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Pseudo-thrombotic thrombocytopenic purpura presenting as multi-organ dysfunction syndrome: A rare complication of pernicious anemia

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Abstract

Objective: We present a rare case of pernicious anemia presented as multi-organ dysfunction syndrome, later found to have pseudo-thrombotic thrombocytopenic purpura.

Methods: An 86-year-old female presented with respiratory distress, altered mental status, acute renal failure and was intubated in emergency room. She was found to have severe anemia, thrombocytopenia, high lactate, high lactate dehydrogenase and low haptoglobin. Peripheral smear revealed multilobulated neutrophils with schistocytes, poikilocytes and anisocytes.

Results: She was admitted to intensive care unit for altered mental status, multi-organ dysfunction syndrome with severe metabolic acidosis in setting of hemolysis. She was intubated and managed with intravenous antibiotics and blood transfusion. Patient improved significantly after blood transfusion. Lactic acid normalized, acute kidney injury resolved and mentation improved after transfusion. Laboratory investigation revealed low vitamin B12, high methylmalonic acid, high homocysteine, high lactate dehydrogenase, low haptoglobin, high anti-parietal antibody and high anti-intrinsic factor antibody. Patient was diagnosed with pernicious anemia and pseudo-thrombotic thrombocytopenic purpura with concomitant intramedullary hemolysis. Her hematological parameters and her clinical condition improved significantly after starting therapy with cyanocobalamin.

Conclusion: Pernicious anemia is a chronic disease with subtle presentation but may present as life-threatening complications. Hemolysis and pseudo-thrombotic thrombocytopenic purpura may present as multi-organ dysfunction syndrome which has dramatic response to appropriate therapy.

Keywords

Pernicious anemia, pseudo-thrombotic thrombocytopenic purpura, multi-organ dysfunction syndrome

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Introduction

Pernicious anemia is an autoimmune disease. It is characterized by the presence of antibodies against parietal cells and intrinsic factor, which in turn affects vitamin B12 absorption. Pernicious anemia is more prevalent in the elderly and often goes undiagnosed.[1] Most of the patients present with fatigue, weakness and some neurological symptoms.[2] We discuss a patient who presented with one of the rarer and life-threatening complications of pernicious anemia: pseudo-thrombotic thrombocytopenic purpura (TTP).

Case presentation

An 86-year-old female with past medical history of right hip replacement in 2015 was brought to emergency room (ER) by emergency medical services (EMS) after her granddaughter found her in altered mental status. Patient had been not feeling well for 2 days before the presentation. Patient had not visited to her primary medical doctor for a long time. Her last hospital visit was 4 years ago for orthopedic admission. There was no history of alcohol use, smoking or use of recreational drug. Patient denied following specific dietary pattern. There was no history of any numbness, tingling or

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difficulty in walking. There was no history of alteration in the bowel or bladder habit, weight loss, or gastric or small bowel surgery.

This was the first episode of such symptoms. Granddaughter endorsed that the patient was not taking any medication and had no significant family history. Patient was intubated in the ER due to respiratory distress and altered mental status. Patient had tachycardia and tachypnea. Her pulse was 110 bpm, blood pressure (BP) was 148/100 mm of Hg, respiratory rate was 32 per minute and was saturating at 80% in 6L on face mask. On examination, patient was dehydrated. She had no evidence of trauma. Chest examination revealed rapid shallow respiration with wheezing. Besides mild pedal edema, there were no other significant physical examination findings.

Initial investigation revealed white blood cell (WBC) count of 6.5×10^3 per μL with normal differential count. Hemoglobin was 3.2 gm/dL (12–16), hematocrit 9.6% (36–46), mean corpuscular volume (MCV) 127 fL (80–100) and platelets 59×10^3 per μL (130–400). Retic count was 7.5% (0.5–1.5) with corrected retic of 1.6%. Lactate dehydrogenase (LDH) was 7077 IU/L (98–192). Haptoglobin level was very low (14 mg/dL).

Serum electrolytes were within normal limits. Arterial blood gas showed severe metabolic acidosis with high anion gap (29 mmol/L). Renal functions were impaired with blood urea nitrogen (BUN) and creatinine of 34 mg/dL (8–20) and 1.9 mg/dL (0.4–1.3), respectively. Serum glucose was 93 mg/dL, osmolality was 308 mOsm/L and lactic acid 20.3 mmol/L (0.5–1.9). Liver function test revealed hyperbilirubinemia with total bilirubin of 3.7 mg/dL (0.3–1.2), direct bilirubin of 1 mg/dL, aspartate transaminase 51 IU/L, alanine transaminase 22 IU/L and alkaline phosphatase of 41 IU/L. Her brain natriuretic peptide (BNP) was 670 pg/mL (0–100). Troponin was negative. Her international normalized ratio (INR) was elevated (2.48) with prothrombin time (PT) and activated partial thromboplastin time (aPTT) of 29 and 24 s, respectively. Toxicology screen was negative for ethylene glycol, salicylates and alcohol. Serum ketones were negative.

