CASE REPORT

Persistent thrombocytopaenia in a young man with splenomegaly, rebound thrombocytosis after splenectomy and subsequent pulmonary embolism: splenic littoral cell angioma and associated events

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SUMMARY

Littoral cell angioma (LCA) is a rare endothelial cell neoplasm in the spleen. Although many cases of LCA are asymptomatic, some present with signs and symptoms related to splenomegaly, whereas others manifest with haematological abnormalities, including anaemia and/or thrombocytopaenia (ie, hypersplenism). We report a case of LCA presenting with chronic thrombocytopaenia, probably due to splenic sequestration of platelets or phagocytosis of platelets by neoplastic cells. Following therapeutic splenectomy, the patient suffered from a marked rebound thrombocytosis and subsequently developed pulmonary embolisms. He was treated with anticoagulant therapy combined with antiplatelet therapy, and his symptoms were quickly resolved. This case emphasises an exclusion of primary splenic disorders in patients with chronic thrombocytopaenia, especially in those with splenomegaly and the contemplation of thromboembolism prophylaxis postsplenectomy.

splenectomy provides the specimen for pathological diagnosis, and the platelet count returns to normal after surgery.

CASE PRESENTATION

Clinical presentation and disease course

A 33-year-old man was found to have thrombocytopaenia (platelet count, 34 000/ μ L) during routine physical examination. An abdominal ultrasound showed mild splenomegaly (14 cm in longitudinal dimension; the patient's height was 1.65 m) and a bone marrow biopsy revealed normocellular marrow with mildly increased megakaryocytes; otherwise, the morphological findings of the bone marrow were unremarkable. Other laboratory tests, including platelet-associated antibodies, were within normal limits. The patient was empirically treated with prednisone and, later, intravenous

BACKGROUND

We report an unusual case of splenic littoral cell angioma (LCA) that presented as insidious thrombocytopaenia and was empirically treated as immune-related thrombocytopaenia purpura (ITP), with partial response. LCA was identified only on repeat abdominal imaging prior to therapeutic splenectomy. Following the splenectomy, our patient had severe rebound thrombocytosis, which ostensibly led to a pulmonary embolism (PE). Splenic LCA is a rare vascular endothelial cell neoplasm derived from the cells that line the red pulp sinuses in the spleen.¹ This neoplasm is sometimes associated with other clinical conditions, including malignant neoplasms, such as adenocarcinoma of the colon, liver, pancreas, thyroid, kidney, ovary and testes, or even lymphoma,^{2–6} and with non-neoplastic clinical conditions such as inflammatory bowel disease.⁷ In terms of clinical course, the majority of patients are asymptomatic, with many tumours noted incidentally on radiographic scanning for some other purpose.^{8–9} Some patients present with constitutional symptoms such as fatigue and fever, or with symptoms related to hypersplenism, including abdominal pain and anaemia,^{10–13} and thrombocytopaenia.^{14–15} Rare cases have been reported to resemble ITP which responds to steroid therapy. In some cases,

Figure 1 CT of the abdomen demonstrates enlarged spleen with multiple round hypodense lesions (arrow). (A) Transverse (cross) section; (B) coronal section.

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immunoglobulin (IVIG), and responded to some extent, but his platelet counts declined on tapering of the prednisone dosage. Three years later, the patient was started on rituximab due to persistent thrombocytopenia. Despite an initial response, he experienced a slow decline in platelet counts over the next year, and alternative management options were discussed, leading to the decision to perform a splenectomy. Before the procedure, a repeat ultrasound revealed splenomegaly with two round or oval homogeneously hypoechoic foci, and a CT scan demonstrated multiple round hypodense lesions (figure 1A, B), concerning for lymphoma or metastatic tumour. The patient subsequently underwent splenectomy, and a diagnosis of splenic littoral angioma was rendered per histopathological features.

