DIAGNOSIS: Endogenous ochronosis (alkaptonuria).

CLINICAL COURSE

A dark-brown color was obtained by adding sodium hydroxide to the normal-colored urine sample (**Figure 5**). Urinary homogentisic acid (HGA) was identified by high-pressure liquid chromatography (4-mmol/mm creatinine). Plasma and synovial fluid HGA levels were normal. High urine HGA levels were also detected in samples from the patient's parents and several of his first-degree relatives. The patient underwent surgical removal of kidney stones that were black, porous, and soft in consistency.

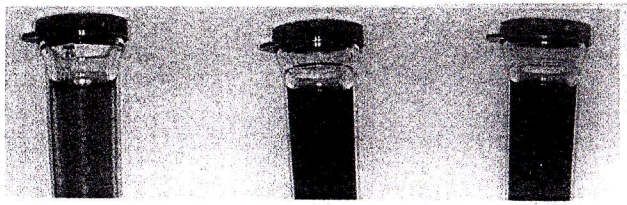

Figure 5.

DISCUSSION

Endogenous ochronosis is a rare autosomal recessive metabolic disease. Since 1858, when the first case was described, approximately 600 cases have been reported.[1] The estimated incidence of endogenous ochronosis is 1:250 000 to 1:1 000 000 persons,[2] although a 10-fold higher incidence is found in some populations, including those of Slovakia and Santo Domingo, where inbreeding may have occurred.[2] It apparently affects both sexes equally.

Pathogenesis relates to the absence of HGA oxidase in the liver and kidney of homozygotes, resulting in a block of the metabolic pathway of tyrosine and phenylalanine and in an accumulation of HGA in cartilage and collagenous tissue. The HGA is then converted to benzoquinone acetic acid and polymerized.[3,4] Ochronosis is the result of binding and chemical reaction of benzoquinone and its polymers with connective tissue.[3]

Typical sites of ochronotic pigment deposition are the eyes, skin, skeletal cartilage, and virtually all collagen-rich organs.[5,6] Eye involvement usually includes the sclera, cornea, conjunctiva, and tarsal plate. The classic eye manifestation is a triangular-shaped scleral pigmentation, with the base facing the cornea at the site of rectus muscle insertion, as seen in our case. Skin sites commonly involved include the nose, cheeks, ears, dorsal surface of the hands, axillae, and apocrine glands. Cartilage of the shoulders, axial and sacroiliac joints, hips, and knees are the most common skeletal sites involved by ochronosis. The progression of ochronotic arthropathy is the most disabling manifestation of ochronosis, appearing in the third or fourth decade of life and more commonly in males.[1,2,4]

Other systems that may be involved include the auditory, genitourinary, cardiovascular, and respiratory tracts.[4,7-10] Less common sites of pigment deposition include the teeth, central nervous system, and endocrine organs.

Histopathologic preparations show a yellow to light-brown ochre color, hence the original designation of ochronosis. Large deposits of the polymer may be seen in the dermis, extracellularly and in macrophages, vascular endothelium, and apocrine gland epithelium, and in the lumen of these glands.

The presence of pigment anomalies that are associated with a positive family history and arthropathy is, in most instances, indicative of ochronosis. Brownish black discoloration of urine, which occurs after exposure to air or the addition of alkali, is the result of HGA oxidation and is also a typical sign of ochronosis. Significant amounts of HGA are excreted in urine within the first days of life; thus, a diaper staining may be observed in affected children and may represent an early diagnostic clue. The diagnosis of ochronosis may be confirmed by measuring HGA plasma levels that sometimes may be low (in the range of 3 mg/dL) because of high renal clearance (up to 4-8 g/d).

In general, the majority of patients may lead a relatively normal life. Nevertheless, the pigmentation and orthopathy worsen with time. Little can be done to interrupt this progression. Pharmacotherapeutic approaches (including vitamin and hormone supplements) and dietary manipulations to correct the metabolic defect are generally unsuccessful.

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Perforating Papules in Chronic Renal Failure

DIAGNOSIS: Metastatic calcinosis cutis with transepidermal elimination.

HISTOPATHOLOGIC FINDINGS

Examination of hematoxylin-eosin–stained sections demonstrated mineralization within the dermis and within dilated follicular infundibulae, appearing as basophilic fine granules and larger deposits of material consistent with calcium. Larger deposits evoked a foreign body–type giant cell reaction. The overlying epidermis showed irregular acanthosis with areas of extensive pseudoepitheliomatous hyperplasia. Focally, the hyperplastic epithelium partially surrounded

In contrast, metastatic calcification is associated with abnormal systemic metabolism and serum levels of calcium and/or phosphorus, and involves mineralization of deep organs throughout the body, with occasional involvement of undamaged skin and subcutaneous tissue. A variety of disease states may result in metastatic calcification of the skin. The most common are renal failure with secondary hyperparathyroidism, the milk-alkali syndrome, vitamin D intoxication, primary hyperparathyroidism, malignancies, and tumoral calcinosis.[2]

The occurrence of metastatic soft tissue calcification in association with renal failure was originally reported by Virchow[3] in 1855. There is decreased filtration of phosphorus and impaired renal production of 1,25-

Metastatic calcinosis cutis typically presents as firm, tender papules, nodules, or plaques that may periodically discharge chalky material. The histopathologic findings consist of the typical amorphous basophilic deposits of calcium salts, which appear black with the von Kossa calcium stain. Transepidermal elimination is defined as the removal of foreign material or altered dermal components through the epidermis or follicular epithelium[4] and occurs in patients receiving dialysis either associated with calcinosis cutis or more commonly as the acquired perforating disease of chronic renal failure.[5] Although cutaneous mineralization decreases if the phosphorus level is reduced by dialysis, further improvement may be achieved with direct intralesional triamcinolone injections and the