


**Clinical Vignette**

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A 71-year-old male patient was referred for the evaluation of a high-grade aortic stenosis. His medical history revealed prosthetic hip and joint replacement due to degenerative arthritis at the age of 55. On physical examination, a 2/4 systolic ejection murmur at the right upper sternal border, kyphosis, and a bluish-black discolouration of the sclera and auriculum were noted (Panels A and B). The patient reported that his urine darkens since childhood (Panel C). Cardiac catheterization demonstrated a severely calcified aortic stenosis (aortic valve area 0.4 cm²/m² body surface; Panel D). On operation, bluish-black discoloration of the aortic intima and extensive calcification and discoloration of the tricuspid aortic valve were found (Panels E and F). On the basis of the bluish-black discolouration of collagenous tissue (sclera, auriculum, aortic valve), history of degenerative arthropathy, and blackening of the urine on standing, diagnosis of alkaptonuria was made and confirmed by increased urinary excretion of homogentisic acid (HGA).

Alkaptonuria is an autosomal recessive inborn error of metabolism of the aromatic amino acids phenylalanine and tyrosine owing to the deficiency of homogentisate 1,2-dioxygenase (HGO) activity in the liver, estimated to affect between one in 250 000 and one in 1 000 000 people. Tissue injury, typically apparent in the fourth to fifth decade as joint pain, is due to the inability to translate HGA to maleylacetoacetic acid, resulting in the accumulation of its oxidation products benzoquinones in collagenous tissues, which appears yellow on microscopic examination (ochronosis). Deficiency in HGO activity has been mapped to chromosome 3q21–q23, with over 80 mutations discovered. Patients are either homozygous or compound heterozygous for loss-of-function mutations, with no relationship between the levels of HGA excretion and the clinical syndrome. Alkaptonic heart disease typically not only involves the calcification of aortic valve, but may also involve the mitral valve, endocardium, and pericardium, as well as the aortic intima and coronary arteries. So far, no effective treatment for alkaptonuria exists.

Panel A. Bluish-black discoloration of the sclera.
Panel B. Bluish-black discoloration of the auriculum.
Panel C. Following standing, the patient’s urine blackened.
Panel D. X-ray (left anterior oblique 45°) of the aortic valve revealed severe calcification.
Panels E and F. Extensive calcification and bluish-black discoloration of the tricuspid aortic valve and discoloration of the aortic intima were found on operation.

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