

An unexpected cause of macroscopic haematuria

A 25-year-old man presented with macroscopic haematuria associated with a body mass index of 20 kg/m² and a severe coagulopathy consistent with vitamin K deficiency. The diagnosis of a profound malabsorption syndrome secondary to coeliac disease was confirmed by small bowel histology and positive coeliac serology. (MJA 2005; 183: 321-323)

Clinical record

A 25-year-old man presented to our hospital's emergency department with frank haematuria and bilateral loin pain. He had been unwell for 10 days with abdominal pain and vomiting. Two days before presentation, he sought medical attention and was prescribed naproxen for the abdominal pain (he only took two of these tablets); he was on no other medications. Two years previously, a diagnosis of irritable bowel syndrome had been made by his doctor, based on a history of loose bowel motions over 2 years and a normal colonoscopy.

At the time of his hospital presentation, our patient had a body mass index (BMI) of 20 kg/m² and appeared pale, but had no sign of bruising. He was afebrile and well hydrated, with unremarkable cardiovascular and respiratory findings. Gastrointestinal examination revealed a red swollen tongue and angular cheilitis (Box 1). There was some mild left renal angle tenderness.

Urinalysis revealed $>500 \times 10^6$ non-glomerular red blood cells per litre (normal range $<13 \times 10^6/L$) but no pyuria. Abdominal ultrasound performed on the day of review was unremarkable. Peripheral blood tests revealed normal electrolyte levels and renal function, with a coagulopathy reflected by an international normalised ratio (INR) of >10 (reference range, <1.4) and activated partial thromboplastin time (APTT) of 115 seconds (reference range, 25–38 seconds) (Box 2). These results were verified with repeat testing. Clotting factor studies revealed severe deficiencies in factors II, VII, IX and X. There were also deficiencies in iron, vitamin B₁₂, and serum folate, vitamin A and vitamin E concentrations (Box 2). Vitamin D levels were normal, but the serum alkaline phosphatase level was twice the upper limit of normal. Results of other liver function tests were normal. Endomysial antibody test results were positive, and tissue transglutaminase antibody (IgA) levels were more than five times the upper limit of normal.

A preliminary diagnosis of vitamin K deficiency, leading to a profound coagulopathy, secondary to a malabsorption syndrome from coeliac disease was made. Duodenal biopsies confirmed the diagnosis of coeliac disease (Box 3). Gastroscopy showed no gastritis or peptic ulcer disease. The duodenal mucosa appeared abnormal and was consistent with villous atrophy. No conclusion could be reached regarding the nonspecific abdominal pain the patient experienced on presentation. Inflammatory bowel disease was a differential diagnosis, but inflammatory markers were only marginally elevated (Box 2).

Parenteral vitamin K was administered, and the prothrombin time reduced to 15 seconds (INR, 1.3) and APTT became normal within 24 hours. The macroscopic haematuria resolved.

The patient was also given parenteral iron and vitamin B₁₂ and oral multivitamin replacement. He was reviewed by the dietetic services and educated about coeliac disease. He also started a gluten-free diet. On clinical review 2 months later, he was feeling well and had put on 15 kg in weight (BMI, 26 kg/m²).

1 Angular cheilitis



This image is similar to but is not of the patient described in this article.

Duodenal biopsies 6 months after the initial presentation revealed variable villous abnormality, consistent with partially treated coeliac disease. The vitamin deficiencies had all resolved, and clotting factor studies were normal. Endomysial antibodies had become negative, and tissue transglutaminase antibody levels (IgA) were within the normal reference range. Bone mineral density at this time was normal.

Genotyping revealed the presence of the HLA DQ2 allele.

Discussion

The most common presentation of coeliac disease is diarrhoea (43%); other reasons for presentation include anaemia (8%), bone disease (6%), weight loss (6%), and abdominal pain (5%).¹ The remaining 32% of patients are asymptomatic or present with vague symptoms. Delay in the diagnosis of coeliac disease is common (mean, 11 years).² About 47% of patients will have been misdiagnosed, and of those with classical symptoms of coeliac disease, 59% have been misdiagnosed as having irritable bowel syndrome.³ The clinical diversity of coeliac disease is recognised, and disorders involving nearly every organ system have been described with this condition.⁴

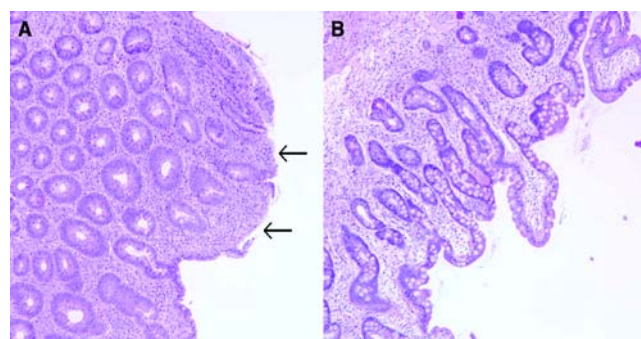
Haematuria is an unusual presenting symptom of coeliac disease.⁵ The haematuria in our patient indicated a systemic bleeding diathesis due to malabsorption of vitamin K, with subsequent prolongation of the prothrombin time and APTT.⁶ In patients with untreated coeliac disease, the prothrombin time is prolonged (INR, ≥ 1.4) in about 20%,⁷ and the coagulopathy is usually asymptomatic,^{8,9} but corrects quickly with administration of vitamin K.¹⁰

