count in this patient could have indicated pseudo-TMA rather than haemolytic anaemia. Other cases reported macrocytic anaemia, but one previously described case had a higher reticulocyte count and laboratory features characteristic of haemolytic anaemia.

In summary, pseudo-TMA resulting from folate deficiency is an uncommon but serious condition that may lead to significant anaemia and require intensive care. Its underlying mechanisms appear to mirror those of B12 deficiency-associated pseudo-TMA. Distinguishing pseudo-TMA due to folate deficiency from true TMA is crucial and relies on several clinical and laboratory features *(Table 1)*. Accurate differentiation helps avoid the use of aggressive therapies such as plasma exchange or immunosuppressants, as pseudo-TMA associated with folate deficiency typically responds rapidly and favourably to vitamin B9 supplementation.

REFERENCES

1. Socha DS, DeSouza SI, Flagg A, Sekeres M, Rogers HJ. Severe megaloblastic anemia: Vitamin deficiency and other causes. *Cleve Clin J Med* 2020;**87**:153-164. doi: 10.3949/ccjm.87a.19072
2. Green R, Datta Mitra A. Megaloblastic Anemias: Nutritional and Other Causes. *Med Clin North Am* 2017;**101**:297-317. doi: 10.1016/j.mcna.2016.09.013
3. Black MM. Effects of vitamin B12 and folate deficiency on brain development in children. *Food Nutr Bull* 2008;**29**:S126-131. doi: 10.1177/15648265080292S117
4. Tran PN, Tran MH. Cobalamin deficiency presenting with thrombotic microangiopathy (TMA) features: A systematic review. *Transfus Apher Sci* 2018;**57**:102-106. doi: 10.1016/j.transci.2018.01.003
5. Larkin E, Konkol S, Geraghty M. Pseudo-thrombotic microangiopathy due to folate deficiency. *BMJ Case Rep* 2023;**16**:e251473. doi: 10.1136/bcr-2022-251473
6. Moreira AP, Vasconcelos M, Costa E Silva T, Relvas C, Espírito Santo J. An Unusual Case of Hemolytic Anemia: A Case Report. *Cureus* 2024;**16**:e75676. doi: 10.7759/cureus.75676
7. Kitamura K, Okumura H, Inaba S, Kawashima A. Pseudo Thrombotic Microangiopathy Caused by Folic Acid Deficiency. *Am J Med* 2025;**138**:e79-e80. doi: 10.1016/j.amjmed.2024.11.034
8. Veyradier A, Coppo P. [ADAMTS13, von Willebrand factor specific cleaving protease]. *Med Sci MS* 2011;**27**:1097-1105. doi: 10.1051/medsci/20112712016
9. Zheng XL, Sadler JE. Pathogenesis of thrombotic microangiopathies. *Annu Rev Pathol* 2008;**3**:249-277. doi: 10.1146/annurev.pathmechdis.3.121806.154311
10. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med* 2014;**371**:654-666. doi: 10.1056/NEJMra1312353
11. Ventura P, Panini R, Tremosini S, Salvioli G. A role for homocysteine increase in haemolysis of megaloblastic anaemias due to vitamin B(12) and folate deficiency: results from an in vitro experience. *Biochim Biophys Acta* 2004;**1739**:33-42. doi: 10.1016/j.bbadis.2004.08.005
12. Wang YH, Yan QH, Xu JY, Li XJ, Cheng MN. High Prevalence and Factors Contributing to Hyperhomocysteinemia, Folate Deficiency, and Vitamin B12 Deficiency among Healthy Adults in Shanghai, China. *Biomed Environ Sci BES* 2019;**32**:63-67. doi: 10.3967/bes2019.010