CASE REPORT

Feeling Blue? It Might Just be Alkaptonuria

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Abstract

Aim: Report a case of alkaptonuria diagnosed following consultation with an otolaryngologist.

Background: Alkaptonuria is a rare genetic disorder with an autosomal recessive inheritance pattern that leads to an increase in homogentisic acid (HGA). Our aim is to raise awareness about the otolaryngology manifestations of the disease and the treatment of this disease.

Case description: A 75-year-old woman presented to an ear, nose, and throat (ENT) consultation with a history of progressive bilateral hearing loss and tinnitus. She had a history of joint pain and morning stiffness, which had previously been attributed to osteoarthritis. Physical examination revealed hyperpigmentation of the conchae, sclerae, and both hands. Laboratory tests showed significantly elevated levels of HGA in her urine, leading to a diagnosis of alkaptonuria.

Conclusion and clinical significance: Alkaptonuria is a rare genetic disorder that can present with a variety of symptoms, including joint and cardiovascular problems. This case highlights the significance of recognizing unusual symptoms, such as blue discoloration of the ears, as potential indicators of alkaptonuria.

Keywords: Alkaptonuria, Blue, Cartilage, Case report, Homogentisic acid, Genetics, Nitisone, Ochronosis.

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Background

Alkaptonuria is a rare autosomal recessive disease impacting a global population ranging from 1 in 250,000 to 1 million individuals.[1] This disorder was first described by Archibald Garrod in 1902 and is attributed to a mutation in the homogentisate 1, 2-dioxygenase (HGD) gene on chromosome 3q13, resulting in the loss of function of the HGD enzyme.[2,3] Consequently, there is an increase in homogentisic acid (HGA), an intermediate substance in the tyrosine breakdown pathway, leading to the formation and buildup of a pigment similar to melanin, which specifically accumulates in connective tissues. This accumulation can give rise to a variety of health issues, including ochronotic osteoarthropathy and cardiovascular diseases such as valvular calcifications. [2–6] Additionally, dark pigmentation of the skin, and sclera may also be observed.[6] Notably, there is no scientific literature indicating any perceivable influence on visual function due to the deposition of pigment in the sclera.[5]

Individuals affected by this condition typically do not show symptoms during infancy or childhood and often remain unaware of their condition until adulthood, when ochronosis develops.[5]

Case Description

A 75-year-old female presented to an ear, nose, and throat (ENT) consultation with a history of progressive bilateral hearing loss and tinnitus. She had a history of joint pain and morning stiffness, which had been previously attributed to osteoarthritis. Physical examination revealed hyperpigmentation of the conchae (Fig. 1), sclerae (Fig. 2), and both hands (Fig. 3), and the tympanic membranes were intact, pearly-grey in color, translucent, and mobile on insufflation. Pure tone audiometry revealed mild sensorineural hearing impairment marked by a decline in high-frequency hearing, typical of presbycusis. The patient was prescribed hearing aids and referred for an internal medicine consultation. Upon further

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Patient consent statement: The author(s) have obtained written informed consent from the patient for publication of the case report details and related images

