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Case Report

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Is thrombotic microangiopathy a paraneoplastic phenomenon? Case report and review of the literature

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Abstract
It is currently recognized that the pathogenesis of malignancy-associated thrombotic microangiopathy (TMA) is distinct from thrombotic thrombocytopenic purpura. This carries important implications in its classification and its management. Here, we report a case of occult malignancy presenting initially as acute kidney injury secondary to TMA and highlight the importance of considering an underlying malignancy in patients not responding to conventional therapy for TMA.

Keywords: malignancy; plasma exchange; thromobotic; microangiopathy

Background

Thrombotic microangiopathy (TMA) is characterized by microvascular endothelial disruption and may be congenital, idiopathic, drug-induced or secondary to a systemic illness. Among the secondary causes of TMA, malignancy-associated TMA is distinct in both the measured activity of A Disintegrin-like and Metalloprotease with Thrombospondin Type 1 Motif 13 (ADAMTS-13) enzyme and in the response to plasma exchange (PLEX). Herein, we describe a case of occult neuroendocrine carcinoma presenting as TMA, while highlighting the importance of malignancy as an overlooked secondary cause of TMA and its implications in the pathogenesis, treatment and prognosis of TMA.

Case report

A 68-year-old woman presented with 1-week of weakness, dyspnea and several episodes of hemoptysis. Her medical history included hypertension, aortic stenosis [aortic valve area of 1.09 cm, mean gradient 19.74 mmHg on two-dimensional echocardiography (2DE)] and chronic obstructive pulmonary disease related to a 60-year smoking history. One month prior to presentation, she had experienced stiffness in her shoulders and was started on a corticosteroid, sulfasalazine and methotrexate for presumed rheumatoid arthritis. She had no recent history of a gastrointestinal illness.

At presentation, she was normotensive (121/76 mmHg). Her hemoglobin was 13.3 g/dL (133 g/L), platelets 241 $\times$ 10^9/L and serum creatinine 1.7 mg/dL (150 μmol/L). Blood cultures were negative, and chest X-ray showed non-specific bilateral interstitial markings. She was admitted with a presumptive diagnosis of congestive heart failure and pneumonia. Her sulfasalazine and methotrexate were held.

Transthoracic 2DE revealed normal left ventricular function and unchanged aortic stenosis. Her right ventricular systolic pressure was estimated to be 57 mmHg. Urinalysis showed trace protein and moderate blood. Abdominal ultrasound revealed normal-sized kidneys without evidence of obstruction.

By her 12th day of admission, her hemoglobin was 9.9 g/dL (99 g/L), platelets 63 $\times$ 10^9/L, serum creatinine 5.9 mg/dL (523 μmol/L) and blood urea nitrogen 120 mg/dL (43 mmol/L). Her LDH was 442 U/L, haptoglobin 1.1 mg/dL (0.11 g/L) and reticulocyte count 143 $\times$ 10^9/L. An autoimmune workup was positive for anti-nuclear antibody (ANA) in anti-centromere pattern (1:320). Her C4 was normal at 0.18 g/L, and C3 was mildly decreased at 0.87 g/L. Antineutrophil cytoplasmic antibodies, rheumatoid factor and antiextractable nuclear antigen antibodies were negative. Red blood cell fragmentation was noted on her blood film, prompting a renal biopsy that was consistent with a TMA (Figure 1). She was transferred to a tertiary care hospital for PLEX.

Her ADAMTS-13 activity (drawn prior to the first cycle of PLEX) was estimated by qualitative collagen binding assay and was normal [1]. She was started on an angiotensin receptor blocker that was eventually changed to an angiotensin-converting enzyme-inhibitor following discontinuation of PLEX. She required ongoing hemodialysis and

