**DIAGNOSIS**

A diagnosis of symptomatic microcytic anaemia was made. The origin of this anaemia could be multifactorial, but can be divided into iron deficiency, thalassaemia or anaemia of chronic disease. Occult blood loss in the gastrointestinal tract, provoked by oral anticoagulant use, was further investigated. Due to the use of oral iron supplementation, identification of melaena was difficult. First the anticoagulants and oral iron supplementation were stopped and both gastroscopy and colonoscopy performed. These showed no abnormalities, except a small submucosal lesion in the antrum, suspect for a gastro-intestinal stromal tumour. An oral iron-loading test showed reduced absorption of iron. Initially, thalassaemia could not be ruled out in the presence of severe iron deficiency. After abundant iron supplementation, the haemoglobin and mean cell volume normalised and haemoglobin electrophoresis was normal.

Ophthalmological evaluation by slit lamp showed mildly blue sclerae, but no further abnormalities. An additional ultrasound showed normal scleral thickness. Although her family history was negative for bone disorders and she had no history of bone fractures, a bone mineral density scan was performed. It showed no signs of osteomalacia or osteoporosis.

The present case may describe an ordinary case from daily clinical practice in the outpatient clinic of internal medicine; nonetheless an important highlight in the physical examination is discussed below.

**DISCUSSION**

In general, one is triggered by pale conjunctivae to diagnose anaemia. This patient, however, had moderately pale conjunctivae as well as remarkable blue sclerae. The presence of blue sclerae is known to occur in osteogenesis imperfecta, inherited disorders of connective tissue and collagen disorders (e.g. Ehlers-Danlos syndrome, pseudoxanthoma elasticum) and long-term corticosteroid therapy. However, a less known cause of blue sclerae is chronic iron deficiency. This association was first described by Osler in 1908 in iron-deficient undernourished teenage girls. Others reported the presence of blue sclerae in iron-deficient patients with other causes of iron shortage. It is unknown what the duration or severity of iron deficiency must be before blue sclerae develop. The mechanism is unclear, but it has been found that iron is an important cofactor in the hydroxylation of proline and lysine residues in collagen synthesis. In vitro tests showed that fibroblasts in culture do not synthesise collagen in the presence of iron-chelating agents.

It is therefore hypothesised that collagen synthesis is impaired in patients with iron deficiency resulting in thin sclerae through which the choroid can be seen, making the sclerae appear blue. In our patient ultrasound of the sclerae showed normal thickness indicating that not only thickness, but also the consistency of the sclerae, may cause blue sclerae.

The association of blue sclerae and mucosal pallor with iron-deficiency anaemia was previously studied by Kalra et al. in 169 unselected hospital inpatients. Blue sclerae were seen significantly more often in patients with iron-deficiency anaemia (87%) than in those with other causes of anaemia (7%). The sensitivity of blue sclerae in patients with iron-deficiency anaemia was 87% with a specificity of 94%. By comparison, mucosal pallor was noted in only 30% of patients with iron-deficiency anaemia, with a sensitivity of only 20% and a specificity of 96% (p < 0.001). Concordance by three independent observers for blue sclerae was seen in 50.3% versus 56.8% for mucosal pallor in the studied patients. They reported that the presence of blue sclerae was unaffected by age, sex, colour of the iris, blood transfusions, skin thickness, pigmentation or perfusion.

Subsequent to this study in inpatients, the same investigators tested the predictive value of blue sclerae in undiagnosed chronic iron deficiency in apparently healthy individuals attending a general practice clinic. Of the 1889 patients screened, blue sclerae were observed in 41 patients. Of them, 34 (83%) had evidence of past or present iron deficiency. To date, more than one year after diagnosis, our patient is doing well and the haemoglobin and iron levels are within normal limits after repeated intravenous iron supplementation. However, the sclerae are still slightly bluish. It is unknown how long it takes to normalise sclerae composition after correction of iron levels. Kalra et al. reported that blue sclerae persisted in some patients, despite correction of the iron deficiency.
In conclusion, blue sclerae is an underestimated, often overlooked, but good indicator of iron deficiency and should become a regular part of clinical examination.

REFERENCES