CASE REPORT

Association of acquired thrombotic thrombocytopaenic purpura in a patient with pernicious anaemia

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SUMMARY

Pernicious anaemia is an autoimmune disease caused by intrinsic factor antibody; it leads to vitamin B₁₂ deficiency and is marked by ineffective erythropoiesis. Haematological features reveal macrocytosis, hyperchromasia and hypersegmented neutrophils. Schistocytes are typically seen in microangiopathy, such as in thrombotic thrombocytopaenic purpura (TTP)/haemolytic uraemic syndrome or disseminated intravascular haemolysis (DIC). We report a case of a patient with severe anaemia who presented to the emergency room. Peripheral smear revealed macrocytosis, hypersegmented neutrophils and marked schistocytosis. The patient also had high reticulocyte count with high serum lactate dehydrogenase, elevated D-dimer, low fibrinogen and low haptoglobin. Vitamin B₁₂ level came back low and the presence of intrinsic factor antibody confirmed pernicious anaemia. ADAMTS13 level was noted to be mildly reduced, which raised the suspicion of the association of acquired TTP with pernicious anaemia. Acquired TTP is another autoimmune disorder and its association with pernicious anaemia needs further evaluation.

BACKGROUND

It is well known that vitamin B₁₂ deficiency can cause alteration of bone marrow morphology resulting in ineffective erythropoiesis and significant intramedullary haemolysis.^{1 2} The common clinical presentation of vitamin B₁₂ deficiency is anaemia with a smooth beefy red tongue. It affects the posterior and lateral columns of the spinal cord and cerebellum. The common neurological features are loss of position and a sense of vibration with limb weakness, sensory ataxia, spasticity and extensor plantar response. Pernicious anaemia is a major cause of vitamin B₁₂ deficiency, and is due to a lack of intrinsic factor, which is involved in vitamin B₁₂ absorption in the small intestine. Haematological manifestation in pernicious anaemia includes macrocytosis, hyperchromasia and hypersegmented neutrophils.

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, is a cleave protease that breaks the ultra-large von Willebrand factor (UL-VWF) platelet thrombi. Deficiency of ADAMTS13 leads to thrombotic microangiopathies (TMAs).³ ADAMTS13 deficiency has also been described in pregnancy (HELLP syndrome and preeclampsia), post-transplant and in malignancy-associated TMAs. Acquired thrombotic

thrombocytopaenic purpura (TTP) is a rare autoimmune disorder caused by autoantibodies against ADAMTS13.

Haemolytic anaemia with schistocytosis and thrombocytopaenia are features of TTP; they are usually absent in vitamin B₁₂ deficiency. However, a few case reports have been presented where pernicious anaemia mimicked acute leukaemia, myelodysplasia or TTP. Also, some authors have worked to differentiate TTP from pseudo-TTP in pernicious anaemia.^{4 5} It was suggested that a patient with high lactate dehydrogenase and inappropriately low reticulocyte count should prompt screening for vitamin B₁₂ deficiency. However, ADAMTS13 deficiency has never been reported in pernicious anaemia.

We report a patient who was diagnosed with pernicious anaemia and found to have TTP-like features. ADAMTS13 was low for this patient, raising the suspicion of association of acquired TTP with pernicious anaemia.

CASE PRESENTATION

A 65-year-old African-American woman was admitted to the hospital because of severe anaemia with heart failure, paraesthesia and weight loss. Her medical history included only hypertension. She had not been seen by a physician for the past 4 years and was currently taking no medication.

The patient was doing well until approximately 1 week before admission, when she began to experience increasing shortness of breath on exertion, which was relieved with rest; she was progressively getting worse. She developed bilateral leg swelling over the same period. She also reported orthopnoea and needed three pillows to sleep. She had no chest pain or palpitations, but she did have a cough with whitish sputum production for 2 weeks. Over the past 2–3 months, she had felt numbness and occasional tingling of her legs. Two days before admission, she noticed difficulty in walking and was unable to climb stairs. She explained that her legs felt too heavy to walk and that she had fallen twice at home. She also mentioned losing nearly 60 pounds in the past 3–4 years.

The patient had smoked half a pack of cigarettes every day for the past 40 years, and used to drink alcohol occasionally, but had quit for the past 6 months. She had never used recreational drugs. She was not allergic to any medication and her family history was non-contributory.

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On examination, her blood pressure was 146/70 mm Hg, pulse 90 bpm, temperature 98.2°F (36.8°C), Oral, respiratory rate 18 breaths/min, height 5'5" (1.651 m), weight 140 pounds (63.5 kg), body mass index (BMI) 23.3 kg/m² and SpO₂ 98.00% on 2 L nasal cannula oxygen. The patient had severe pale conjunctiva without any mucosal or skin petechiae. She had bilateral basal crepitation with bilateral pedal oedema. She had no lymphadenopathy or organomegaly. Stool guaiac was negative. On neurological examination, her muscle power was 5/5 in all four limbs, and lower limb reflexes were diminished. Fine touch and position sense were diminished approximately 70% in the lower limbs, with normal pain sensation. Romberg's test was positive with swaying and a tendency to fall with closed eyes. Finger-nose test and heel-to-toe gait were normal. The remaining physical examinations were normal.

