Cholangiocarcinoma presenting with acquired thrombotic thrombocytopenic purpura confirmed by positive autoantibodies of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13

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To the Editor: Thrombotic thrombocytopenic purpura (TTP) is a type of life-threatening thrombotic microangiopathy (TMA) clinically characterized by severe thrombocytopenia, microangiopathic hemolytic anemia, and symptoms of regional ischemia/infarction including neurologic dysfunction and renal insufficiency.[1] Its diagnosis is confirmed by a low activity of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), a protease of von Willebrand factor (vWF), and a detectable level of its inhibitory autoantibodies. Most TTP patients suffer from acquired TTP secondary to infection, autoimmune diseases, pregnancy, drugs, and so on. However, acquired TTP is rarely the first manifestation of a solid tumor. Herein, we report a case of acquired TTP with underlying cholangiocarcinoma in an elderly woman treated with bortezomib.

A 66-year-old female patient was admitted with a 10-day history of fatigue and dull headache. Her blood platelet count was reduced dramatically to 2×10^9/L, with a hemoglobin level of 77 g/L. Schistocytes were found in her peripheral blood smear, and she had an elevated blood lactate dehydrogenase (LDH) level of 721 U/L and serum creatine level of 104 μmol/L (reference level: 45–84 μmol/L). Coomb test was negative. TTP was suspected and subsequently confirmed by a severe drop in plasma ADAMST13 activity (6%) and detectable ADAMST13 autoantibodies. Plasma ADAMST13 activity was measured by fluorescence resonance energy transfer assay (Molecular Devices Flexstation 3, San Jose, California, USA) using vWF86 peptide (a region from Q1599 to P1611C of vWF) as the substrate. Plasma ADAMST13 autoantibodies were measured by a mixing test where equal volumes of the patient's plasma and negative control plasma were mixed with normal pooled plasma respectively and incubated at 37°C. ADAMST13 autoantibodies were positive if the ADAMTS13 activity of the mixture containing patient's plasma was 25% to 75% of that of the mixture containing negative control plasma. The patient immediately received total plasma exchange and methylprednisolone. Subcutaneous bortezomib (1.3 mg/m^2, twice a week) was added 4 days later (along with plasma exchange) for four times due to her persistently low blood platelet count. Her blood platelet levels returned to 127×10^9/L, blood LDH 262 U/L, plasma ADAMST13 activity 119%, and the inhibitor in plasma undetectable. Her blood cytomegalovirus virus-DNA, blood Epstein-Barr virus-DNA, and serum antinuclear antibodies were negative. Computed tomography and magnetic resonance cholangiopancreatography showed a mass with nearby intrahepatic cholangiectasis [Figure 1]. A left hepatectomy was then performed, and the final histopathology revealed a cholangiocarcinoma (T1aM0N0). The patient died from tumor recurrence four months later with a normal blood platelet count.

Due to the evasive clinical differences between TTP and other kinds of secondary TMA in solid tumor patients,[2] we recommend the test for ADAMTS13 activity and the inhibitor level for the diagnosis of acquired TTP. Similar to our patient, an epiglottic squamous cell carcinoma

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000727

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Chinese Medical Journal 2020;133(12)
Received: 20-10-2019 **Edited by:** Qiang Shi

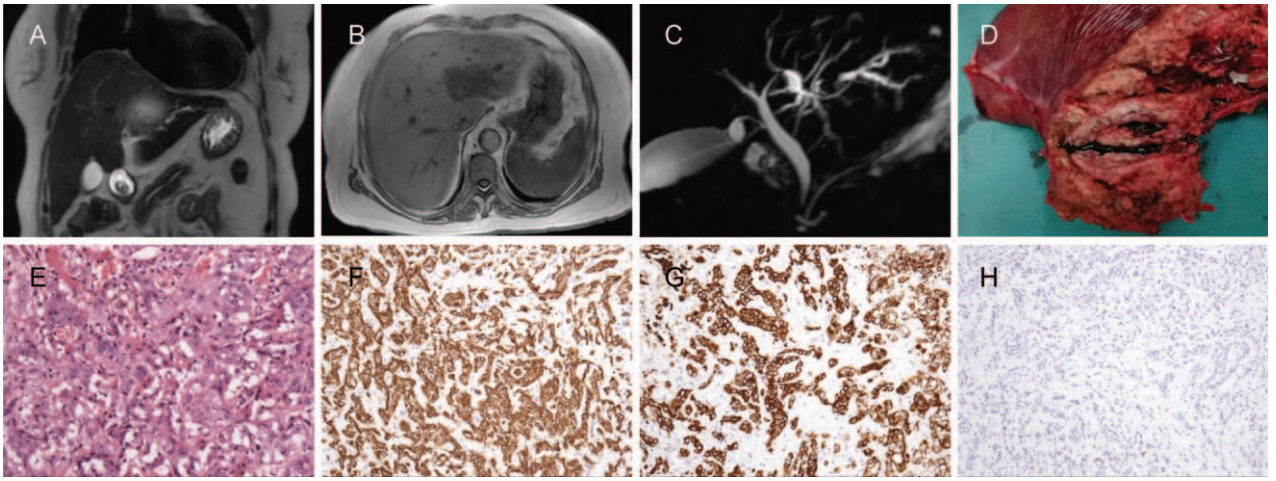

Figure 1: Magnetic resonance cholangiopancreatography, operative specimen, and pathologic findings. (A–C) Magnetic resonance cholangiopancreatography demonstrated the mass in the left lobe. (D) The operative specimen. (E) Hematoxylin/eosin staining of cholangiocarcinoma cells (original magnification, × 200). (F–H) Immunohistochemistry staining of cytokeratin 7 (+) (original magnification, × 100), cytokeratin 19 (+) (original magnification, × 100), and hepatocyte (−) tumor cells (original magnification × 100).

patient was also diagnosed as TTP (confirmed by ADAMTS13 activity) before tumor treatment,[3] indicating the role of solid tumor instead of drugs or surgery, the two reported causes of TTP,[1,2] in the pathogenesis. The mechanism of tumor-associated TTP remains elusive. Evidence showed that cytokines which inhibit ADAMTS13 activity, including interleukin-6, tumor necrosis factor-α, and interferon-γ, were increased in human tumor samples; a significant reduction of serum ADAMTS13 activity was also observed in tumor patients,[4] which might contribute to TTP onset. This concludes our case report of cholangiocarcinoma with the first manifestation as TTP confirmed by ADAMTS13 activity and its inhibitor.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patients understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Acknowledgement

The authors would like to thank Dr. Hao Cai for his work in the assessment of ADAMTS13 activity and plasma autoantibodies.

Conflicts of interest

None.

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How to cite this article: Li YT, Du HZ, Wang CY, Zhu TN, Pan BJ, Zhang L. Cholangiocarcinoma presenting with acquired thrombotic thrombocytopenic purpura confirmed by positive autoantibodies of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13. Chin Med J 2020;133:1495–1496. doi: 10.1097/CM9.0000000000000727