CASE REPORT

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Brucellosis in a Patient with Ochronosis – A Rare Case

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Abstract

Alkaptonuria, an inborn error of metabolism, is due to deficient activity of homogentisic acid dioxygenase(HGD) enzyme. It is known to commonly present as spondyloarthritis, especially in the third decade. We discuss the case of a 49-year-old lady, who had presented with fever, backache, and multiple joint pains for 8 months, aggravated since the past 1 week. This case highlights the need to consider an additional diagnosis especially when there is no clinical improvement and the fever persists. Having a high index of clinical suspicion for a treatable cause like brucellosis is favourable, as it can lead to a better outcome.

Key words: Brucellosis, ochronosis, spondyloarthritis.

Introduction

Alkaptonuria is an autosomal recessive inborn error of metabolism characterised by a defect in the catabolic pathway of tyrosine, due to deficient activity of homogentisic acid dioxygenase (HGD) enzyme. This results in elevated levels of homogentisic acid (HGA), which upon polymerisation, forms a pigment which gets deposited in tissues, typically in the ear cartilage and sclera, leading to a condition called ochronosis. Affected patients are usually asymptomatic in childhood. There is also pigment deposition in large joints and spine, typically in the lumbosacral region. Calcification of multiple intervertebral discs is a characteristic radiological finding. Development of ochronotic arthritis and subsequent ankylosis results in limitation of the range of motion. The diagnosis is confirmed by quantitative measurement of HGA in urine and mutation analysis of the HGD gene. Tyrosine levels are normal.

Case description

A 49-year-old lady, no premorbid conditions, post-menopausal, presented to our outpatient department with complaints of fever, backache, and multiple joint pains for 8 months, aggravated since the past 1 week. She denied any scaly skin lesions and prolonged diarrhoea. However, she had exposure to cattle as she was a farmer. General physical examination revealed a hyperpigmented lesion on the lateral aspect of left sclera (Fig. 1), hyperpigmentation of left concha, and hyperpigmented macules on the left forearm and left shin (Fig. 2). Local examination revealed severe limitation in the range of movement of bilateral hip joints, knee joints and ankle joints. Straight leg raising (SLR) was positive. Figure of 4 test was positive bilaterally, suggesting a possible sacroiliitis. Rest of the systemic examination was unremarkable.

Complete haemogram revealed high ESR (95 mm/hr). X-ray showed loss of lumbar lordosis, intervertebral disc calcification, and decrease in intervertebral joint spaces, lumbar vertebral body lesions, and sacroiliitis (Fig. 3). MRI spine was confirmative of the same. Due to the comparatively young age of onset of the above-mentioned bone pathologies, and general hyperpigmentation, ochronosis was suspected. Homogentisic aciduria was measured, which came as positive (by qualitative testing). Urine sample turned black on exposure to silver nitrate (Fig. 4).

Presence of fever during admission pointed to a

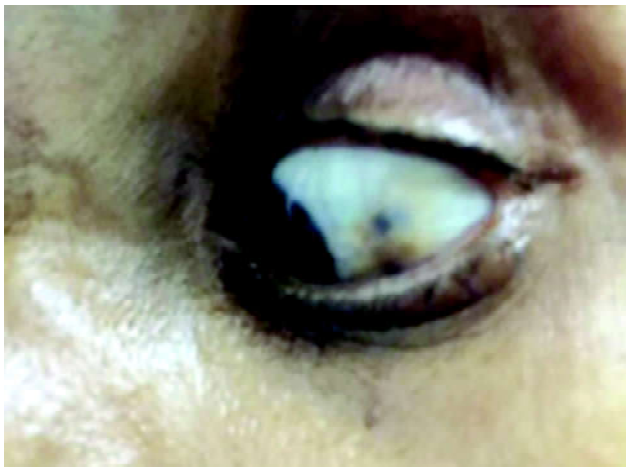

Fig. 1: *Hyperpigmented lesion in the left bulbar conjunctiva.*

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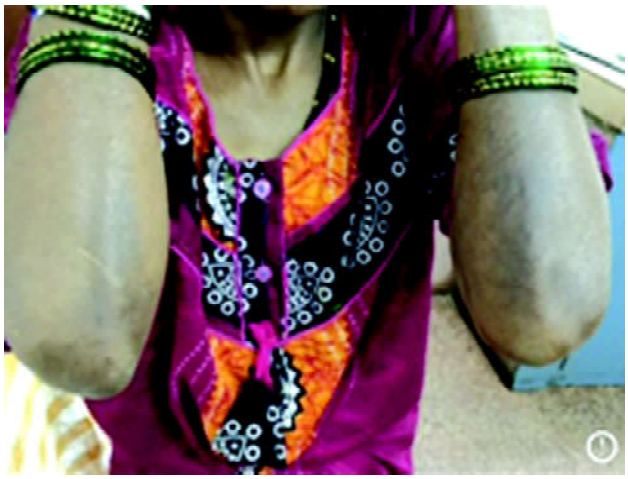