2 Results of laboratory tests

Investigation	Result	Reference range
Haemoglobin	123	130–180 g/L
White cell count	12.4	4.0–11.0 × 10 ⁹ /L
Platelets	727	150–400 × 10 ⁹ /L
Mean corpuscular volume	73	82–95 fL
Mean corpuscular haemoglobin	23.3	24–32 pg
Reticulocytes	74	10–90 × 10 ⁹ /L
Differential white cell count		
Neutrophils	9.52	2.0–7.5 × 10 ⁹ /L
Lymphocytes	1.48	1.0–4.0 × 10 ⁹ /L
Monocytes	1.25	0.1–0.8 × 10 ⁹ /L
Eosinophils	0.12	< 0.4 × 10 ⁹ /L
Basophils	0.02	< 0.2 × 10 ⁹ /L
Blood film	Microcytosis with moderate hypochromasia, and small numbers of elongated cells. Neutrophilia with no left shift and thrombocytosis.	
CRP	22.4	1.6–8.7 mg/L
ESR	14	5–12 mm/hour
Alkaline phosphatase	249	40–129 U/L
Tissue transglutaminase antibody	101	< 20 U/mL
Serum folate	4.7	> 6.8 nmol/L
Red cell folate	Not measured	
Vitamin B ₁₂	93	132–857 pmol/L
Vitamin A	0.1	0.8–3.1 μmol/L
Vitamin D	38	30–110 nmol/L
Vitamin E	4.9	> 18.6 μmol/L
Ferritin	10	24–336 μg/L
International normalised ratio	> 10	< 1.4
Activated partial thromboplastin time	115	25–38 seconds
Factor II	15%	50%–120%
Factor VII	3%	50%–120%
Factor IX	17%	50%–120%
Factor X	5%	50%–120%

In the long-term treatment of coeliac disease, a gluten-free diet is paramount and leads to resolution of the underlying small bowel villous abnormality. A partial histological response to a gluten-free diet may reflect poor compliance, accidental exposure to gluten-containing food products, or slow recovery. Our patient claimed close adherence to the diet and was provided with adequate education and dietetic review. Histological recovery can be delayed, with 35% of patients still showing features of coeliac disease up to 2 years after commencing a gluten-free diet.^{11,12} Failure to achieve histological recovery can occur in the absence of

3 Duodenal biopsies



A At time of diagnosis. There is severe villous abnormality associated with marked enterocyte damage (black arrows), in keeping with untreated coeliac disease.
B After 6 months of gluten-free diet. There is partial improvement of the previous villous abnormality, but a moderate villous abnormality with associated crypt hyperplasia remains. ♦

gluten.¹³ The use of serology tests as surrogate markers for histological resolution is controversial.^{14–16} Some coeliac patients with negative results for endomysial and tissue transglutaminase antibodies have persistent villous abnormalities, necessitating the use of biopsies to monitor the response to a gluten-free diet (as in our patient).

On HLA genotyping, our patient possessed the HLA DQ2 allele, which is present in more than 90% of patients with coeliac disease, but in only 20% of the general population.¹⁷ Endomysial IgA antibodies have a sensitivity of 90% and specificity of 100%, tissue transglutaminase IgA has a sensitivity and specificity of 98%. Sensitivities for the IgG class endomysial and tissue transglutaminase antibodies are around 40%.¹⁸ Deficiency of IgA occurs in 1.7%–2.6% of coeliac patients, and these patients have negative results on IgA antibody testing. Total serum IgA levels should be tested together with IgG (endomysial, tissue transglutaminase) to improve the overall sensitivity of antibody testing.¹⁹

Our patient demonstrates the need to be aware of the various presenting features of coeliac disease, and reminds us that coeliac disease is often misdiagnosed.

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ALFRED GRAUAUG, known to everyone as "Fred" or "Freddy", will be forever remembered as the pioneer of neonatal medicine in Western Australia.

Fred was born in Vienna, Austria, on 11 August 1935, but grew up in Sydney, where he attended Sydney Grammar School and the University of Sydney, graduating in 1960.

His postgraduate training included several years at the Royal Alexandra Hospital for Children, Sydney, and the Princess Margaret Hospital, Perth. When he arrived at King Edward Memorial Hospital (KEMH), Perth, in 1968, neonatology was not yet a subspecialty of paediatrics, and babies were cared for in "special nurseries". Under Fred's leadership, there was rapid progress to a fully equipped neonatal intensive care unit, which today has become one of the largest and best in the world.

Fred was the first Director of the Neonatal Unit at KEMH. He held this position from 1968 to 1997, after which he continued as a neonatologist at KEMH and the nearby St John of God Hospital. His appointment by the University of Western Australia as a Senior Lecturer and subsequently Associate Professor in Neonatology was the first academic appointment in that specialty in the state.

He was the first to use ventilators for respiratory problems in premature babies in WA. He established the first neonatal transport system, the first retinopathy of prematurity screening program and the first neonatal intensive care nursing course in Australia. He was a founding member of the Asia and Oceania Perinatal Society, and held positions on state, college and hospital committees.



OBITUARY

Before he knew of his illness (metastatic adenocarcinoma of the lung), Fred announced that his retirement from KEMH would be on 30 June 2005, two months before his 70th birthday. He would be one of the few intensivists to have continued working full-time in this demanding role at this age.

Fred was known for his dedication, vision, energy, drive, determination, resilience and success. Fred valued multidisciplinary and multicultural clinical teams. Although he had a strong commitment to work, he managed to preserve a balance between work and the other aspects of his life.

He was passionately involved in the Medical Association for the Prevention of War, of which he was State President for a time. With his wife Heather, he was an active supporter of the arts.

Fred died on 13 July 2005. He will be sadly missed by the medical, nursing and other staff of KEMH and St John of God Hospital, by paediatric colleagues around Australia, and by his countless patients and their families. He is survived by Heather and their children David, Richard, Elizabeth, William, Emma, Michael, Alexandra and Sally. Fred's first wife, Anne, died in 1978.

Karen Simmer and Jeffrey Tompkins