Imaging scans were negative except mild cardiomegaly on chest x-ray. Computed tomography (CT) of head and abdomen was negative. CT with pulmonary embolism (PE) protocol was negative for PE. She was admitted to intensive care unit (ICU) for altered mental status, multi-organ dysfunction syndrome with severe metabolic acidosis in setting of hemolysis. She was managed with intravenous antibiotics and blood transfusion. Patient received 3 units of blood. Patient improved significantly after blood transfusion. Lactic acid normalized within 10 h of admission. Antibiotics were discontinued when culture reports were negative. Acute kidney injury resolved and mentation improved after transfusion. She was weaned off ventilator in 2 days.

Fecal occult blood tests were both negative. Ferritin was 588 ng/mL (15–150), total iron-binding capacity (TIBC) 194 μg/dL (250–450), transferrin 155 mg/dL (200–370) and iron saturation 91% (15–55). Peripheral smear showed large red blood cells (RBCs) with hypersegmented (6–7 lobes) neutrophils with 1% schistocytes, poikilocytes and anisocytosis (Figures 1 and 2). Anemia work-up revealed mixed picture of megaloblastic anemia and hemolytic anemia.

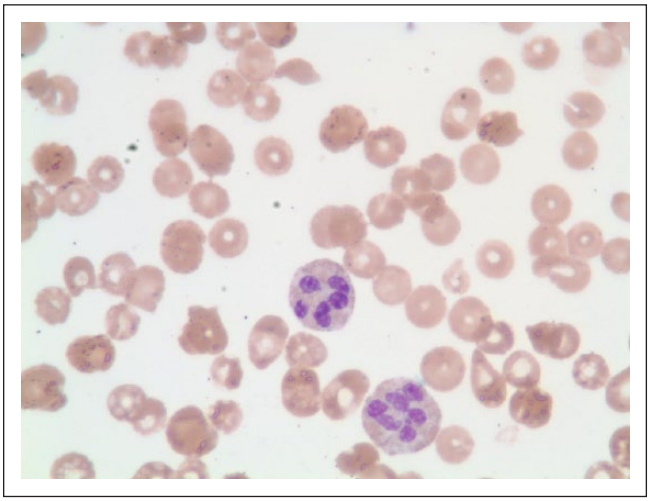

Figure 1. Peripheral smear revealing anisocytosis, poikilocytosis and two hypersegmented neutrophils.

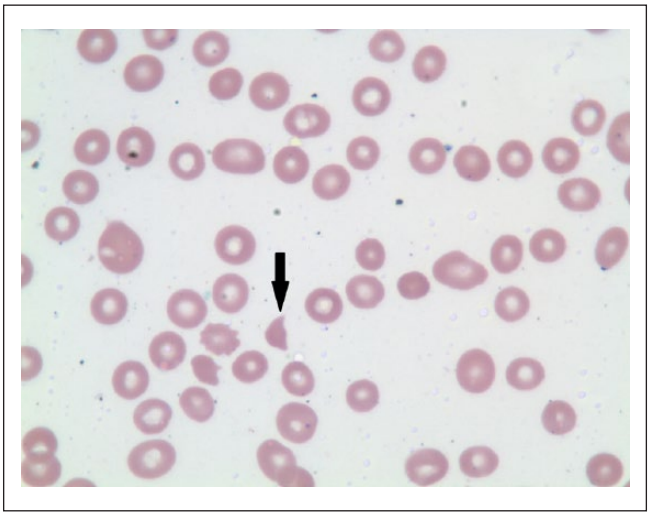

Figure 2. Peripheral smear revealing schistocyte (dark arrow).

Further work-up for anemia revealed that vitamin B12 was 38 pg/mL (211–946), methylmalonic acid 753 nmol/L (0–378), homocysteine 99.3 μmol/L (0–15), anti-parietal antibodies 21.7 units (0–20) and anti-intrinsic factor antibodies 4.7 AU/mL (0–1.1). Direct and indirect Coombs tests were negative, fibrinogen was 185 mg/dL (193–507) and D-dimer was 5170 ng/mL (0–500). Serology was negative for HIV and hepatitis virus. Patient was diagnosed with pernicious anemia and pseudo-TTP with concomitant intramedullary hemolysis.

Patient was started on parenteral vitamin B12. Her hematological parameters and her clinical condition improved

Table 1. Blood parameters at the time of presentation and at the time of discharge.

