A rare disease causing carpal tunnel syndrome

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ABSTRACT

Carpal tunnel syndrome (CTS) is a common form of median nerve compression, occurring when the median nerve is compressed at the wrist. Symptoms include hand pain, numbness, and tingling in the median nerve's distribution. Risk factors are obesity, repetitive wrist movements, pregnancy, genetics, and rheumatoid inflammation. A 75-year-old with ochronosis, causing pigmentation and chronic joint inflammation, presented with bilateral CTS linked to ochronotic arthritis.

Introduction

Carpal tunnel syndrome (CTS) is recognized as the most prevalent entrapment neuropathy, impacting approximately 3-6% of the adult population.[1] It occurs more frequently in females than in males,[2] with the highest prevalence observed in females who have a body mass index (BMI) higher than 29 and the lowest prevalence in males with a BMI lower than 25.[3]

CTS occurs when the median nerve is compressed in the carpal tunnel, causing pain, paresthesia, and sometimes weakness in the thumb, index finger, middle finger, and radial side of the ring finger. This can reduce grip strength and hand function. Prolonged CTS may also cause muscle wasting at the base of the thumb.

Compression in the carpal tunnel often results from increased compartmental pressure, commonly due to hypertrophy of the synovial tissue around the forearm's extrinsic tendons. This hypertrophy can arise from extensive use, wrist trauma, or conditions like arthritis.[4] Other causes include small anatomic space, mass lesions (*e.g.*, cysts, neoplasms), acromegaly, obesity,[3] pregnancy,[5] oral contraceptive use, or systemic illnesses such as hypothyroidism, and renal failure. Neuropathic factors include diabetes, amyloidosis, alcoholism, vitamin imbalances, and toxicity.[6-8] Increased pressure in the intracarpal canal contributes to clinical CTS by directly damaging the nerve, impairing axonal transport, and causing median nerve ischemia due to microvasculature dysfunction.[6-8]

Ochronosis is a rare autosomal recessive disorder where dark pigment accumulates in connective tissues, giving an ochre hue under a microscope. This condition, first described by Virchow, results from excessive homogentisic acid (HGA) due to a lack of homogentisic oxidase.[9,10] The surplus HGA binds to collagen, causing chronic inflammation, osteoarthritis, tendon ruptures, and aortic stenosis. HGA also darkens urine when left standing, which helps confirm the diagnosis through elevated urine HGA levels.[11] No cases of ochronosis with bilateral CTS have been reported in medical literature.

Case Report

A 75-year-old male presented with a prolonged history of upper extremity pain and diminished hand function. The patient described wrist and finger discomfort, numbness, paresthesia, reduced grip strength, intermittent clumsiness, and an increased propensity for dropping objects. These sensory disturbances, predominantly affecting the thumb,

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index, middle, and ring fingers, initially manifested nocturnally but progressed to occur during daytime activities such as driving or reading. More recently, he reported progressive loss of sensation and muscle strength.

His medical history is significant for aortic valve replacement and bilateral hip arthroplasty at age 60. Histopathological analysis of the cartilage from the hip replacement revealed pigmented amorphous deposits in both articular cartilage and synovium, papillary hyperplasia, and granulomatous inflammation with giant cells and non-birefringent pigment ingestion observed under polarized light. For chronic shoulder pain associated with severe glenohumeral and acromioclavicular osteoarthritis, the patient regularly used non-steroidal anti-inflammatory medications.

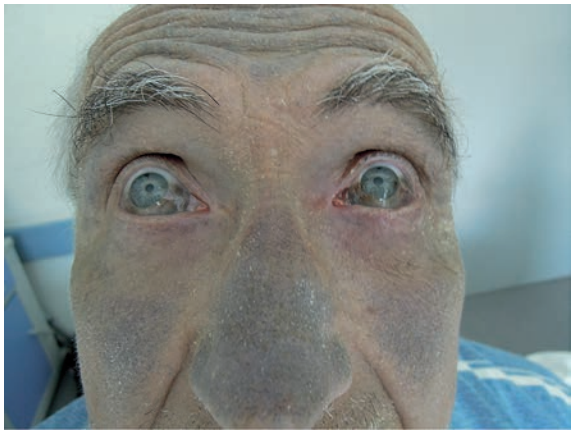

Figure 1. Dark discoloration of the sclera and facial skin.

