CASE REPORT

Splenectomy complicated by sustained extreme thrombocytosis and extensive portosplenomesenteric vein thrombosis in pyrimidine 5'-nucleotidase deficiency

Hassan A Al-Jafar,¹ Ali Taqi,² John Patrick Madda,³ Thamer A Abdullah⁴

¹Department of Haematology, Amiri Hospital, Kuwait City, Kuwait

²Department of Surgery, Amiri Hospital, Kuwait City, Kuwait

³Department of Histopathology, Amiri Hospital, Kuwait City, Kuwait

⁴Department of Radiology, Amiri Hospital, Kuwait City, Kuwait

Correspondence to

Dr Hassan A Al-Jafar,
cbc9@hotmail.com

SUMMARY

Reactive and redistributional thrombocytosis is a well-known postsplenectomy occurrence. Usually it is transient and it rarely reaches extreme levels. We report a rare case of haemolytic anaemia where splenectomy was carried out following trauma to a massively enlarged spleen and was followed by extreme sustained thrombocytosis associated with extensive portal, splenic and mesenteric vein thrombosis despite standard antithrombotic prophylaxis.

BACKGROUND

Splenectomy is a common surgical procedure; it is performed 35 000 times annually in the USA alone.¹ It may be performed for therapeutic purposes in certain congenital haemolytic anaemias and other haematological disorders, and may also be performed as a diagnostic tool in storage diseases, for example in Niemann-Pick disease. Splenectomy may also be required for splenic rupture following trauma. In addition, blunt trauma to a massively enlarged spleen carries the risk of delayed splenic rupture, as described by Perasalo in 1949²; this can occur over a long time-span, ranging from less than a month to several years, and can be an indication for splenectomy.^{3, 4}

Thrombocytosis, defined as a platelet count of more than $450 \times 10^9/L$, may be primary or secondary. Primary causes include congenital cases and haematological neoplasms, such as essential thrombocythaemia. Secondary cases include reactive thrombocytosis (RT) and redistribution of platelets in hyposplenism. Causes of secondary thrombocytosis include non-haematological neoplasms, chronic inflammatory disorders, infections, iron deficiency anaemia and chronic blood loss. The term sustained thrombocytosis has been used to refer to thrombocytosis of more than 2 weeks duration. Extreme thrombocytosis has been defined as a platelet count $>1000 \times 10^9/L$, a finding which is demonstrated in only 2–5.8% of patients presenting with thrombocytosis.⁵

Portal vein thrombosis is a recognised complication of splenectomy. Studies suggest that it occurs most often when thrombocytosis is due to a haematological neoplasm rather than when it is reactive or redistributional.⁶ This patient was diagnosed postoperatively to have pyrimidine 5'-nucleotidase (P5'N) deficiency. This type of rare haemolytic

anaemia could be the reason of the successive events of sustained extreme RT and portomesenteric venous thrombosis postsplenectomy although it was not reported previously.

P5'N is a rare congenital haemolytic anaemia, fewer than a hundred cases having been diagnosed worldwide.⁷ P5'N deficiency usually causes mild-to-moderate haemolytic anaemia with a moderate enlargement of the spleen. It can cause neonatal jaundice and gallstones. Occasional blood transfusions may be needed. Patients with P5'N deficiency should be monitored with regard to the iron status, particularly after splenectomy as in some cases serum ferritin level increased postsplenectomy.⁸

CASE PRESENTATION

A 21-year-old woman had anaemia and severe jaundice since birth. She had required immediate blood transfusion at birth but thereafter had needed only infrequent transfusions. She had a cholecystectomy at the age of 15 because of gallstones. At presentation she had massive splenomegaly, 23 cm by abdominal ultrasound, with mild hepatomegaly. She had no other thrombotic risk factors. Before splenectomy her laboratory investigations showed haemoglobin (Hb) concentration 81 (120–150) g/L, reticulocytes 13.7% (0.5–2.5%), mean corpuscular volume (MCV) 94 (83–101) fL, mean corpuscular haemoglobin (MCH) 32 (27–32) pg, mean cell haemoglobin concentration (MCHC) 335 (315–345) g/L, red cell distribution width (RDW) 21.3% (11.6–14), white cell count $3.8 (4-10 \times 10^9/L)$, platelets $123 (150-410 \times 10^9/L)$ and serum ferritin 190.4 (11–306.8) ng/mL. Blood film morphology showed normochromic normocytic anaemia with basophilic stippling, normal leucocyte and platelets morphology (figure 1).