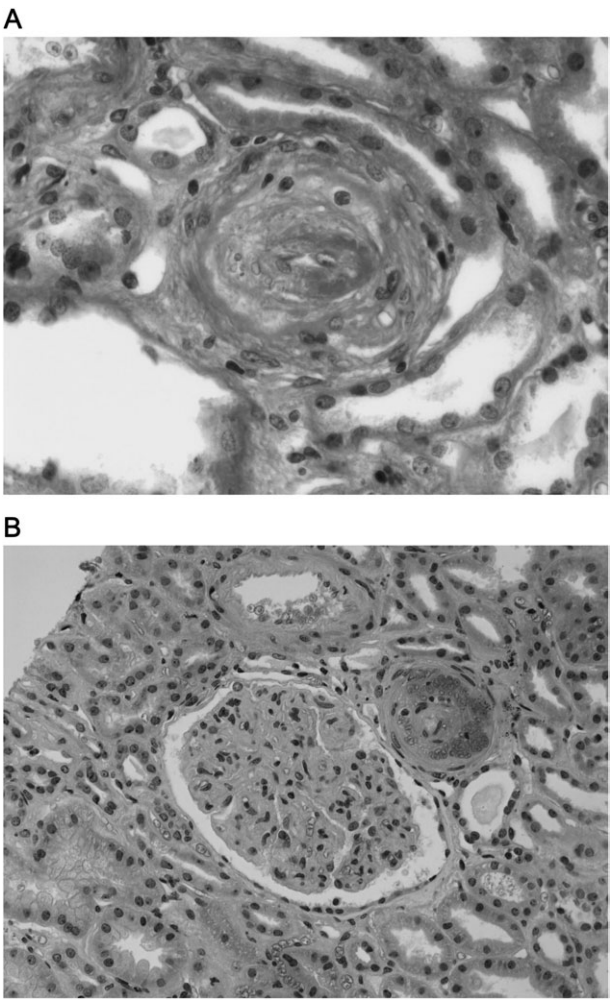

Fig. 1. Renal biopsy. (**A**) Interlobular artery showing marked edematous intimal expansion with fibrin deposition. (**B**) Global glomerular capillary wall thickening with intimal expansion and intramural hemorrhage in adjacent artery.

platelet transfusions. Bone marrow biopsy was normal. She received nine daily 1–1.5 plasma volume exchanges with cryosupernatant plasma, without a response in platelet count [platelets were 49×10^9/L and hemoglobin 8.4 g/dL (84 g/L) on Day 9]. PLEX was discontinued due to lack of response.

A thoracic computed tomography scan demonstrated a 4.4 cm by 3.1 cm mediastinal mass which was not seen on chest X-ray as well as enlarged mediastinal lymph nodes (largest 1.5 cm) and pleural effusions (Figure 2A and B). A biopsy was not pursued because of her deteriorating status. She died on her 31st day of admission following sudden onset of confusion and hepatitis.

Autopsy findings included an acute organized lung injury, extensive steatohepatitis and renal cortical infarctions. A high-grade malignancy was found in her mediastinum involving multiple lymph nodes. Tumor cells showed marked variability in size and shape, with nuclei having a characteristic 'salt and pepper' pattern by hematoxylin and eosin staining (Figure 2C). Immunostaining on the largest node was positive for CD56, synaptophysin, chromogranin (Figure 2D), low-molecular weight cytokeratin and pan-keratin but was negative for TTF-1, S100 and CD45. Transmission electron microscopy revealed intracytoplasmic membrane-bound neuroendocrine granules within tumor cells (Figure 2E). Overall, these findings were consistent with neuroendocrine carcinoma and did not support a diagnosis of melanoma, lymphoma or bronchogenic carcinoma. No definitive primary lesion was identified.

A post-mortem quantitative enzyme immunoassay for ADAMTS-13 activity using frozen serum demonstrated actually revealed mild deficiency prior to PLEX at 0.45 U/mL [2].

Discussion

Rarely is TMA the first manifestation of malignancy. In our case, a diagnosis of scleroderma renal crisis (SCR) was entertained, although in hindsight this was unlikely given the absence of hypertension or manifestations of scleroderma both clinically and on renal biopsy [3, 4]. Although our patient was positive for ANA in an anticentromere pattern, in cohorts of patients with scleroderma a positive anticentromere pattern is considered protective against SCR [4, 5].

Malignancy-associated TMA is most often seen with adenocarcinomas, specifically gastric, breast and lung [6]. While ADAMTS-13 deficiency is considered pathogenic in thrombotic thrombocytopenic purpura (TTP), ADAMTS-13 activity is most commonly normal in malignancy-associated TMA, suggesting an alternative or additional pathogenesis. Studt *et al.* [7] measured ADAMTS-13 levels in 308 patients with TMA, 14 of which had malignancy-associated TMA. Of the 14, only 2 had very low ADAMTS-13 levels compared to 60–77% of the studied patients with TTP. Our patient was actually deficient. However, given the discrepancy between various ADAMTS-13 assays as exemplified by our case, reports should be compared with particular consideration of the assay technique used.

Response to therapy also distinguishes malignancy-associated TMA from TTP. Unlike the 80% reduction in mortality seen with PLEX in TTP, response to PLEX in malignancy-associated TMA appears to be much lower [7, 8]. In a study by Francis *et al.* [9], none of the 10 patients with occult malignancy presenting as TMA who had received PLEX survived compared to a control group of 133 patients with TTP who had received PLEX and had a 30-day survival of 90%. A registry-based study by Lesesne *et al.* [6] demonstrated a median survival time of only 29 days in 37 patients with malignancy-associated TMA who received PLEX.