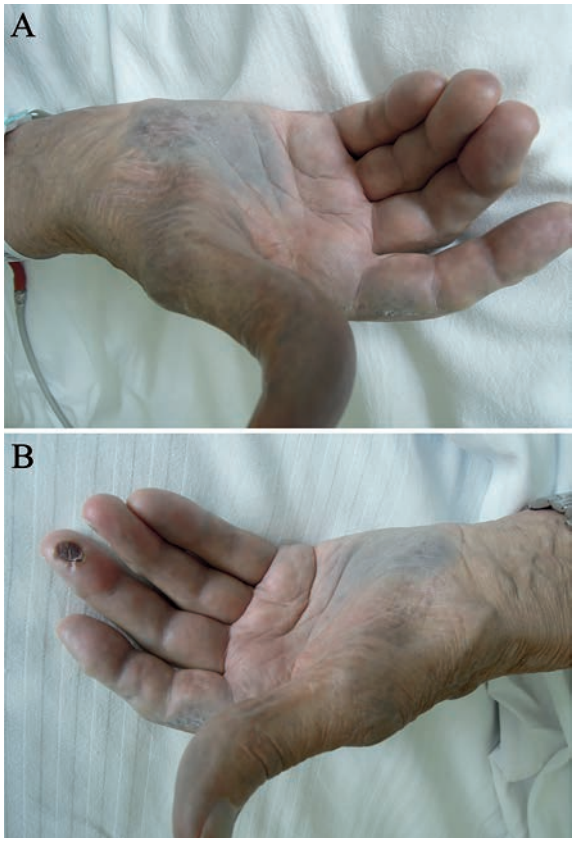

Figure 2. Bluish-black pigmentation of the hands and marked thenar eminence wasting (A and B). Additionally, a trophic ulcer was present on the left middle finger, indicative of compromised protective sensation (B).

Physical examination revealed dark discoloration of the sclera and facial skin (Figure 1), bluish-black pigmentation of the hands, and marked thenar eminence wasting (Figure 2A and B). Additionally, a trophic ulcer was present on the left middle finger, indicative of compromised protective sensation (Figure 2B). Clinical findings (reduced grip strength, thenar muscle atrophy, positive Tinel's and Phalen's signs, and digital sensory deficits) raised suspicion for CTS secondary to ochronotic arthropathy.

Laboratory findings were unremarkable except for mild anemia. Further testing excluded common etiologies of CTS, including abnormal thyroid-stimulating hormone, rheumatoid factor, anti-citrullinated peptide antibodies, and antinuclear antibody serology. Notably, the patient's urine was darkly pigmented and demonstrated elevated HGA levels (Table 1). Diagnosis was confirmed by identification of a pathogenic mutation in the *HGD* gene, which results in the production of the enzyme homogentisate 1,2-dioxygenase (HGO).

Table 1. Blood and urine investigations.

	Results	Normal values
White blood cells ($\times 10^3/\mu L$)	8.2	4.20-11.00
Red blood cells ($\times 10^6/\mu L$)	3.55	4.20-6.00
Hb (g/dL)	10.9	13-17
MCV (fl)	93.8	80-100
Platelets ($\times 10^3/\mu L$)	445	130-450
CRP (mg/L)	7	0.5-5
Glucose (mg/dL)	110	60-110
Creatinine (mg/dL)	0.67	0.67-1.17
GOT (U/L)	21	5-45
GPT (U/L)	15	4-45
Bilirubin (mg/dL)	0.95	0-1.2
Sodium (mmol/L)	141	133-146
Potassium (mmol/L)	4.5	3.5-5.4
Calcium (mmol/L)	4.8	4.2-5.1
Phosphate (mg/dL)	3.5	2.4-4.7
TSH (µUI/mL)	2.1	0.4-4
RF (U/L)	<10	<10
Anti-CCP antibodies (U/mL)	0.7	<20
ANA	Neg	Neg
Urine HGA (mg/24h)	2900	0-5 mg/24 h

Hb, hemoglobin; MCV, mean corpuscular volume; CRP, C-Reactive protein; GOT, glutamic-oxaloacetic transaminase; GPT, glutamate pyruvate transaminase; TSH, thyroid-stimulating hormone; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; ANA, antinuclear antibody; HGA, homogentisic acid.

Discussion

Ochronosis, also known as alkaptonuria, is a rare autosomal recessive metabolic disorder resulting from deficient activity of HGO in the liver.[12] HGO deficiency leads to the excretion of large amounts of HGA in the urine,[13,14] which darkens upon standing. In urine and tissues, HGA oxidizes to benzoquinones, subsequently forming melanin-like polymers that irreversibly bind to collagen, causing blue-brown pigmentation.

Accumulation of HGA and its metabolites in collagen-rich connective tissues such as the sclera, cartilage, skin, tendons, ligaments, and intima of large vessels results in ochronosis, characterized by increased pigmentation of cartilaginous tissues and bone, arthritis, joint degeneration, and impairment of cardiac valves.[11,13,14]

The condition progresses to persistent joint pain and inflammation, predominantly affecting the spine and larger joints, including the knee, hip, and shoulder, followed by deterioration and calcification of tendons, ligaments, intervertebral discs, and increased bone resorption. The affected connective tissues become more fragile over time, contributing to degenerative alterations and osteoarthritis. Tendon and ligament ruptures and nephrolithiasis may also occur.