Following the surgery, the patient's platelet counts rapidly increased, reaching 1 000 000/ μ L by 1 week after the splenectomy. At this point, the patient experienced a sharp pain below his right shoulder blade, progressive dyspnoea, fever and sweating. A CT pulmonary angiogram demonstrated pulmonary emboli (PE) within the segmental and subsegmental arteries of the right middle and lower lobes. At the time, his plasma D-dimer level was markedly increased at 3004 ng/mL (normal range, <500 ng/mL), as was his plasma fibrinogen level (721 mg/dL; normal range, 213–435 mg/dL), whereas the prothrombin time and activated partial thromboplastin time were within normal ranges. The patient was immediately treated with enoxaparin (Lovenox), and later switched to rivaroxaban (Xarelto), in addition to acetylsalicylic acid, 81 mg/day. His symptoms quickly resolved with the anticoagulant therapy combined with antiplatelet therapy, despite persistent thrombocytosis. The D-dimer level began to decrease 1 month after anticoagulant/antiplatelet treatment, and returned to normal another month later. The platelet count declined approximately in step with the D-dimer; however, at the time of writing, it was sustained at a level of 500 000–600 000/ μ L (figure 2).

Pathological findings

The patient's spleen weighed 310 g, and sectioning revealed four round, haemorrhagic, spongy, cystic nodules ranging from 0.5 cm to 5.5 cm in diameter. The cut surface of the nodules was red-brown in colour and appeared incompletely encapsulated. The H&E stained section showed a haphazard arrangement of anastomosing vascular channels with an ill-defined border with the uninvolved splenic tissue (figure 3A). The cells lining the vascular channels (neoplastic endothelial cells)

appeared plump and cuboidal, with many containing large intracytoplasmic eosinophilic globules, and some having yellow-brown pigmentation (hemosiderin). No mitotic activity was visible among the neoplastic cells. The lumina contained abundant desquamated cuboidal cells and macrophages, with some macrophages displaying phagocytic activities and others loaded with hemosiderin (figure 3B). A Prussian blue stain showed increased iron particles in the tumour. Immunohistochemically, the neoplastic cells expressed CD31 (figure 3C), patchy CD34, ERG, CD68, CD21 and von Willebrand's factor/factor 8-related antigen (figure 3D). These stains highlight the anastomosing pattern of the neoplastic growth. Anti-CD163 stained many histiocytes within the vascular lumina of the tumour. The neoplastic cells were negative for WT-1, CD8 (figure 3E) and pancytokeratin. Anti-CD61 highlighted abundant platelets and platelet granules in the vascular lumina and cytoplasm of the tumour cells (figure 3F). MIB-1 (Ki-67) staining was positive in rare nuclei among the neoplastic endothelial cells. The diagnosis of splenic littoral angioma was thus established.

DISCUSSION

LCA is a neoplastic proliferation of vascular endothelial cells unique to the spleen. It was initially described by Falk *et al*¹ during the 1990s, and was considered histiocytic in cell origin at that time because of its positivity for CD68 and phagocytic activities. It has been reported that LCA is associated with malignant neoplasms including both haematolymphoid^{5 6} and non-haematological neoplasms,^{2–4} and with chronic inflammatory bowel disease such as Crohn's disease.⁷ The clinical presentation of LCA ranges from asymptomatic⁸ to that of symptoms related to mass effects including left upper quadrant abdominal pain, abdominal distension, etc.^{1 8} Some cases have been reported presenting as anaemia^{11–13} and/or thrombocytopenia.^{14 15} In the present case, the patient initially presented with thrombocytopenia without clear aetiology, and, due to his partial response to immunomodulatory therapy, the thrombocytopenia was reasonably considered immune-mediated in aetiology. The well-defined lesions in the spleen were unexpectedly identified by radiographic scans before therapeutic splenectomy for 'immune-mediated' thrombocytopenia. Although the diagnosis of LCA should be based on histological and immunohistochemical features, radiological examinations often suggest the vascular nature of this tumour, given its hypoattenuated or hypointense lesions on CT, MRI, or on sonographic imaging.^{2 3 7 8 10 11 14} Nonetheless, the differential diagnosis usually includes primary splenic lymphoma, other vascular tumours such as haemangioma, haemangioendothelioma, lymphangioma, haemangiopericytoma, angiosarcoma and peliosis, and certain infectious processes.

