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Case Report

Acute-Onset Multifocal Hand Dysfunction Due to Alkaptonuria

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Alkaptonuria is a rare metabolic disorder characterized by the accumulation of homogentisic acid. Its effects on the central nervous system are well-recognized; however, cases of pathologic homogentisic acid deposition in the peripheral nervous system are less well-described. We report the case of a 72-year-old man with a prior history of alkaptonuria presenting with bilateral carpal tunnel and left-sided cubital tunnel symptoms. This case is of note because the patient demonstrated a rapid onset of symptoms due to pathology at multiple foci.

Alkaptonuria is a rare metabolic disorder characterized by the accumulation of homogentisic acid (HGA), with an incidence of 1 in 250,000 to 1 million.[1] Deposition of HGA is well-recognized in the central nervous system, but corresponding changes in the peripheral nervous system are less well-described. We report the case of a 72-year-old man with a prior history of alkaptonuria presenting with bilateral carpal tunnel and left-sided cubital tunnel symptoms. This case is of note because the patient demonstrated a rapid onset of symptoms due to pathology at multiple foci.

Case Report

A 72-year-old man presented with acute-onset bilateral hand paresthesia awakening him nightly over 6 weeks. The accompanying weakness caused difficulty in driving and limited participation in activities, such as bowls. The patient reported that he had no prior issues in either hand. His medical history included alkaptonuria and chronic renal disease, and he had previously undergone aortic valve replacement.

Examination revealed bilateral thenar wasting and an adducted posture of his right thumb. He reported decreased sensation in the bilateral median nerve and left ulnar nerve distributions, and both his carpal tunnels were positive for Durkan and Tinel tests. In addition Tinel test was positive at the left cubital tunnel of the patient. The right thumb adduction limited functional opposition, which was exacerbated by severe weakness of both abductor pollicis brevii, as well as ulna-innervated musculature on the left. He exhibited tenderness over his right little and ring finger A1 pulleys (Fig. 1).

Radiographs showed a preserved first carpometacarpal joint but arthritic metacarpophalangeal joint. Neurophysiologic testing revealed severe left carpal tunnel conduction delay, with absent conduction on the right. Further, there was reduced ulna motor and absent sensory potentials across both elbows.

The patient underwent bilateral open carpal tunnel and left cubital tunnel decompressions. The ulnar nerve was not subluxing and left in situ. A1 pulley releases were performed on the right little and ring fingers. The right thumb metacarpophalangeal joint was decorticated and fused in a functional position using a locking plate. Following this, opponensplasty was performed using the ring finger flexor digitorum superficialis (looped around flexor carpi ulnaris to alter line-of-pull). Widespread brownish staining of both intra- and extra-articular tissues was noted (including the tendon sheath and perineural elements), and

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Statement of informed consent: Appropriate informed consent was obtained from the individual in this study.

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Figure 1. Preoperative clinical images demonstrating black discolouration and thenar wasting with lack of opposition (left image, active opposition, right image at rest) in a patient with alkaptonuria of the hands.