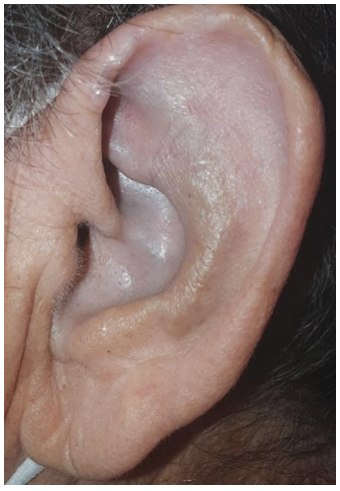

Fig. 1: Hyperpigmentation of the conchae

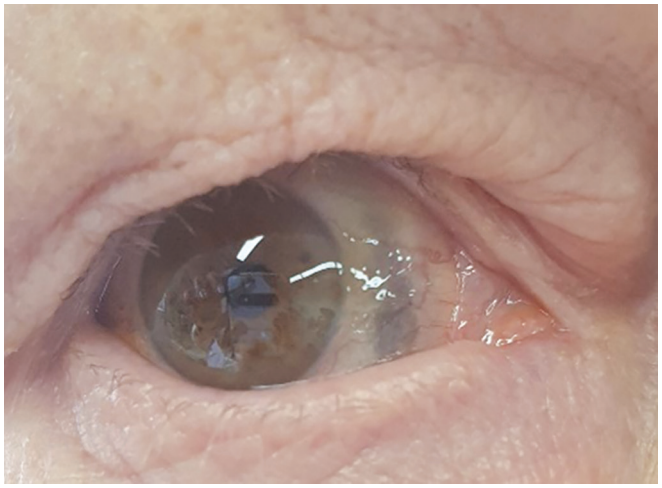

Fig. 2: Hyperpigmentation of the sclerae

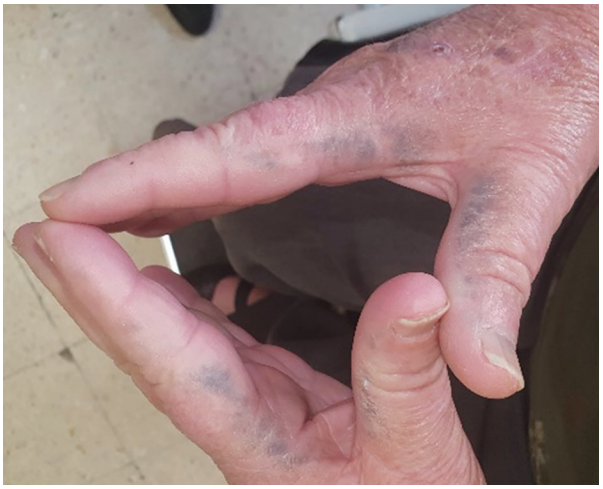

Fig. 3: Hyperpigmentation of both hands

examination, it was evident that the urine exhibited a characteristic dark appearance following alkalinization with potassium hydroxide (KOH), and laboratory tests showed significantly elevated levels of HGA in her urine, leading to a diagnosis of alkaptonuria.

Discussion

Alkaptonuria exhibits three distinct characteristics: ochronotic osteoarthropathy, homogentisic aciduria, and ochronosis. Ochronosis, resulting from the polymerization of HGA, typically emerges in the third to fifth decade of life, leading to the deposition of a melanin-like pigment in the ears and eyes.[4]

In a study conducted by Steven and colleagues, a range of ENT findings were documented in individuals with alkaptonuria, including external ear discoloration (60%), discolored earwax (65%), discolored tympanic membrane (10%), stained middle ear structures (5%), otalgia (15%), tinnitus (30%), and high-frequency hearing loss (50%).[6]

While clinical history is often indicative, the gold-standard diagnostic test for alkaptonuria is a urine test for HGA. Quantification of HGA in a 24-hour urine sample is accomplished through gas chromatography-mass spectrometry analysis.[3] Moreover, the identification of a genetic defect within the homogentisate 1, 2-dioxygenase-coding gene located on the 3q chromosome reinforces the diagnosis of alkaptonuria.[4]

Historically, there has been a lack of definitively established treatments aimed at averting the complications associated with alkaptonuria. Dietary protein restriction has been suggested to reduce HGA excretion, and ascorbic acid has been used as an antioxidant to inhibit the conversion of HGA into ochronotic pigment, although its effectiveness remains unproven.[2,5]

A major breakthrough for alkaptonuria occurred in 2020 when a novel therapeutic approach known as nitisinone was introduced. This treatment effectively reduces the levels of HGA in both plasma and urine, reshaping the progression and intensity of the condition, with a particular focus on mitigating ochronosis, the central hallmark of the disease.[5] Ongoing investigations will persistently probe into the mechanisms through which nitisinone operates and its potential applications in addressing other disorders, with the overarching aim of enhancing patient well-being and overall quality of life.[2]

Conclusion and Clinical Significance

Alkaptonuria is an uncommon genetic disorder that can present with a variety of symptoms, including joint and cardiovascular problems. This case report underscores the significance of identifying atypical manifestations, such as blue discoloration of the ears, as potential indicators of alkaptonuria. Otolaryngologists should possess awareness of the ENT manifestations associated with alkaptonuria, since early diagnosis and management of this condition are crucial to prevent further joint damage and cardiovascular complications.

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