In summary, occult metastatic disease can present as acute kidney insufficiency and TMA and most often occurs in patients with adenocarcinomas. Malignancy-associated TMA has a worse prognosis than TTP and appears less responsive to PLEX, even when ADAMTS-13 activity is deficient. In TTP, a poor response to PLEX should prompt investigation into alternative diagnoses, of which occult neoplastic disease should be considered.

Conflict of interest statement. None declared.

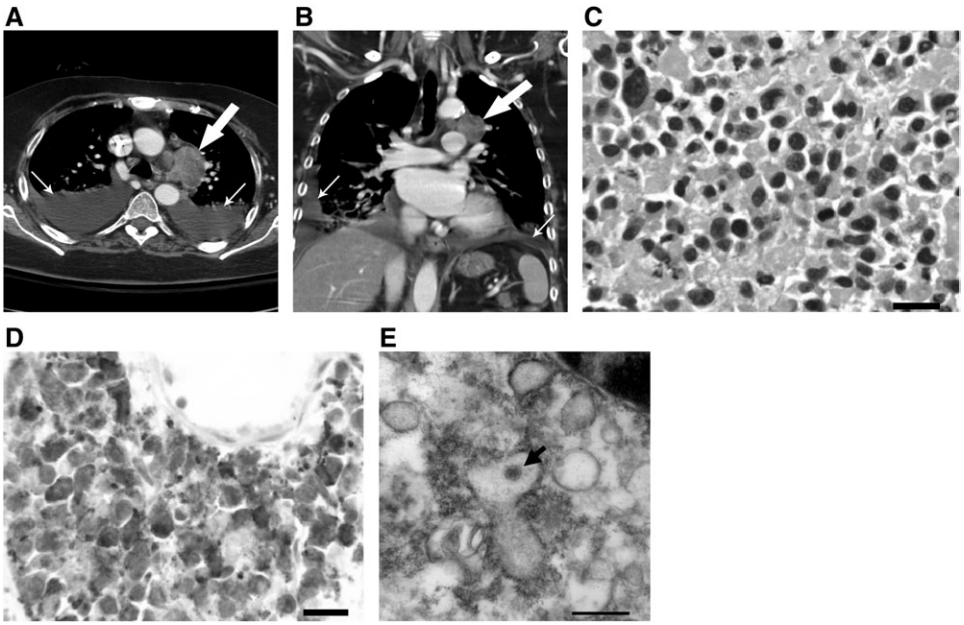

Fig. 2. Images of mediastinal tumor. (**A** and **B**) Contrast-enhanced axial and coronal computed tomography scans of the chest demonstrate a 3.8 × 3.6 × 2.5 cm heterogeneous aorticopulmonary window lymph node (thick arrow) and bilateral pleural effusions (thin arrows). (**C**) Poorly differentiated cells showing 'salt and pepper'-type chromatin pattern (hematoxylin and eosin stain; bar: 20 mm). (**D**) Immunostain shows tumor cells positive for chromogranin (brown color; hematoxylin counterstain; bar: 20 mm). (**E**) TEM shows membrane-bound granule at center (arrow) (bar: 500 nm). These features indicate neuroendocrine differentiation.

References

1. Rick ME, Austin H, Leitman SF *et al.* Clinical usefulness of a functional assay for the von Willebrand factor cleaving protease (ADAMTS 13) and its inhibitor in a patient with thrombotic thrombocytopenic purpura. *Am J Hematol* 2004; 75: 96–100
2. Kato S, Matsumoto M, Matsuyama T *et al.* Novel monoclonal antibody-based enzyme immunoassay for determining plasma levels of ADAMTS13 activity. *Transfusion* 2006; 46: 1444–1452
3. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med* 2009; 360: 1989–2003
4. Penn H, Howie AJ, Kingdon EJ *et al.* Scleroderma renal crisis: patient characteristics and long-term outcomes. *QJM* 2007; 100: 485–494
5. Penn H, Denton CP. Diagnosis, management and prevention of scleroderma renal disease. *Curr Opin Rheumatol* 2008; 20: 692–696
6. Lesesne JB, Rothschild N, Erickson B *et al.* Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. *J Clin Oncol* 1989; 7: 781–789
7. Studt JD, Kremer Hovinga JA, Alberio L *et al.* Von Willebrand factor-cleaving protease (ADAMTS-13) activity in thrombotic microangiopathies: diagnostic experience 2001/2002 of a single research laboratory. *Swiss Med Wkly* 2003; 133: 325–332
8. Tsai HM. Advances in the pathogenesis, diagnosis, and treatment of thrombotic thrombocytopenic purpura. *J Am Soc Nephrol* 2003; 14: 1072–1081
9. Francis KK, Kalyanam N, Terrell DR *et al.* Disseminated malignancy misdiagnosed as thrombotic thrombocytopenic purpura: a report of 10 patients and a systematic review of published cases. *Oncologist* 2007; 12: 11–19

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