	Day of admission	Day of discharge
Hb (gm/dL)/Hct (%)	3.2/9.6	8.1/24.3
Platelets (per µL)	59,000	292,000
MCV (fL)	126.9	98.9
WBC (per µL)	6.5	5.9
Blood urea nitrogen (mg/dL)	34	8
Creatinine (mg/dL)	1.9	0.7
Bilirubin total (mg/dL)	3.7	0.7
Direct (mg/dL)	1	NA
Indirect (mg/dL)	2.7	NA
Haptoglobin (mg/dL)	14	144
LDH (IU/L)	7077	720
INR	2.46	1.11
PT (s)	29.1	12.9
aPTT (s)	24.6	28.1
Schistocytes (%)	1	0
D-dimer (ng/mL)	5170	NA

Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; WBC: white blood cell; LDH: lactate dehydrogenase; INR: international normalized ratio; PT: prothrombin time; aPTT: activated partial thromboplastin time.

significantly after starting therapy with cyanocobalamin. Her blood parameters at the time of presentation and at the time of discharge are shown in Table 1.

Discussion

Thrombotic microangiopathy is a well-defined clinicopathological entity. It is characterized by microangiopathic hypochromic anemia, thrombocytopenia and organ damage.[3] Similar findings have been documented in patients with vitamin B12 deficiency and termed as "pseudo" thrombotic microangiopathy.[4–6] Andres et al.[7] described it in six patients with vitamin B12 deficiency with similar features. Since then a number of case reports on the condition have been published with similar findings. Patients with thrombotic microangiopathy normally have renal failure and altered mentation. Infrequently, patients with pseudo-thrombotic microangiopathy have renal dysfunction and also altered mentation.[8] According to the International Council for Standardization in Haematology (ICSH) recommendations, the presence of ⩾1% schistocytes on a peripheral blood smear in the absence of other moderate RBC changes is a clinically significant criterion for the diagnosis of thrombotic microangiopathy.[9,10] However, schistocytes were observed above 1% in many diseases other than thrombotic microangiopathy and in these cases, schistocytes were usually detected together with other RBC morphologic changes.[11]

Multi-organ failure is defined as dysfunction of more than one organ in the body. It is a part of continuum of spectrum of both infectious (sepsis, septic shock) and noninfectious conditions. In view of multi-organ failure with severe metabolic acidosis and severe anemia with lactic acidosis, our patient was managed empirically in line of sepsis. However, the cultures were negative and organ failure resolved with blood transfusion. Lactic acidosis and multi-organ failure have been previously documented in severely anemic patients.[12,13] Coronato et al.[14] described lactic acidosis in pernicious anemia. Lactic acidosis in anemia is common especially in setting of acute blood loss or hemolysis.[15–18]

TTP was of significant concern in our patient in view of thrombocytopenia, hemolysis with presence of schistocytes, altered mentation and deranged renal functions.[3] Rapid correction of renal function, improvement in mental status following transfusion, macrocytic peripheral smear with hypersegmented neutrophils and very high LDH with inappropriate retic response to hemolysis in setting of normal iron profile, however, argued against TTP.[6,8] Case series by Walter et al. and Noel et al. have noted a pattern in patients with TTP and pseudo-thrombotic microangiopathy. In the setting of a very high LDH level (>2500 IU/L) and reticulocytopenia with features of thrombotic microangiopathy (prolonged PT, low fibrinogen, high D-dimer, low platelets, schistocytes and multi-organ dysfunction), the term pseudo-thrombotic microangiopathy is justified. The case series by Noel compared the laboratory variables between pseudo-thrombotic microangiopathy and TTP, and Walter has compared the laboratory variables between pseudo-TTP and TTP, but none of the series have compared coagulation profile between the groups.[6,8]

Differentiating pseudo-TTP from TTP is potentially challenging even if both are under consideration.[8] A number of parameters including renal function, MCV, neutrophil hypersegmentation, patient age, and LDH can alter the pretest probability for either diagnosis.[8] Our patient also had significantly elevated D-dimer level. Elevated D-dimer in vitamin B12 deficient patients has been previously documented.[19] Elevated D-dimer in our patient may be due to elevated homocysteine level. It causes endothelial damage activating coagulation cascade and subsequent thrombolytic pathway leading to elevation in the level of D-dimer.[20]

Patient was managed as pseudo-TTP induced by cyanocobalamin deficiency with parenteral vitamin B12 to which patient responded dramatically. Acute kidney failure and impaired mentation in our patient were likely due to dehydration and severe hypoxia as consequence of anemia that improved on transfusion and hydration. Walter et al.[8] had previously reported a case of pseudo-TTP with acute kidney injury and altered mentation.

Both pseudo-TTP and TTP can present as hemolytic anemia with thrombocytopenia and schistocytosis[8] and pose a diagnostic and treatment dilemma. Because TTP is life-threatening and associated with a high mortality rate, patients are often triaged to a higher level of care for timely treatment with plasmapheresis.[21] Distinguishing between the two can facilitate avoiding aggressive treatments and ICU stays.[5]

Conclusion

Pernicious anemia is a chronic disease presenting more subtly with fatigue, dyspnea, dyspepsia and neurological features. Dramatic and life-threatening complications in these patients are possible due to concomitant hemolysis secondary to intramedullary hemolysis and pseudo-TTP.[4,5,22,23]

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual case report.

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Informed consent

Written informed consent was obtained from the patient's next of kin for her anonymized information to be published in this article.

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