INVESTIGATIONS

Initial laboratory tests revealed haemoglobin 3.9 g/L (reference range 12.0–16.0 g/L), haematocrit 11.7% (reference range 37.0–47.0%), mean corpuscular volume 115.7 fL (reference range 81.0–99.0 fL), mean corpuscular haemoglobin 38.6 pg (reference range 27.0–31.0 pg), red cell distribution width 47.7% (reference range 11.5–14.5%), white cell count 8.9 K/μL (reference range 4.8–10.8 K/μL) and platelet count 58 K/μL (130–400 K/μL). On complete metabolic panel, normal blood urea nitrogen/Cr with mild elevation of alanine transaminase/aspartate transaminase was noted. Chest X-ray was consistent with pulmonary oedema and ECG was unremarkable, with brain natriuretic peptide of 4690.

A peripheral smear was reviewed and showed macro-ovalocytes, anisopoikilocytosis, schistocytes and nucleated red blood cells with hypersegmented neutrophils (figure 1).

Subsequent laboratory tests showed reticulocyte count of 15.1% (reference range 0.5–2.0%) with retic index 2.6%, LDH 8861 U/L (reference range 313–618 U/L), haptoglobin <7 mg/dL (reference range 43–212 mg/dL), fibrinogen 218 mg/dL (reference range 243–451 mg/dL) and D-dimer 3360 ng/mL (reference range 45–500 ng/mL). Anaemia studies were obtained. The level of vitamin B₁₂ was very low, 159 pg/mL (reference range 239–931 pg/mL), and the folate level was 10.4 ng/mL (reference range 2.8–19.9 ng/mL). Iron studies revealed normal serum iron of 141 μg/dL (reference range 37–170 μg/dL), mildly elevated ferritin 277 ng/dL (reference range 11.1–264.0 ng/dL) with low total iron binding capacity

190 μg/dL (reference range 265–497 μg/dL). Coombs test was negative. The patient also had a high homocystine level of 74 μmol/L (reference range <10 μmol/L). Pernicious anaemia was confirmed by the presence of intrinsic factor antibody. ADAMTS13 activity level, initially sent for TTP work up, was reported at 42% (normal activity reference range 68–163%).

DIAGNOSIS

Pernicious anaemia.

TREATMENT

The patient was started on daily intramuscular injection of vitamin B₁₂.

OUTCOME AND FOLLOW-UP

The patient showed remarkable improvement of symptomatic and haematological count. In regard to neurological involvement, her sensory symptoms had improved at discharge 2 weeks after admission. She was able to walk 25 feet with a rolling walker. She attended subacute rehabilitation and, at 8-week follow-up visit, denied tingling/numbness and had not had any more falls. Her walking distance had improved to 100 feet with a walker.

DISCUSSION

The clinical presentation of this patient, with a display of severe macrocytic anaemia with paraesthesia and sensory ataxia, was typical of vitamin B₁₂ deficiency. Laboratory analysis revealed low vitamin B₁₂ along with the presence of intrinsic factor antibody, confirming pernicious anaemia. Our patient, at presentation, also had features suggestive of TTP. It has been reported previously in different case reports that TTP-like features (microangiopathy) can be seen in patients with pernicious anaemia. Tadakamalla *et al*⁶ presented a similar case and mentioned TTP as a rare presentation of pernicious anaemia.

The ADAMTS13 level was mildly low in this case. In acquired TTP, the ADAMTS13 level is usually higher than 20% and patients have a high level of anti-ADAMTS13 autoantibodies.³ A limitation of this report is the lack of anti-ADAMTS13 antibody results. Acquired TTP can rarely be associated with other autoimmune disorders, such as pernicious anaemia, and the incidence of acquired TTP is 0.2–1/100 000.⁷

Acquired TTP usually presents with thrombocytopenia and severe fragmentation haemolysis with central neurological signs. Renal failure, which was not seen in our patient, is common in acquired TTP. Patients who have acquired TTP with elevated anti-ADAMTS13 antibodies may often require aggressive plasma exchange therapy and, rarely, may need intense immunosuppressive therapy.⁸ Our patient received vitamin B₁₂ treatment with clinical and haematological improvement of symptoms and did not require plasma exchange.

Pernicious anaemia is an autoimmune disorder that may rarely be associated with other autoimmune disorders such as acquired TTP. TTP-like features are not uncommon in presentations of pernicious anaemia. It is unclear if the low level of ADAMTS13, which is likely due to autoantibodies against ADAMTS13, has any therapeutic significance in patients with overwhelming evidence of pernicious anaemia.

The TTP-like features in pernicious anaemia may be explained by the ineffective erythropoiesis, or may need further evaluation to ascertain acquired TTP in association with pernicious anaemia. This association of pernicious anaemia with acquired TTP needs to be further investigated.

Figure 1 Peripheral smear showing macro-ovalocytes, anisopoikilocytosis, schistocytes and nucleated red blood cells with hypersegmented neutrophils.

Learning points

- ▶ Pernicious anaemia may present with thrombotic thrombocytopenic purpura (TTP)-like features.
- ▶ Serum ADAMTS13 or anti-ADAMTS13 antibody is necessary to check the association of TTP with pernicious anaemia.
- ▶ It is crucial to differentiate TTP from pernicious anaemia as the management plan for TTP and pernicious anaemia is not the same.

Contributors SP prepared the manuscript, reviewed the literature and added the references. JC was the direct care provider and reviewed the manuscript. BRD reviewed the manuscript and helped with the literature search.

Competing interests None declared.

Patient consent Obtained.

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