The precise origin of the neoplastic cells in LCA is unclear, as they share some, but not all, immunophenotypic characteristics with normal sinusoid-lining littoral cells. The endothelial cells in LCA express CD31 and factor VIII-related antigen as well as CD68 and CD21 in a majority of the cases. The neoplastic cells are usually negative for CD34 and CD8.^{16 17} The latter antigen is uniquely expressed by the cells lining the splenic sinuses, and typically highlights the red pulp architecture in normal splenic tissue. Therefore, the negativity for CD8 argues against the littoral cell origin in LCA. Interestingly, although the histological appearance of the tumour in our case was classic for LCA, it did express patchy, moderate CD34, in contrast with the CD34-negative normal littoral cells. On the other hand, the histiocytic marker profile CD68+/CD163 is consistent between LCA and normal littoral cells. O'Malley *et al* recently reported that including Ets-related gene (ERG) and Wilms tumour-1

Figure 2 Dynamic changes of platelet counts during the disease course with the inset showing a detail of platelet changes after splenectomy. An arrowhead indicates the date of surgery.

Figure 3 Histopathology of splenic littoral cell angioma. (A) Low magnification of a section demonstrating the border between the tumour and normal splenic tissue. Note the haphazard arrangement of anastomosing vascular channels and adjacent normal splenic tissue in the upper right corner. H&E stain, $\times 40$. (B) Higher magnification of the same section. Note the plump cuboidal cells lining the vascular channels, the cells with intracytoplasmic eosinophilic globules, and the intraluminal cuboidal cells and macrophages with hemosiderin pigment. H&E stain, $\times 600$. (C) CD31 stain, $\times 40$. (D) von Willebrand factor/stain, $\times 20$. Note the anastomosing vascular channels in the tumour highlighted by the two endothelial cell antigen stains, and normal splenic tissue in the right upper corner. (E) CD8 stain, $\times 40$. Note negative stain in the tumour and normal splenic sinuses highlighted by the stain (right upper corner). (F) CD61 stain, $\times 200$. Note the platelet granules within the endothelial cells.

(WT-1) could contribute to a distinction between LCA and other splenic vascular lesions in the differential, such as hamartomas, haemangiomas and sclerosing angiomatoid nodular transformation, with LCA being positive for ERG and negative for WT-1. ERG is nearly universally positive in endothelial tissue, including normal and tumour tissue, with the exception of peliosis, whereas WT-1 is positive in normal endothelium and most related tumours, but negative in LCA and cavernous haemangioma.¹⁶ Serendipitously, there is no real histological overlap between cavernous haemangioma and LCA. Of note, normal LC express WT-1, thus fuelling the controversy over the accuracy of the name LCA. Nevertheless, on balance, the mixed endothelial-histiocytic phenotypes of LCA and LC are more similar than they are disparate, and some immunophenotypic differences may reflect the underlying mechanisms of neoplasia rather than a different cell of origin.

Interestingly, the CD61 immunostain in the current case highlighted numerous platelet granules within the neoplastic cells, suggesting thrombophagocytosis by the neoplastic cells as a cause of chronic thrombocytopaenia in the patient, although the sequestration of platelets in the enlarged spleen could be an alternative explanation.

