Novel treatment (new drug/intervention; established drug/procedure in new situation)

H pylori-induced thrombocytopenia in a Caucasian female: a case reportHarith Altemimi,¹ James Brown,² Kai En Low,¹ Saba Al-Juboori,¹ Peter Coates³¹ Queen Elizabeth Hospital, King's Lynn, UK² ITU, NHS, King's Lynn, UK³ Department of Haematology, Queen Elizabeth Hospital, King's Lynn, UK

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Summary

We present a rare, but increasingly recognised, cause of thrombocytopenia in a 69-year-old Caucasian female. Complete haematological investigation, including blood films and autoantibody screen, did not reveal a cause for her thrombocytopenia. Omission of potentially offending medication did not improve the low platelet count. She had no features of systemic infection or inflammatory disease on history and examination. In light of persistent thrombocytopenia, *Helicobacter pylori* stool antigen was tested, and found to be positive. Platelet count improved after eradication therapy for *H pylori*. This prevented the need for steroid and immunoglobulin treatment in this patient.

BACKGROUND

Thrombocytopenia has a broad range of causes and can broadly be divided into immune and non-immune aetiologies. Non-immune factors should be excluded before considering immune causes. Immune thrombocytopenic purpura (ITP) is characterised by immune-mediated destruction of circulating platelets. In cases of persistent thrombocytopenia, *Helicobacter pylori* as an aetiological cause of ITP is gaining prominence among the haematological community.

Treatment of ITP generally involves immunosuppressive therapies with inherent risks.

H pylori colonisation increases with age and testing is reliable, cheap and non-invasive. Eradication therapy can be instigated if test results are positive.

As an emerging cause of thrombocytopenia is still keenly debated even within the haematological community, testing for *H pylori* may not necessarily be foremost in a general physician's thought processes. We aim to raise awareness of this potentially reversible cause.

CASE PRESENTATION

A 69-year-old Caucasian lady, presenting with shortness of breath on mild exertion and known pre-existing normocytic anaemia underwent investigation for both conditions.

She was an ex-smoker who stopped 30 years previously and had minimal alcohol intake. Medical history included type II diabetes mellitus, hypertension and a transient ischaemic attack. She had no family history of note. Her weight had been stable at 80 kg.

Oesophageogastroduodenoscopy and colonoscopy were normal. Chest radiograph was normal, as was echocardiogram. A myocardial perfusion scan showed reversible ischaemia. She was listed for an elective percutaneous coronary intervention. Although no cause for the anaemia was found, she was started on vitamin B₁₂.

On the morning of the elective angioplasty, she was found to have a platelet count of $86 \times 10^9/l$, and repeat measurement immediately prior to the procedure was found to be $136 \times 10^9/l$.

The procedure was uneventful, with insertion of a bare-metal stent for a tight lesion in the left anterior descending artery. In addition to her usual medication (ramipril, furosemide, simvastatin, glyceryl trinitrate, metformin, ferrous sulphate, vitamin B₁₂, acarbose), her regular aspirin dose of 75 mg was increased to 300 mg for 6 weeks, clopidogrel was added for 1 month, and long-term carvedilol and amlodipine commenced.

Two months later, a routine full blood count showed a decreased platelet level of $104 \times 10^9/l$ (figure 1). The patient then started to develop easy bruising, and it was noted that her platelet count had fallen to $61 \times 10^9/l$. Her general practitioner stopped aspirin completely and referred her to the haematologist for further assessment by which time the platelet count had fallen further to $41 \times 10^9/l$. The platelet counts were obtained from both ethylenediaminetetraacetic acid and citrate blood tubes, with no evidence of clumping. Haemoglobin concentrations had improved since vitamin B₁₂ supplementation, however.

History and examination revealed no risk factors for blood-borne viruses, and no splenomegaly, hepatomegaly or lymphadenopathy. She displayed no petechiae, but showed signs of easy bruising. Her liver function tests were normal. A blood film showed no haematological malignancies, and only an isolated thrombocytopenia. Her erythrocyte sedimentation rate was 40, but she had no evidence of systemic vasculitis, both clinically and biochemically, as evidenced by a full negative autoantibody screen. Chest radiograph did not show intrathoracic lymphadenopathy.

A diagnosis of ITP was made. The haematologist, in agreement with the cardiologist, advised that aspirin be withheld as long as the platelet remains below $50 \times 10^9/l$. The patient was anxious about this measure in view of the

Figure 1 Time course of platelet count through investigation and treatment.

Figure 2 Causes of thrombocytopenia.

bare metal stent and her previous TIA. A medication review resulted in carvedilol being discontinued. Amlodipine was continued as it only very rarely causes thrombocytopenia. Her other regular medications had not been implicated with thrombocytopenia, and were therefore continued. Throughout this she remained clinically well, and it was decided to observe the platelet levels following adjustment to her medication, rather than treating the ITP.

Seven months after her initial presentation, her platelet count still did not improve. At this stage, *H pylori* stool antigen testing was then considered, for which she tested positive. Eradication therapy consisting of a 2-week course of lansoprazole (30 mg once daily), clarithromycin (500 mg twice daily) and metronidazole (400 mg twice daily) was given.

OUTCOME AND FOLLOW-UP

Repeat platelet count at 3 months posteradication was $177 \times 10^9/l$. Aspirin was therefore restarted. A further platelet count at 7 months posteradication was $202 \times 10^9/l$. Patient remained well and has reported no further problems.

DISCUSSION

ITP is a common condition, with an estimated incidence of between 1:1000 and 1:10 000. It is more common in females than males by a ratio of 2–3:1.¹ It may present with purpura, petechiae and can cause complications such as potentially fatal internal bleeding (gastrointestinal, intracerebral). Mortality for ITP is estimated at 4% overall, due largely to those with severe refractory thrombocytopenia.¹ Outcomes for most patients with ITP are generally good, however.

ITP is a diagnosis of exclusion, as other causes are more common and often more readily reversible. Non-immune causes of thrombocytopenia, including hypersplenism, myelodysplasia, sepsis, viral infection, acute leukaemia and drug-induced bone marrow suppression, should first be considered. Immune thrombocytopenia can be divided into primary (idiopathic) and secondary causes (figure 2).

Blood films generally show an isolated thrombocytopenia with an increased mean platelet volume. Between 15% and 25% of ITP cases show an expression of antinuclear and antiphospholipid antibodies. Clotting screen and thyroid function tests are generally normal. Specific tests for ITP are still in development.

A stepwise approach is generally adopted in the management of ITP.

- ▶ Observation with treatment of underlying cause
- ▶ Corticosteroids, immunoglobulin G and anti-D
- ▶ Splenectomy
- ▶ Rituximab
- ▶ Immunosuppressants.

Roughly 10% of patients with ITP have remission, if left untreated.² Standard practice is to commence treatment with steroid with or without immunoglobulin and with immunoglobulin when platelet count falls below $20 \times 10^9/l$ or below $50 \times 10^9/l$ in the presence of bleeding.³ Most strategies other than observation have significant side-effect profiles.

Risks of steroid treatment are manifold, and furthermore, chronic steroid use often fails in ITP treatment. The use of intravenous immunoglobulins is also not without risk.

Traditionally, if steroids and immunoglobulins fail, splenectomy was the third line with associated risks of infection and perioperative complications, including up to a 1% mortality.⁴

Rituximab (anti-CD-20 monoclonal antibody) has been associated with an improvement in platelet count response in 60% of patients but is associated with virus reactivation and acute toxicity.⁵

In postsplenectomy refractory thrombocytopenia, numerous agents have been utilised, including immunosuppressants (cyclophosphamide, mycophenolate mofetil, azathioprine and ciclosporin) and androgenic treatment (Danazol). There is no substantial evidence for the use of any single agent. Each has its own inherent risks.

By contrast, treatment of *H pylori*-induced ITP is more favourable in terms of side effects, with some promising clinical response to eradication therapy.⁶

H pylori is a commensal Gram-negative bacterium that colonises the human stomach in more than 50% of the world's population. It is associated with chronic gastritis, peptic ulcer disease and gastrointestinal neoplasia. *H pylori* infection is increasingly being implicated in diseases beyond the gastrointestinal tract, including the cardiovascular and neurological systems.⁷ Research suggests, in line with most chronic infections, that there is a complex interaction between host and pathogen, and that particular genetic polymorphisms of both will predispose to certain disease manifestations. For instance, the balance between Th1 and Th2 responses in gastric mucosa contributes to severity of gastritis, and the persistence of *H pylori* colonisation.⁷

H pylori colonisation can be diagnosed with non-invasive methods, namely ¹³C-urea breath test and antigen detection in faeces (sensitivity and specificity 90–95% in both cases).⁸ *H pylori* stool antigen testing offers excellent specificity and sensitivity compared with invasive methods, and is a more accurate indicator of active disease than serology.⁹

The mechanism of how *H pylori* causes ITP is incompletely understood, but may involve antibody molecular mimicry and platelet aggregation.^{10 11} The virulence factors expressed by different strains of *H pylori* may contribute to this process with bacteria expressing the cytokine-associated gene A (*CagA*) implicated in cross-reactivity with platelet membranes. Recent work by Yeh *et al*¹² postulate that in addition to causing platelet aggregation, specific *H pylori* strains may cause platelet apoptosis via the P-selectin receptor on platelet cell surfaces, further reducing platelet counts.

Treatment options invariably include a proton pump inhibitor and a combination of antibiotics for 2 weeks. Eradication therapy is successful in 80–85% of patients.¹³

Overall, the literature concerning this area is inconclusive, with response rates of platelet counts following eradication therapy for *H pylori* varying widely between studies. In certain countries, where the prevalence of *H pylori* is higher, the response to eradication therapy is more pronounced in terms of platelet response.⁶ In Japan, the endemic strain of *H pylori* tends to have higher *CagA* expression rates. This may explain the increased response rate to eradication therapy.

Haematologists are increasingly including testing for *H pylori* as part of their ITP investigation. Further studies are being conducted into the association between *H pylori*-associated ITP and the effect of eradication.

Learning points

- ▶ *H pylori* infection incidence increases with age, and associated increase in mortality.
- ▶ *H pylori* (*CagA*-producing strains) appear to be able to cause ITP in some individuals via an incompletely understood mechanism.
- ▶ There are sensitive and specific tests for *H pylori*, and it is treatable.
- ▶ ITP is a diagnosis of exclusion that carries a small but well-recognised mortality risk. Treatment options for ITP carry unfavourable side-effect profiles.
- ▶ Eradication therapy for *H pylori* is well tolerated, relatively inexpensive and provides an avenue for avoiding unnecessary medical and surgical intervention in patients who respond well, particularly older patients.

Competing interests None.

Patient consent Obtained.

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