A direct antiglobulin (Coombs) test was negative. Normal results were obtained for Hb electrophoresis, Hb H preparation, glucose-6-phosphate dehydrogenase assay, coagulation profile, immunophenotyping (CD55 and CD59) and Fluorescein-labeled proaerolysin (FLAER) test for paroxysmal nocturnal haemoglobinuria, osmotic fragility and hepatitis serology. Renal function, total protein and albumin were normal; bilirubin 120 (3–25) $\mu\text{mol/L}$, direct bilirubin 8 (1.7–8.6) $\mu\text{mol/L}$, alanine aminotransferase 68 (10–60) IU/L, aspartate aminotransferase 81 (10–42) IU/L, lactate dehydrogenase

CrossMark

To cite: Al-Jafar HA, Taqi A, Madda JP, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-201061

Figure 1 Basophilic stippling in the peripheral blood smear.

(LDH) 1136 (90–248) IU/L and urate 719 (150–450) $\mu\text{mol/L}$. A bone marrow aspirate and trephine biopsy conducted to investigate the cause of the unexplained massive splenomegaly showed a hyperactive bone marrow with trilineage hyperplasia and also showed foamy macrophages. Immunophenotyping and cytogenetic analysis on a bone marrow aspirate were normal. Three months after presentation the patient was involved in a serious road traffic accident; there was no evidence of intra-abdominal bleeding (figure 2).

Splenectomy was performed because of the risk of delayed rupture following blunt trauma to a massively enlarged unhealthy spleen with persistent left hypochondrial pain and tenderness. Histopathology showed an abnormal congested spleen, extramedullary haemopoiesis and expansion of the red pulp. Some large foamy histiocytes were present, raising the possibility of Niemann-Pick disease. Five days after surgery, she was discharged on prophylactic daily subcutaneous enoxaparin 40 mg daily with platelet count being $660 \times 10^9/\text{L}$. On day 13, she visited surgical outpatient department where she was quite well; a liver biopsy was performed to further investigate the foamy histiocytes but showed only a non-specific inflammatory reaction with mild steatosis. On day 20, she contacted her treating doctor reporting of back pain and was advised to attend the hospital immediately; she did this late the next morning. She was still on prophylactic enoxaparin 40 mg daily. Doppler ultrasound showed acute extensive portosplenomesenteric venous thrombosis (PSMVT) and mild hepatomegaly. Platelet count was $1780 \times 10^9/\text{L}$. Plateletpheresis was performed and the patient was then admitted to the intensive care unit for actilyse thrombolytic therapy, which was continued for 7 days.

Figure 2 The suspicious foamy cells in the trephine biopsy.

Hydroxycarbamide 2 g twice daily, aspirin 81 mg and allopurinol 200 mg were also prescribed. After 1 week, a therapeutic dose of enoxaparin was added. Two weeks later, she developed severe skin rashes, which subsided when hydroxycarbamide was replaced by anagrelide 1 mg twice daily; this was also stopped after 10 days because of severe palpitations. After 7 days on low-molecular weight heparin, oral coumadin 4 mg daily was started to maintain the international normalised ratio (INR) initially between 3 and 3.5. The patient was discharged on once daily oral folic acid 5 mg, aspirin 81 mg and coumadin 4 mg. She remains on this therapy 19 months later. At the time of splenectomy, the specific cause of the splenomegaly and the haemolytic anaemia was not known. Subsequently the presplenectomy film was reviewed and a diagnosis of P5'N deficiency was suggested on the basis of marked basophilic stippling. Severe deficiency was subsequently confirmed with both heterozygous parents showing moderate deficiency. Assay results were 1 nmol/h/mg Hb in the patient and 4 and 6, respectively, in her parents (normal range 9–20).⁹

Fourteen months following splenectomy, Doppler and CT studies showed homogeneous enhancement of the portal vein with no evidence of a filling defect. There were multiple collaterals around the portahepatis and the proximal superior mesenteric vein. The distal proximal superior mesenteric vein appeared patent. There was mild hepatomegaly.

Nineteen months postsplenectomy the patient had a moderate improvement in Hb and the LDH is now normal. The reticulocyte count and bilirubin are not overall very different from pre-splenectomy. The laboratory results are Hb 91 g/L, reticulocytes 10%, MCV 112 fL, MCH 36 pg, MCHC 320 g/L, RDW 17.3%, white cell count $11.2 \times 10^9/\text{L}$, platelets $1038 \times 10^9/\text{L}$. Biochemical results show normal liver enzymes, renal function, thyroid function test, total protein and albumin but high total bilirubin 117 $\mu\text{mol/L}$, direct bilirubin 9 (1.7–8.6) $\mu\text{mol/L}$, urate 472 $\mu\text{mol/L}$ and ferritin 525 ng/mL. No *JAK2* mutation was detected. Both *HFE* genes were normal the PC282Y genotype: CC and RH63D genotype: HH. The blood film is leucoerythroblastic with some giant platelets and basophilic stippling. The patient continues on once daily oral aspirin 81 mg, coumadin 4 mg to keep the INR at 2–3 and folic acid 5 mg.

