Other full case

Concurrent thrombotic thrombocytopenic purpura and immune thrombocytopenic purpura in a patient with metastatic neuroendocrine tumour successfully treated with rituximab-CVP

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Summary

We report a case of concurrent thrombotic thrombocytopenic purpura (TTP) and immune thrombocytopenic purpura (ITP) in a 63-year-old woman who had been receiving treatment with bevacizumab for metastatic neuroendocrine tumour (NET). At diagnosis, she had severe anaemia and thrombocytopenia with elevated lactate dehydrogenase and many schistocytes on the peripheral blood smear. She was treated with frequent fresh frozen plasma infusions and plasmapheresis with poor response. Later, she was found to have platelet surface glycoprotein antibodies in the serum and received four cycles of rituximab, vincristine, cyclophosphamide (rituximab-CVP) and steroids in addition to plasma therapy. The haemoglobin and platelet counts improved. To our knowledge, this is the first reported case of concurrent TTP and ITP in a patient with metastatic NET diagnosed while receiving bevacizumab therapy, who was successfully treated with the combination of rituximab, vincristine, cyclophosphamide and steroids.

BACKGROUND

Thrombotic thrombocytopenic purpura (TTP) and autoimmune (idiopathic) thrombocytopenic purpura (ITP) are two, typically distinct clinical entities that present independently¹ of each other. While the diagnosis of ITP is ordinarily made after the exclusion of other causes of thrombocytopenia, the diagnosis of TTP entails the presence of certain characteristics, including a microangiopathic haemolytic anaemia, thrombocytopenia and microvascular thromboses resulting in indiscriminate injury of the central nervous system, the kidney and other organs.² Additionally, a specific enzyme deficiency also allows differentiation between these two common acquired bleeding disorders; a severe deficiency of ADAMTS13 is frequently, but not always, demonstrated in TTP. Despite the usual independent occurrence of the two entities, ITP and TTP have been found to occur simultaneously, most often in HIV-positive patients.^{3–5} However, sequential or concurrent development of ITP and TTP has been reported in HIV-negative patients, suggesting dual autoimmune processes to which certain individuals are uniquely predisposed.¹ We present the case of a patient with a mixed ITP and TTP clinical picture, presenting with asymptomatic anaemia and thrombocytopenia found upon routine haematological analysis during treatment with bevacizumab (Avastin) for a previously diagnosed neuroendocrine tumour (NET). We provide a detailed clinical analysis in conjunction with a brief literature review.

CASE PRESENTATION

The patient is a 63-year-old Hispanic woman who was found to have a haemoglobin level of 6.4 mg/dl and a platelet count of 16 000/mm³ as an incidental finding during a follow-up visit. At that time, she was receiving bevacizumab and temozolomide every 2 weeks and octreotide long-acting release every 4 weeks for metastatic NET for 4 months. When she was diagnosed with NET and also during her treatment with bevacizumab, the complete blood count, lactate dehydrogenase (LDH), coagulation parameters and chemistry profile were within normal limits. At the follow-up visit, she was found to have pallor and jaundice, although she was totally asymptomatic. Further work-up showed an indirect bilirubin of 2.6 mg/dl, LDH of 4233 U/l, haptoglobin of <10 mg/dl, reticulocyte count of 8.3%, creatinine of 1.2 mg/dl and many schistocytes in the peripheral blood smear. Direct Coombs' test was negative and ADAMTS13 activity was normal. Disseminated intravascular coagulation (DIC) parameters were normal: prothrombin time (PT) 13.1 s, INR 1.12, activated partial thromboplastin time (aPTT) 27.4 s and a fibrinogen level of 353.34 mg/dl. Antinuclear antibodies and HIV serology were negative. CD 55 and CD 59 on leucocytes were normal. Upon admission, bevacizumab, temozolomide and octreotide were discontinued and she was started on plasmapheresis and fresh frozen plasma (FFP) infusions for the treatment of a presumptive diagnosis of TTP for 7 weeks; however, the low platelet count persisted between 10 000

and 20 000/mm³. Serum platelet surface glycoprotein antibodies came back positive against GPIIb/IIIa, GPIb/IX and GPIa/IIa. Consequently, she was started on 2 g/kg of intravenous immunoglobulins, 2 mg of vincristine and 40 mg of dexamethasone without any effect. Therefore, rituximab 375 mg/m² on day 1, cyclophosphamide 200 mg daily on days 1–4, vincristine on day 1, and dexamethasone 40 mg daily on days 1–4 were given every 3 weeks for a total of four cycles. Within 8 weeks of the initiation of rituximab, her platelet count increased to 84 000/mm³ and haemoglobin increased to 9.2 g/dl; LDH and reticulocyte count decreased to 265 and 2.1, respectively. At 1 year of surveillance, her haemoglobin and platelet counts are still within the normal range and she has not had any clinical signs or symptoms of TTP or ITP.