Fig. 2: *Figure showing forearm lesions.*

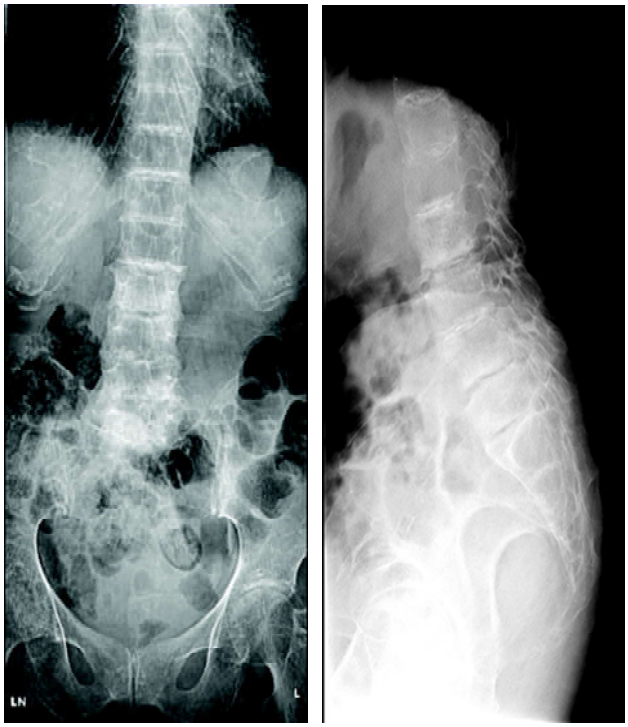

Fig 3: *X-rays showing calcification of intervertebral discs, reduced joint space, and reactive sclerosis.*

Fig. 4: *Change of colour of urine to black on exposure to silver nitrate.*

secondary cause, other than ochronosis. Her chest X-ray was normal and Mantoux test was negative – ruling-out the possibility of tuberculosis. Blood cultures were sterile. Echocardiogram ruled-out infective endocarditis. Brucella agglutination test was strongly positive (1:640) suggesting Brucellosis. Her clinical picture favoured coexistent Ochronosis with brucellosis. She was treated with a 6 week course of Rifampicin and Doxycycline after which her symptoms significantly improved, and she had no further fever.

For Ochronosis she was started on high-dose of oral vitamin C and N-acetylcysteine. Nitisinone could not be started due to financial constraints. Thereafter she came back for follow-up only after 1.5 years, at that time fever was absent, back ache had decreased, blood culture was sterile and Brucella agglutination titre had reduced.

Discussion

Axial spondyloarthritis is a potentially debilitating inflammatory arthritis of the spine, usually presenting as chronic back pain in the third decade of life[1]. It is often associated with one or more features like synovitis, enthesitis, dactylitis, and oligoarthritis. Non articular features include uveitis, psoriasis, and inflammatory bowel disease. Differential diagnoses to be considered are ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease related arthropathy and reactive arthritis. Infective spondylodiscitis secondary to staphylococcus and tuberculosis should be borne in mind in such scenarios in the presence of fever and low back ache[2].

Ochronosis, an autosomal recessive disorder was first described by Virchow to denote a brownish-black pigmentation of connective tissue in patients with alkaptonuria[3]. The predominant deposition of homogentisic acid in cartilage (including the intervertebral discs and articular cartilage) causes collagen brittleness and consequent breakdown of the tissue, which in turn leads to spondylosis and large joint arthropathy. Though ochronosis is a rare entity, it must be suspected in classical presentations, like scleral and ear cartilage pigmentation. Characteristic findings on X-ray include articular space narrowing, osseous ankylosis, calcifications, osteophytosis, reactive sclerosis of the articular surfaces. Early identification is crucial, as delayed intervention after arthritis sets in, may not lead to resolution[4].

Clinically, there can be a significant overlap between ochronosis and brucellosis, especially regarding the presence of back pain. In patients with ochronosis, persistence of fever should encourage towards evaluating further, for another co-existing cause. Also, considering history of significant exposure to cattle, brucellosis is a

possibility that needs to be ruled-out. There is no approved treatment for alkaptonuria. Nitisinone has been studied and found to decrease the HGA levels by >95%[1,5]. But it is not beneficial in patients with well-established arthritis[5]. Dietary restriction of tyrosine and phenylalanine reduce HGA excretion, although the clinical effect is limited[5]. Ascorbic acid inhibits the conversion of HGA into polymers, but its efficacy has not been demonstrated for ochronosis[6].

Brucellosis, also known as undulant fever is a zoonotic infection caused by *Brucella spp* and is transmitted to humans from infected animals. It typically presents with insidious onset of fever, malaise, night sweats, and arthralgia. Osteoarticular disease can occur in up to 70% of patients. Other presentations include peripheral arthritis, sacroiliitis and spondylitis[7]. Other non-articular complications are genitourinary involvement, neurologic involvement (meningitis, encephalitis, brain abscess, radiculitis, neuritis), cardiovascular (endocarditis, myocarditis, pericarditis, endarteritis, thrombophlebitis, mycotic aneurysms), pulmonary involvement (bronchitis, interstitial pneumonitis, pleural effusion, empyema, hilar lymphadenopathy), hepatic or splenic abscesses, ocular involvement (uveitis, corneal ulcers, choroiditis, optic neuritis, papilloedema, endophthalmitis).

Hence, suspecting an additional diagnosis of brucellosis was beneficial in this patient, as it led to early diagnosis and prompt treatment with partial resolution of symptoms.

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