INVESTIGATIONS

- ▶ Complete blood count
- ▶ Reticulocytes
- ▶ Blood film
- ▶ Hb electrophoresis
- ▶ A. Hb H preparation
- ▶ Glucose-6-phosphatase assay
- ▶ Coomb's test
- ▶ Osmotic fragility
- ▶ Coagulation profile
- ▶ Hepatitis serology
- ▶ Serum ferritin
- ▶ Vitamin B₁₂ and folate
- ▶ Liver function test, urate, LDH
- ▶ Renal function test
- ▶ CD55, CD59
- ▶ FLAER test
- ▶ Bone marrow and trephine biopsy
- ▶ Immunophenotyping study
- ▶ Cytogenetics study
- ▶ AK2 mutation test
- ▶ Spleen histopathology
- ▶ Liver histopathology

- ▶ Abdominal X-ray
- ▶ Abdominal ultrasound
- ▶ Abdominal Doppler study
- ▶ Abdominal CT
- ▶ P5'N assay
- ▶ Heinz bodies
- ▶ HFE genotyping

DIFFERENTIAL DIAGNOSIS

Non-spherocytic haemolytic anaemia (the patient was without diagnosis for more than 22 years although she sought diagnosis in four countries before we got her diagnosis confirmed in London).

TREATMENT

- ▶ Aspirin
- ▶ Coumadin
- ▶ Zyloric acid
- ▶ Hydroxycarbamide
- ▶ Anagrelide

OUTCOME AND FOLLOW-UP

- ▶ The outcome of this splenectomy is unexpected extensive sustained thrombocytosis for more than 19 months.
- ▶ The patient developed extensive PSMVT although she was on prophylactic anticoagulants.
- ▶ We are still assessing the benefit of splenectomy on her from a haematological point of view because this case is very rare and some cases benefit from splenectomy while others do not.
- ▶ The patient is still under follow-up regarding her sustained extreme thrombocytosis. The extreme thrombocytosis is not yet controlled.
- ▶ Serum ferritin level has to be monitored in such patients.

DISCUSSION

The results of splenectomy in patients with congenital haemolytic anaemia vary according to the underlying defect. In hereditary spherocytosis, splenectomy is highly efficacious whereas, in hereditary stomatocytosis, splenectomy is considered contraindicated because it is ineffective and is often followed by thrombotic complications.¹⁰ P5'N deficiency anaemia occupies an intermediate position; splenectomy is not generally of much benefit although improvement has been reported in some patients.¹¹ In this case splenectomy was not performed for the haemolytic anaemia per se but because of abdominal blunt trauma to a massively enlarged spleen to avoid delayed splenic rupture, which is a potentially life-threatening complication. Five per cent of post-traumatic splenic ruptures can be missed, even by CT.¹² It might be not enough to rely on imaging alone because 18% of spontaneous post-traumatic splenic ruptures are found to have histopathological findings which could have contributed to the rupture.¹³ When splenectomy is effective at ameliorating haemolysis, postsplenectomy thrombocytosis is usually only moderate and the risk of thrombosis is not high. However when there is ongoing haemolysis, extreme thrombocytosis may occur and persist, with a much higher thrombotic risk.¹⁴ RT is generally felt to be a self-limiting process which resolves with resolution of the underlying disorder.¹⁵ Generally speaking RT is not a risk factor for thromboembolic complications although it is a common complication after splenectomy especially in patients with splenomegaly. In such situations a high index of suspicion is necessary for early diagnosis and prompt anticoagulation for successful outcome.¹⁶ Prophylaxis for thrombosis is usually by enoxaparin 40 mg for 6 days on

average.¹⁷ In this patient although prophylactic anticoagulation was given for a longer time, extensive PSMVT nevertheless had occurred. This patient shows unusually long-term sustained extreme thrombocytosis, which could be explained by the persistent haemolysis. The urate level was high before splenectomy and stayed high, indicating ongoing bone marrow hyperactivity. The patient is considered to still have a high risk of thrombosis, so coumadin and aspirin therapy are therefore being continued. The normal HFE genotype in this patient means that there is no potential additional risk factor for iron accumulation although the investigations showed marked increase in serum ferritin postsplenectomy as has been seen in other P5'N-deficient cases and in other enzymopathies.¹⁸

CONCLUSION

When splenectomy is effective at ameliorating haemolysis, post-splenectomy thrombocytosis is usually only moderate and the risk of thrombosis is not high. However, when there is ongoing haemolysis, extreme thrombocytosis may occur and persist, with a much higher thrombotic risk. The criteria for splenectomy in P5'N deficiency are not clear because of the rarity of the condition. RT is often self-limiting but prophylactic anticoagulation should be offered postsurgery especially when splenectomy is performed for massive splenomegaly. There should be a high suspicion of postsplenectomy thrombosis in patients who have had massive splenomegaly.