In the published cases presenting with thrombocytopaenia and/or anaemia, the cytopenias typically resolved after splenectomy.^{11 12 14 15} In our patient, the platelet count increased rapidly after splenectomy, to more than $1\,400\,000/\mu\text{L}$, consistent with severe postsplenectomy reactive thrombocytosis. Reactive thrombocytosis has been observed in 75–82% of patients with splenectomy, and it resolves spontaneously

without complication in the majority of cases, over 2–3 months. Of these, 5% have been reported to develop TE, including rare cases of PE.^{18–20} In our case, the postsplenectomy thrombocytosis was sustained over $1\,000\,000/\mu\text{L}$ for approximately 6 weeks before gradually decreasing to $500\,000\text{--}600\,000/\mu\text{L}$. One week after surgery, while at the peak of thrombocytosis, our patient suffered from PE, diagnosed with angiographic CT, and was treated accordingly with resolution of symptoms. According to the literature, the risk for TE correlates with the extent of reactive thrombocytosis, and the incidence further increases if patients have additional risk factors, including preceding surgery.²⁰ It appears that the most common indications for splenectomy, such as hereditary spherocytosis, thalassaemia, sickle cell diseases and other red blood cell disorders, are associated with a higher prevalence of TE after splenectomy. Hirsh and Dacie reported a retrospective analysis of 80 cases of splenectomy for red cell survival defects, and demonstrated 13% TE associated with postsplenectomy thrombocytosis.²¹ The authors did suggest that additional factors likely contribute to the events, because a significant number of patients in their series had no evidence of thromboembolic events despite persistent thrombocytosis. Other hypothetical mechanisms include hypercoagulability, platelet activation, disturbance of vascular endothelium and altered serum lipid profiles. Among these hypotheses, hypercoagulability mediated by postsplenectomy platelet activation, and circulating abnormal red blood cells or their components, have garnered considerable attention.²⁰ However, as suggested, clinical TE may result from a combination of the aforementioned aetiologies following splenectomy.

The evidence guiding postsplenectomy TE prophylaxis is minimal. Although the risk of TE postsplenectomy is estimated to be 10%,²² the majority of splenectomies are performed for a primary haematological disorder. In particular, in the thalassaemia literature, where rates of postsplenectomy TE may be as high as 30%, at least short-term prophylaxis with unfractionated or low-molecular-weight heparin is recommended,²³ although there are no suggestions for how long 'short-term' actually is. One small series of patients with significant clinical similarities to our patient seems to suggest longer than 30-day prophylaxis, particularly when there is very high thrombocytosis (ie, over 1 000 000/ μ L).²² Despite extending their prophylaxis to 30 days, these authors report TE in one patient on day 35 postsplenectomy.

In summary, splenic LCA may be associated with chronic thrombocytopaenia due to splenic sequestration of platelets or phagocytosis of platelets by neoplastic cells, and splenectomy can cause rebound thrombocytosis with a risk of thromboembolism. The present case emphasises an exclusion of primary splenic disorders in patients with chronic thrombocytopaenia, especially in those with splenomegaly, before considering an immune aetiology. Given that a life-threatening thromboembolism, such as PE, may occur, a prophylactic anticoagulant therapy and/or antiplatelet therapy may be needed for those with marked rebound thrombocytosis to prevent thromboembolic events, although there is no established standard prophylaxis for thromboembolism after splenectomy.

Patient's perspective

I was diagnosed with and treated for ITP in 2010, after my GP noted a very low platelet count. I then went through a typical course of treatment for ITP (steroids—multiple times, IVIGs, Rituximab) as well as several different diagnostic tests (scans, bone marrow biopsy, etc). I generally maintained a resistance to splenectomy as treatment. It seemed like a stroke of luck that my haematologist ordered another scan of my spleen and discovered what we now know was an angioma. I resigned myself to splenectomy (essentially running out of choices!) and the result has me currently in remission from all ITP symptoms.

Learning points

- Primary splenic causes of thrombocytopaenia should be ruled out, particularly when there is splenomegaly.
- Littoral cell angioma of the spleen may primarily sequester or destroy platelets and manifest as thrombocytopaenia.
- Severe postsplenectomy reactive thrombocytosis may persist for several weeks to months after surgery.
- There is a significant risk of thromboembolism associated with postsplenectomy thrombocytosis, suggesting the development of guidelines for standard anticoagulant prophylaxis.

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