DISCUSSION

The diagnosis of TTP is suggested by a pentad of clinical features: thrombocytopenia, microangiopathic haemolytic anaemia, neurological and renal abnormalities, and fever. This uncommon but serious blood disorder is characterised by widespread platelet and von Willebrand factor (VWF)-rich thrombi in the capillaries and arterioles systemically.⁶ The mainstay of TTP treatment is plasma exchange and/or plasma infusion. Prior to the availability of this therapy, TTP was fatal in 90% of patients.⁷ As plasma exchange has proven efficacious in the treatment of TTP, the thresholds for clinical suspicion and when to initiate treatment have been lowered. Now, only thrombocytopenia and microangiopathic anaemia, without other apparent aetiology, are sufficient to make the diagnosis of TTP and begin appropriate therapy.²

In our patient, the aetiology of microangiopathic haemolytic anaemia and thrombocytopenia is unclear; underlying malignancy and treatment with bevacizumab could be the postulated mechanisms for microangiopathic development and immune dysfunction. Thrombotic microangiopathy can occur in almost any cancer but is seen more frequently with chemotherapy and metastases of adenocarcinoma of the pancreas, lung, prostate, stomach, colon, ovary, breast or unknown primary site.⁸ The hypercoagulable state of malignancy can lead to intermittent signs of DIC which can suggest a diagnosis of TTP; in our patient DIC was excluded due to normal PT, aPTT and fibrinogen values. Severe ADAMTS13 deficiency almost never occurs in cancer-associated thrombotic microangiopathy, where plasma exchange is ineffective.^{2 8}

Bevacizumab (Avastin) inhibits angiogenesis by blocking the vascular endothelial growth factor receptor on the surface of endothelial cells. It has been approved in various solid tumours including metastatic colorectal cancer, lung cancer and breast cancer.^{9–13} However, in the literature, thrombotic microangiopathy has been associated with bevacizumab when used in treatment for renal cell carcinoma.^{14 15} Several case reports of microangiopathic haemolytic anaemia have been documented in patients with solid tumours while receiving concomitant bevacizumab and sunitinib. Of the 25 cases described, five of 12 patients at the highest sunitinib dose level exhibited laboratory findings consistent with microangiopathic haemolytic anaemia and two were diagnosed with typical cardinal signs and symptoms of TTP including severe thrombocy-

topenia, anaemia, reticulocytosis, reductions in serum haptoglobin, schistocytes on peripheral smear, modest increases in serum creatinine levels and severe hypertension.^{16 17} The clinical features improve once the medications are discontinued.¹⁶ Therefore, the microangiopathic haemolytic anaemia and thrombocytopenia in this patient were not caused by bevacizumab.

Autoimmune or idiopathic thrombocytopenic purpura is a diagnosis of exclusion, made only after other causes of thrombocytopenia have been successfully ruled out. Although detection of platelet-associated antibodies is not a defining specific characteristic of ITP, the presence of these antibodies in the serum is consistent with an autoimmune mechanism of thrombocytopenia.^{1 18} While TTP and ITP rarely occur simultaneously, several studies have documented the concurrent or subsequent development of TTP and ITP in the same individual, suggesting a possible immunological component in TTP.¹ Although both entities can manifest similarly, the presence of the enzyme ADAMTS13 can aid in the differentiation of TTP from ITP. A disintegrin-like and metalloprotease with thrombospondin type-1 motif, ADAMTS13 is an enzyme that circulates in plasma and cleaves VWF in a shear-dependent manner.¹⁸ Deficient VWF cleavage leads to the accumulation of superactive forms of VWF and VWF-platelet aggregation, explaining why a severe deficiency of ADAMTS13 causes the disseminated microvascular thromboses characteristic of TTP.^{2 19} The accumulation of superactive VWF also helps explain why plasmapheresis is an established and efficacious treatment modality for cases of ADAMTS13 deficient TTP.² However, severe ADAMTS13 deficiency occurs in only 43–72% of patients with idiopathic TTP.^{2 19} A normal level of ADAMTS13 does not exclude the diagnosis of TTP. Although the mechanism of response is not clear, plasma exchange remains the mainstay of therapy for patients with idiopathic TTP.²

Rituximab is a human/murine chimeric monoclonal antibody that specifically targets the transmembrane protein CD20 of B cells; when bound, it leads to a significant depletion of peripheral B cells. This agent has been used in the treatment of rheumatoid arthritis, systemic lupus erythematosus, ITP, multiple sclerosis, autoimmune haemolytic anaemia, TTP, graft versus host disease, clotting factor inhibitor, Graves' disease and B-cell lymphomas.^{20–23} Successful in the treatment of haematological autoimmune disorders, rituximab is only mildly toxic in comparison to combination chemotherapy, which may yield more side effects. However combination chemotherapy (ie, cyclophosphamide, rituximab and steroids) can be more effective when compared to monotherapy with steroids or rituximab.^{24 25} In cases of acquired haemophilia, the combined regimen has proven to result in greater odds of remission and lower odds of death when compared to both dual therapy and steroids alone.²⁵ While it has been used as therapy for patients with refractory ITP and TTP, to our knowledge there have been no reported cases of concurrent TTP and ITP treated with rituximab. We present the first case of concurrent TTP and ITP in a patient with metastatic NET who was successfully treated with rituximab-CVP. Whether the combination of rituximab with CVP is more effective or not remains to be studied further and confirmed.

Learning points

- ▶ Thrombotic thrombocytopenic purpura (TTP) and immune thrombocytopenic purpura (ITP) are common acquired bleeding disorders that more often occur independently.
- ▶ Cases of simultaneous TTP and ITP have been reported and have mostly occurred in HIV-positive patients.
- ▶ However, to our knowledge, we present the first case of concurrent TTP and ITP in a patient with metastatic neuroendocrine tumour while receiving bevacizumab therapy.
- ▶ Also, although the patient had been refractory to fresh frozen plasma exchange and infusion, she improved haematologically with rituximab-CVP therapy.

Competing interests None.

Patient consent Obtained.

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