Currently, there are no reported cases linking CTS to ochronosis. The carpal tunnel contains tendons and other connective tissue structures, including nine flexor tendons and a robust flexor retinaculum within a limited space bordered by the transverse ligament and carpal bones. Therefore, osteoarthritis of the carpal bones and abnormalities of the retinaculum and tendons may contribute to the development of CTS. In this patient, advanced age was the only predisposing factor identified for CTS (Table 2).

Table 2. Predisposing factors implicated in carpal tunnel syndrome.

Anatomical and genetic factors
Smaller carpal tunnel (often genetic)
Family history of carpal tunnel syndrome
Repetitive use/occupational stress
Repetitive hand or wrist movements
Use of vibrating tools
Poor wrist ergonomics or posture
Medical conditions
Diabetes
Hypothyroidism
Rheumatoid arthritis
Osteoarthritis
Obesity
Acromegalia
Amyloidosis
Neuropathies
Kidney failure
Sarcoidosis
Crystal arthropathies (*e.g.*, gout, pseudogout)
Sclerodermia
Infections (Lyme disease, tuberculosis, leprosy)
Hormonal/metabolic changes
Pregnancy (especially the third trimester)
Oral contraceptive use
Trauma/structural causes
Wrist fractures
Tendon inflammation (tenosynovitis)
Ganglion cysts or tumors in the carpal tunnel
Hematoma
Advanced age (degenerative changes, decreased nerve resilience, cumulative mechanical stress, comorbidities)

Conclusions

CTS is the most common peripheral nerve entrapment syndrome, first studied in 1854 by Paget. Collagen fibrils are the basic elements of tendons, ligaments, and bones, all of which are specialized connective tissues, and the basic elements of the carpal tunnel.

Ochronosis causes deposition of ochronotic pigment in the tendons and ligaments. Besides, it can cause chronic osteoarthritis of large and small joints.

Alterations in some properties of collagen, such as elasticity and endurance, may translate into changes in carpal tunnel pressure, leading to median nerve compression. Increased thickness of connective tissues of the carpal tunnel, inflammation, and edema may impair the nerve blood supply, leading to manifestations of CTS.

References

1. Pourmemari MH, Heliövaara M, Viikari-Juntura E, Shiri R. Carpal tunnel release: lifetime prevalence, annual incidence, and risk factors. Muscle Nerve 2018;58:497-502.
2. Atroshi I, Gummesson C, Johnsson R, et al. Prevalence of carpal tunnel syndrome in a general population. JAMA 1999;282:153-8.
3. Werner RA, Albers JW, Franzblau A, et al. The relationship between body mass index and the diagnosis of carpal tunnel syndrome. Muscle Nerve 1994;17:632-6.
4. Feldon P, Terrono AL. Carpal tunnel syndrome in rheumatoid arthritis. Tech Orthop 2006;21:42-7.
5. Osterman M, Ilyas AM, Matzon JL. Carpal tunnel syndrome in pregnancy. Orthop Clin North Am 2012;43:515-20.
6. Werner RA, Andary M. Carpal tunnel syndrome: pathophysiology and clinical neurophysiology. Clin Neurophysiol 2002;113:1373-81.
7. Aboonq MS. Pathophysiology of carpal tunnel syndrome. Neurosciences 2015;20:4-9.
8. Singh R, Gamble G, Cundy T. Lifetime risk of symptomatic carpal tunnel syndrome in type 1 diabetes. Diabet Med 2005;22:625-30.
9. Garrod E. The incidence of alkaptonuria: a study in chemical individuality. Lancet 1902;2:1616-20.
10. Garrod E. The Croonian lectures on inborn errors of metabolism. Lancet 1908;172:214-20.
11. Phornphutkul C, Introne WJ, Perry MB et al. Natural history of alkaptonuria. N Engl J Med 2002;347:2111-21.
12. La Du BN, Zannoni VG, Laster L et al. The nature of the defect in tyrosine metabolism in alkaptonuria. J Biol Chem 1958;230:251-60.
13. La Du BN. Alkaptonuria. In: Royce PM, Steinmann B, eds. Connective tissue and its heritable disorders. 2nd ed. New York: John Wiley; 2002. pp. 809-25.
14. O'Brien WM, La Du BN, Bunim, JJ. Biochemical, pathologic and clinical aspects of alcaptonuria, ochronosis and ochronotic arthropathy: review of world literature (1584-1962). Am J Med 1963;34:813-38.