Learning points

- ▶ Blood film is still a very important tool of diagnosing the most rare haematology disorders.
- ▶ Postsplenectomy in splenomegaly cases is more liable for thrombocytosis.
- ▶ Postsplenectomy venous thromboembolic events venous thromboembolism must be expected and need prompt anticoagulant therapy.
- ▶ Postsplenectomy awareness to the patient to attend the hospital for regular outpatient department visits and for any unusual symptoms.
- ▶ All measures should be taken to differentiate reactive thrombocytosis from primary thrombocytosis for proper management.

Acknowledgements The authors would like to thank Emilia Escuredo and Guy's and St. Thomas Hospitals, London for diagnostic tests identifying pyrimidine 5'-nucleotidase enzyme level deficiency, to TDL Genetics for haemochromatosis genotyping and to Al Bisher & Al Kazemi Medical laboratory, Kuwait for their professional medical laboratory work and transporting this patient's samples to London.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Krauth MT, Lechner K, Neugebauer EA, *et al.* The postoperative splenic/portal vein thrombosis after splenectomy and its prevention an unresolved issue. *Haematologica* 2008;93:1227–32.
- 2 Khan SA, Muhammad I, Laabei F, *et al.* An unusual presentation of non pathological delayed splenic a case report rupture. *Cases J* 2009;2:6450.
- 3 Chan CKMChiu HS, Chung CH. Delayed rupture of occult splenic injury: a case report. *Hong Kong J Emerg Med* 2003;10:188–90.
- 4 Deva AK, Thompson JF. Delayed rupture of the spleen 5 1/2 years after conservative management of traumatic splenic injury. *Aust N Z J Surg* 1996;66:494–5.

- 5 Jonathan SB, William JH. Thrombocytosis: diagnostic evaluation, thrombotic risk stratification, and risk-based management strategies. *Thrombosis* 2011;2011:536062.
- 6 Harris W, Marcaccio M. Incidence of portal vein thrombosis after laparoscopic splenectomy. *Can J Surg* 2005;48:352–4.
- 7 Hoffbrandetal AV. *Postgraduate haematology*. 6th edn. Wiley Blackwell, chapter 9, disorder of red cell metabolism 152–3.
- 8 Bianchi P, Fermo E, Alfinito F, *et al*. Molecular characterization of six unrelated Italian patients affected by pyrimidine 5'-nucleotidase deficiency. *Br J Haematol* 2003;122:847–51.
- 9 Al-Jafar HA, Layton DM, Robertson L, *et al*. Diagnosis of pyrimidine 5'-nucleotidase deficiency suspected from a blood film. *Am J Hematol*. Published Online First: 29 Jul 2013. doi:10.1002/ajh.23556
- 10 Stewart GW, Amess JA, Eber SW, *et al*. Thrombo-embolic disease after splenectomy for hereditary stomatocytosis. *Br J Haematol* 1996;93:303–10.
- 11 Ozsoylu S, Gurgey A. A case of hemolytic anemia due to erythrocyte pyrimidine 5'-nucleotidase deficiency. *Acta Haematol* 1981;66:56–8.
- 12 Forsythe Rm, Harbrecht BG, Peitzman aB. Blunt splenic trauma. *Scand J Surg* 2006;95:146–51.
- 13 Al-Kindi H. Splenic pathology in traumatic rupture of the spleen: a five year study. *Oman Med J* 2009;24:81–3.
- 14 Hirsh J, Dacie JV. Persistent post-splenectomy thrombocytosis and thrombo-embolism: a consequence of continuing anaemia. *Br J Haematol* 1966;12:44–53.
- 15 Denton A, Davis P. Extreme thrombocytosis in admissions to paediatric intensive care: no requirement for treatment. *Arch Dis Child* 2007;92:515–16.
- 16 Al Saeed M. Portal vein thrombosis after splenectomy. *Egypt J Hosp Med* 2012;48:496–503.
- 17 Macias-Robles MD, Peliz MG, Gonzalez-Ordonez AJ. Prophylaxis with enoxaparin can produce a giant abdominal wall haematoma when associated with low doses of aspirin among elderly patients suffering cough attacks. *Blood Coagul Fibrinolysis* 2005;16:217–19.
- 18 Zanella A, Bianchi P, Fermo E, *et al*. Hereditary pyrimidine 5'-nucleotidase deficiency: from genetics to clinical manifestations. *Br J Haematol* 2006;133:113–23.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow