Unusual association of diseases/symptoms

Autoimmune pernicious anaemia as a cause of collapse, heart failure and marked pancytopenia in a young patient

Justin Carey,¹ Ebru Hack²¹Department of Infectious Diseases, Fremantle Hospital and Health Service, Fremantle, Western Australia, Australia;²Department of Acute Medicine, Princess Alexandra Hospital, Harlow, UK**Correspondence to** Dr Justin Carey, drjustincarey@gmail.com**Summary**

A 35-year-old woman with a history of vitiligo, hypothyroidism and amenorrhoea presented with collapse and clinical features of cardiac failure. Laboratory investigations revealed pancytopenia, the cause of which was found to be vitamin B12 deficiency due to pernicious anaemia. Treatment with intramuscular hydroxycobalamin was commenced and the patient improved steadily with concomitant improvement in her haematological indices. Clinical features of pernicious anaemia which can include marked pancytopenia, diagnostic approach, associated conditions and approach to treatment are discussed. The importance of surveillance for gastrointestinal malignancy is emphasised.

BACKGROUND

This is an interesting case because although the individual conditions are not unusual and together comprise the classic textbook group of autoimmune conditions, the florid nature of the presentation is uncommon, in this case comprising of profound pancytopenia, collapse and heart failure in a young patient. We felt it would be useful to discuss the investigations and management plan in this case for other junior doctors to learn from particularly as the initial investigations did not demonstrate a severe vitamin B12 deficiency and to provide context for what is a commonly requested test in daily practice.

CASE PRESENTATION

A 35-year-old patient of black Cypriot origin presented to accident and emergency department with a collapse at work. She had felt dizzy and unwell in the morning and reported some unintentional recent weight loss. She had a long-standing history of vitiligo since the age of 8 and had recently been diagnosed with hypothyroidism, for which she was taking levothyroxine. She also reported amenorrhoea for the preceding 6 months. She denied palpitations but reported some right-sided abdominal pain. On examination, the patient appeared generally unwell. She had a 6 cm raised jugular venous pressure and soft ejection systolic murmur audible throughout the precordium. She had severe angular stomatitis, 2 cm palpable hepatomegally and pallor of the conjunctiva. The rest of the examination was normal and the patient was haemodynamically stable.

INVESTIGATIONS

The initial blood results showed a profound pancytopenia, with a haemoglobin of 5.2 (normal range 11.5–16.0 g/dl), white cell count of 1.2 ($4.0\text{--}11.0\times 10^9/\text{l}$), neutrophils of 0.3 ($2.0\text{--}8.0\times 10^9/\text{l}$), lymphocytes 0.8 ($1\text{--}4.8\times 10^9/\text{l}$), monocytes of 0.0 ($0.2\text{--}1\times 10^9/\text{l}$) and platelets of 27 ($150\text{--}400\times 10^9/\text{l}$). The mean cell volume was 110 (76–96), lactate

dehydrogenase (LDH) was 1984 and serum bilirubin was 33 ($<17\text{ }\mu\text{mol/l}$). Free thyroxine (T4) was 7.1 (9–19 pmol/l) and thyroid stimulating hormone was 30.28 (0.35–4.94), despite being on treatment for hypothyroidism. Given the history of autoimmune disorders, it was felt that her presentation may represent an acute manifestation of severe pernicious anaemia. The blood film showed grossly abnormal red cells, hypersegmented neutrophils and absent blast cells. The B12 levels were 152 (200–1000 ng/l) and folate was 11.2 (4.0–18.0 ug/l). As the B12 levels were only marginally low, iron studies were undertaken to exclude iron deficiency as a possible co-contributor to the anaemia and this revealed a ferritin level of 248 (9–120 ug/l). On the advice of the haematology team,

Cellularity	Increased
Megakaryocytes	Raised in number and morphologically abnormal
Erythropoiesis	Hypercellular and megaloblastic
Granulopoiesis	Reduced cellularity with giant metamyelocytes
Conclusion: Megaloblastic bone marrow	

Figure 1 Bone marrow biopsy results.

Gastric Parietal Cells	Weak Positive
Smooth Muscle	Negative
Mitochondrial	Negative
ANA	Negative
Thyroid Peroxidase	Positive
Thyroid Microsomal	Positive
Intrinsic Factor	Positive

Figure 2 Autoantibody screen results.

a bone marrow biopsy was performed to exclude other causes of pancytopenia. This showed a highly megaloblastic picture (figure 1) confirming the diagnosis of severe B12 deficiency, most likely secondary to autoimmune pernicious anaemia.

Gastric parietal cell antibodies were also weakly positive and antibodies to intrinsic factor was highly raised 8.2 (<1.20 u/ml), further suggesting pernicious anaemia (figure 2).

TREATMENT

Given the neutropaenia, the patient was isolated in a side room. She had a single recorded episode of low-grade fever, however it was felt that she would not need to be treated for neutropaenic sepsis as there was no sustained fever and no clinical evidence of infection, but she was closely monitored. Red cell and platelet transfusions were not initially deemed necessary as the patient remained haemodynamically stable with no evidence of bleeding. The primary aim of treatment was the correction of the underlying cause of the marrow failure and pancytopenia with parenteral vitamin replacement. However, one unit of red blood cells was given following a further drop in haemoglobin to 4.9 g/dl. The platelet count dropped further to 18 but platelet transfusion was withheld as there was no active bleeding and platelet levels remained above 10. She was commenced on intramuscular

hydroxycobalamin 1000 microgram daily. Daily LDH, full blood count and reticulocytes were taken to measure response to treatment.

OUTCOME AND FOLLOW-UP

The haemoglobin and leucocyte response to treatment was initially slow but the patient remained stable and clinically well and the reticulocyte count responded quickly, rising to 187 (20–100 $10^9/l$) 2 days after the first injection, suggesting improvement in the blood count was likely to follow. The blood count values had not returned to normal after 2 weeks but showed a good improvement (figure 3) and it was felt the patient was well enough to be discharged home.

Given the 6 month history of amenorrhea an endocrine review was requested and oestrogen, luteinising hormone (LH) and follicular stimulating hormone (FSH) levels were checked. Oestradiol was <37 (77–921 pmol/l), FSH was 54.4 (2.5–19.5 u/l) and LH and prolactin were normal. Testosterone levels were 0.7 (2–4 nmol/l) and dehydroepiandrosterone sulphate was normal. It was felt that her amenorrhoea was probably secondary to primary ovarian failure, ovarian antibodies were requested and she was referred for outpatient endocrinology review.

DISCUSSION

Definition

Pernicious anaemia (PA) has been defined as ‘a megaloblastic anaemia due to cobalamin (vitamin B12) deficiency resulting from malabsorption of cobalamin due to gastric atrophy’.¹ It is an immune-mediated condition the mechanism of which is exploited in diagnosis and which is reflected in the association with a number of other autoimmune conditions.

Diagnostic criteria

Classically the Schilling test was used to diagnose PA. This involved the use of a radiolabelled form of vitamin B12, the urinary excretion of which was measured with or without the co-administration of oral intrinsic factor. This test has now fallen out of favour with the limited availability of reagents to perform the test and the increasing acceptance of intrinsic factor (IF) antibody assays. Intrinsic factor antibodies have been implicated in the development of pernicious anaemia¹ and their detection is highly suggestive of the diagnosis² although their absence does not preclude it.³ Other tests which may support your diagnosis include gastric parietal cell antibodies and serum gastrin and pepsinogen levels.

Examination of the blood film will reveal macrocytosis and anisocytosis¹ (erythrocytes of varying sizes) and may also demonstrate poikilocytosis (abnormally shaped red cells, poikilocytes, in peripheral blood) and hypersegmented neutrophils.^{1–4} Bone marrow examination is not usually required to make the diagnosis but would be expected to demonstrate megaloblastic erythropoiesis.

Clinical features

It is important to note that deficiency of B12 may not result in significant anaemia and deficiency may be longstanding before clinical manifestations occur.⁵

Figure 3 Response in haemoglobin concentration and white cell count in response to vitamin B12 replacement.

Clinical features include:

- ▶ Those associated with anaemia of any cause (eg, fatigue, dyspnoea).
- ▶ Pancytopenia
- ▶ Neurological manifestations – neuropathy, weakness, ataxia, dementia, disorders of affect.
- ▶ Gastrointestinal – glossitis, mouth ulcers, altered bowel habit, weight loss.

Certain patient groups are at increased risk of developing vitamin B12 deficiency including the older, alcoholics, patients who have undergone gastric surgery and vegans.²

Associated conditions

Pernicious anaemia is associated with other auto-immune conditions and an increased risk of gastrointestinal malignancy.⁶

Associated conditions include

- ▶ Hypothyroidism with both antithyroglobulin and antithyroid peroxidase antibodies more commonly detected in IF-positive patients.³
- ▶ Vitiligo⁴ and, less commonly, skin hyperpigmentation.⁷
- ▶ Associations have also been made with diabetes mellitus, both type 1 and 2.^{3,8}

It has been proposed that pernicious anaemia is associated with a greater risk of oesophageal and gastric cancer,⁵ particularly within the first 5 years of diagnosis³ and in IF-positive patients.⁹ The exact mechanism resulting in this increased risk has not yet been elucidated.⁵

TREATMENT

Replacement of vitamin B12 is the mainstay of treatment and a parenteral route is normally preferred initially (eg, 1 mg hydroxycobalamin intramuscularly three times per week for 2 weeks)¹⁰ although some authors claim equal efficacy of parenteral and oral treatments.⁶ Treatment should result in a rise in haemoglobin count and reduction

of mean cell volume. Recovery of neurological and psychological deficit may be slow and/or partial particularly if the B12 deficiency has remained untreated for a long period of time. Associated conditions should be considered and excluded or treated as appropriate (eg, fasting blood glucose, thyroid function tests).

It is important to be vigilant for the onset of gastrointestinal malignancy, with some authors advocating regular endoscopy even in the absence of alarm symptoms.^{1,11} In centres where this approach is not adopted a low threshold for further investigation should be maintained.

Learning points

- ▶ Pernicious anaemia can be associated with significant anaemia and pancytopenia.
- ▶ Pernicious anaemia may also be associated with neurological deficits that may not completely resolve with treatment.
- ▶ Pernicious anaemia may be seen in association with other autoimmune conditions, including hypothyroidism.
- ▶ Treatment is with parenteral or oral replacement of vitamin B12 which should result in resolution of the anaemia and symptomatic improvement.
- ▶ It is important to consider the increased risk of gastrointestinal malignancy in these patients.

Acknowledgements Dr Piero Reynolds (Consultant Rheumatologist and Physician, Homerton Hospital). Dr Pippa Dwan (Foundation Year 2 Doctor).

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Chanarin I. Pernicious anaemia. *BMJ* 1992;**304**:1584–5.

2. **Schrier SL.** Diagnosis and treatment of vitamin B12 and folic acid deficiency. UpToDate. http://www.uptodate.com.ezproxy.fh.health.wa.gov.au:2048/contents/diagnosis-and-treatment-of-vitamin-b12-and-folic-acid-deficiency?source=search_result&search=b12+deficiency&selectedTitle=1%7E150 (accessed 8 December 2011).
3. **Chan JC,** Liu HS, Kho BC, *et al.* Longitudinal study of Chinese patients with pernicious anaemia. *Postgrad Med J* 2008;**84**:644–50.
4. **Egli F,** Walter R. Images in clinical medicine. Vitiligo and pernicious anemia. *N Engl J Med* 2004;**350**:2698.
5. **Ye W,** Nyrén O. Risk of cancers of the oesophagus and stomach by histology or subsite in patients hospitalised for pernicious anaemia. *Gut* 2003;**52**:938–41.
6. **Marks PW,** Zukerberg LR. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 30-2004. A 37-year-old woman with paresthesias of the arms and legs. *N Engl J Med* 2004;**351**:1333–41.
7. **Sherley-Dale AC,** Goulding JM, Leithead J, *et al.* Pigmentary changes in pernicious anaemia: an important but under-recognized phenomenon. *Clin Exp Dermatol* 2011;**36**:93–5.
8. **Dahshan A,** Poulick J, Tolia V. Special feature: pathological case of the month. Pernicious anemia and gastric atrophy in an adolescent female with multiorgan problems. *Arch Pediatr Adolesc Med* 2001;**155**:609–10.
9. **Patel A.** Vitamin B-12 deficiency. Monitor for up to two years after symptoms resolve. *BMJ* 2010;**340**:c3319.
10. **Hudson B.** Vitamin B-12 deficiency. *BMJ* 2010;**340**:c2305.
11. **Hvas AM,** Nexø E. Diagnosis and treatment of vitamin B12 deficiency—an update. *Haematologica* 2006;**91**:1506–12.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 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.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Carey J, Hack E. Autoimmune pernicious anaemia as a cause of collapse, heart failure and marked pancytopenia in a young patient. *BMJ Case Reports* 2012;10.1136/bcr.01.2012.5576, Published XXX

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

Keep up to date with all published cases by signing up for an alert (all we need is your email address) <http://casereports.bmj.com/cgi/alerts/etoc>