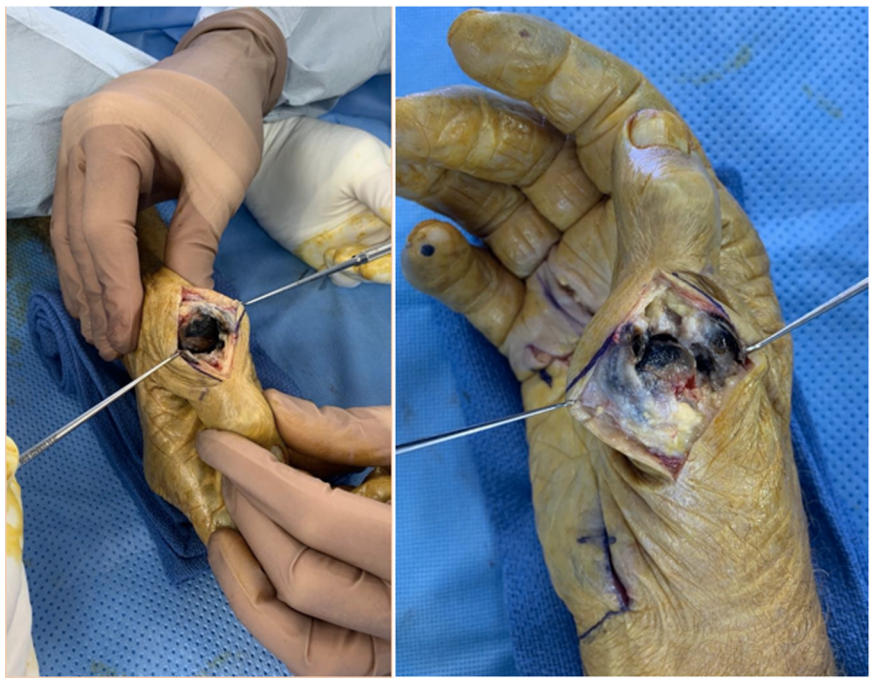

Figure 2. Intraoperative images demonstrating brown discoloration of tissues. Image to the left demonstrates extra-articular discoloration, whilst the image to the right demonstrates intra-articular discoloration.

histopathologic sampling was performed, confirming infiltration with HGA (Fig. 2).

After surgery, a dorsal slab was applied, and hand therapy with active exercises was commenced after 2 days. During the 6-week follow-up, well-matured scars and bilaterally resolving paresthesia were observed. The patient also demonstrated good opposition on his right side (Fig. 3). Histopathology revealed papillary hyperplasia, calcific debris, and pigmented collagen consistent with alkaptonuria (Fig. 4).

Discussion

Alkaptonuria is a rare metabolic disorder characterized by the accumulation and deposition of HGA (an intermediate breakdown product of tyrosine and phenylalanine) due to a complete failure of its enzyme, homogentisate 1,2-dioxygenase. Alkaptonuria is the first human disorder described with an autosomal recessive pattern of inheritance; it is now recognized that a small subtype is transmitted in an autosomal dominant fashion. Mutations may affect the structure, function, or solubility of the enzyme, resulting in the oxidization of its substrate to a pigmented polymer (benzoquinone) that binds irreversibly to collagen fibers.[2] This deposition causes an ocher-colored discoloration of tissues, leading to the disorder's alternate appellation of endogenous ochronosis.

Most patients present in their third decade of life with characteristic areas of pigmentation, such as the sclera (Osler sign); ear cartilage; nasal, buccal, or genital mucosa; and the palms and soles

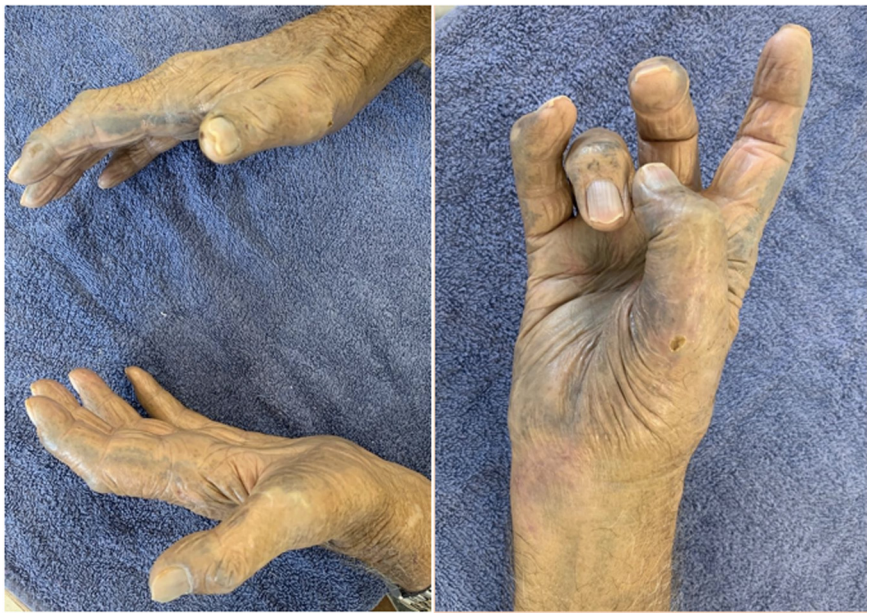

Figure 3. Post-operative images demonstrating the patient's clinical range of motion. Image on the left demonstrates the different resting hand postures between the right and left hand. Image on the right demonstrates intact opposition on the right hand.

