Pigmented sclera: a diagnostic challenge?

Q1: What is the diagnosis in the male patient?

Dark pigmented spots in sclera were seen in both eyes (fig 1; see p 491). The combination of chronic arthritis, dark urine, pigmentation, and family history suggests the diagnosis of alkaptonuria.

Q2: Does his sister have the same condition?

The sister also has alkaptonuria (fig 2; see p 491), Alkaptonuria is an autosomal recessive disorder. Siblings are more likely to suffer from the condition than parents or offspring. Usually there is a history of consanguineous marriage in the parents of affected offspring. However, the parents of the brother and sister reported here were unrelated to each other before marriage and hailed from widely different geographical areas of the UK. One in 1000 persons in the UK is a carrier for the alkaptonuria gene.

Q3: What further investigations would you perform to confirm your diagnosis?

The diagnosis of alkaptonuria is made by demonstrating homogentisic aciduria (fig 1 below). Analytical methods for homogentisic acid are readily available. Methods for demonstrating defective enzyme activity or abnormal genes are only available as research tools. Previously, diagnosis was often made early on in life as nappies turned black due to freshly passed acidic urine becoming alkaline on prolonged exposure to air. Alkalising the urine in this brother and sister produced an immediate dark colour (fig 1).

The urine estimation by chromatography confirmed the presence of large amounts of homogentisic acid in these siblings.

Q4: What are the clinical features of this disease?

The clinical features of alkaptonuria are summarised in box 1. The deposition of melanin-like pigment in tissues is called ochronosis.

Figure 1 Urine colour (Neat, unalkalinised: Alk, alkalinised).

Figure 2 Metabolism of phenylalanine and tyrosine.

Q5: How would you manage this condition?

The treatment is mainly symptomatic and palliative in the form of analgesics and joint replacement. Reducing the conversion of homogentisic acid to the benzoquinone metabolite is an attractive therapeutic objective; the use of reducing agents such as vitamin C in this regard has had mixed success. A recent approach tested the idea that the production of homogentisic acid could be suppressed by inhibiting the enzyme hydroxyphenylpyruvate dioxygenase (fig 2 below).
excretion." A recent approach is based on the principle of enzyme inhibition. NTBC or nitritinone (Orfadin) is a potent inhibitor of the enzyme that generates homogentisic acid (hydroxyphenylpyruvate dioxygenase) and effectively reduces the homogentisic acid load in animals as well as humans with alkaptonuria. These treatment are unsatisfactory either due to a lack of efficacy or because of concerns about safety. Lastly, the gene therapy to cure alkaptonuria is still some distance in the future.

Final diagnosis
Alkaptonuria in a man presenting with homogentisic aciduria, ochronosis, arthritis, and renal calculi.

References

Upper gastrointestinal haemorrhage

Q1: What is the diagnosis?
Dieulafoy’s lesion in the stomach. Recommended treatment is thermal ablation.
Dieulafoy’s lesion is an important cause of upper gastrointestinal haemorrhage and may account for up to 5% of acute haemorrhages. Dieulafoy et al described it in 1897 as exulceratio simplex, cirrhotic aneurysm. The histological appearance is characteristic: a relatively large calibre artery that lies close to the mucosal surface, likely as a congenital anomaly. Most Dieulafoy lesions are diagnosed by their endoscopic features. The features are arterial bleeding or non-bleeding visible vessel stigmata, all with normal surrounding mcosa. However, this lesion is commonly missed as illustrated by our case and the initial endoscopy is diagnostic in only 63% of cases. It is potentially life threatening and massive haemorrhage can occur with erosion of the mucosa and arterial wall.

Q2: What is the most appropriate endoscopic haemostatic method?
The study by Norton et al suggests endoscopic haemostasis was achieved in 94% of cases. Various endoscopic haemostatic methods have been advocated but most experience has been with thermal ablation (heater probe), which should be available in most centres. Long term recurrence was not evident after successful endoscopic ablation. A recent study advocates endoscopic haemoclip application as an alternative effective and safe method with long term benefits. Our patient was initially treated with an injection of epinephrine to slow down the bleeding rate followed by thermal ablation to achieve haemostasis (fig 1 below). The patient made an uneventful recovery with no further bleed within six months of follow up.

Final diagnosis
Dieulafoy’s lesion.

References
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