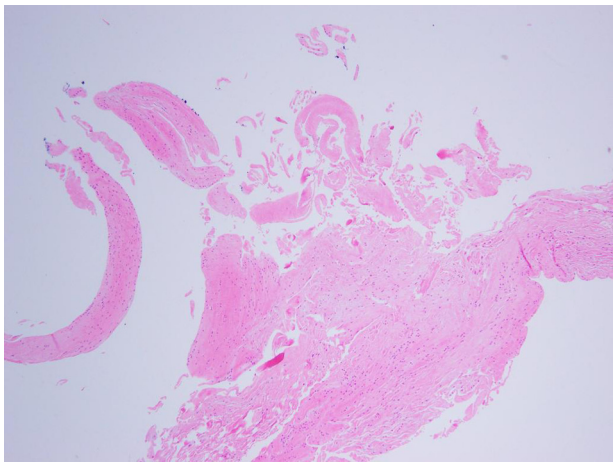

Figure 4. Histologic slide of intraoperative samples demonstrating yellow-brown pigmented collagen fibers.

along the lines of transgradience. Degenerative arthropathy is clinically apparent by the fourth decade, particularly in large joints, (such as hips and shoulders) and the spine. Altered tissue quality can lead to spontaneous rupture of ligaments or tendons.[3]

Although HGA deposition in the central nervous system is a recognized sequela, the corresponding changes in the peripheral nervous system have not been established. Regardless, patients may exhibit a broad range of neurologic signs and symptoms. A statistically significant greater prevalence of extremity numbness, weakness, and neuropathic pain; tinnitus and hearing problems; visual blurring; and tremors were demonstrated in patients with alkaptonuria when compared with healthy controls.[4] Significant differences in neurophysiologic studies between patients with alkaptonuria and controls have not been shown, and peripheral neurologic symptoms are thus likely to be a result of vertebral degeneration and foraminal stenosis. However, a single case with severe generalized polyneuropathy of both axonal and demyelinating types has been described.[4] Central symptoms such as ocular or aural dysfunction may be related to the deposition of material into and distortion of connective tissues, such as the tympanic membrane and orbital musculature.

Radiographic findings include joint space narrowing, sclerosis, and vertebral disc calcification. Hematoxylin and eosin staining of skin biopsies show yellow-brown pigmented crescentic-shaped collagen fibers.[5] These yellow-brown granules may also be seen in endothelium, sweat glands, and cartilage.

The treatment should be multidisciplinary and include regular screening for visual and auditory acuity as well as dermatologic review to exclude differentials. Nonsurgical management of arthropathy includes anti-inflammatory medication, hand therapy, lifestyle modification, and analgesia—failing this, arthroplasty may be indicated. Central and peripheral neurologic symptoms may require decompression.

This case is of note because the patient demonstrated a rapid onset of symptoms due to pathology at multiple foci. Although his small joint arthropathy may have been present previously, the patient did not recall any prior impairment. Additionally, the patient's neurologic symptoms were due to direct peripheral compression and demonstrated neurophysiologic findings that were consistent with severe neuropathy, unlike the majority of patients with alkaptonuria. Alkaptonuria can present with a spectrum of symptoms, require a high index of suspicion for diagnosis, and necessitate a multimodal and multidisciplinary therapeutic approach. Although the diagnosis of alkaptonuria did not directly impact our decision making or treatment modalities, this case highlights that the patients with this diagnosis are at risk of developing significant nerve compression, potentially necessitating tendon transfers, and therefore, early intervention may be required. These patients are at increased risk of multiple nerve compressions, and therefore, other sites may need to be screened as well.

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