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A diagnostic trap in axial pain: Ochronotic spondylopathy masquerading as ankylosing spondylitis

Aksiyel ağrıda tanısal bir tuzak: Ankilozan spondiliti taklit eden okronotik spondilopati

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To the Editor,

Alkaptonuria is a rare autosomal recessive disorder caused by homogentisate 1,2-dioxygenase deficiency, leading to systemic accumulation of homogentisic acid (HGA). Its hallmark, ochronosis, results from HGA polymer deposition in connective tissues, causing pathognomonic pigmentation and degenerative arthropathy. Because axial pain and stiffness often dominate the presentation, ochronotic spondylopathy frequently mimics ankylosing spondylitis (AS), leading to misdiagnosis and inappropriate immunomodulatory therapy.[1,2]

We report a 47-year-old male who has had chronic axial pain since his mid-twenties. He had a four-year history of treatment for presumed AS with methotrexate, sulfasalazine, and non-steroidal anti-inflammatory drugs, achieving only partial relief. The initial diagnosis was based on chronic inflammatory back pain and a positive human leukocyte antigen (HLA)-B27 test. On examination, bluish-grey discoloration were seen in both auricles (Figure 1). Spinal mobility was restricted and painful; chest expansion was 4 cm, and the modified Schober excursion was 3 cm. Laboratory testing showed elevated C-reactive protein (CRP), while erythrocyte sedimentation rate was within normal limits. Radiographs demonstrated multilevel intervertebral disc narrowing with prominent "wafer-like" calcifications and subchondral sclerosis. Contrast-enhanced sacroiliac magnetic resonance imaging performed as part of our assessment showed no evidence of sacroiliitis (Figure 2). A simple bedside observation strongly supported the diagnosis: the patient's urine darkened significantly after standing for 24 hours (Figure 3). Measurements

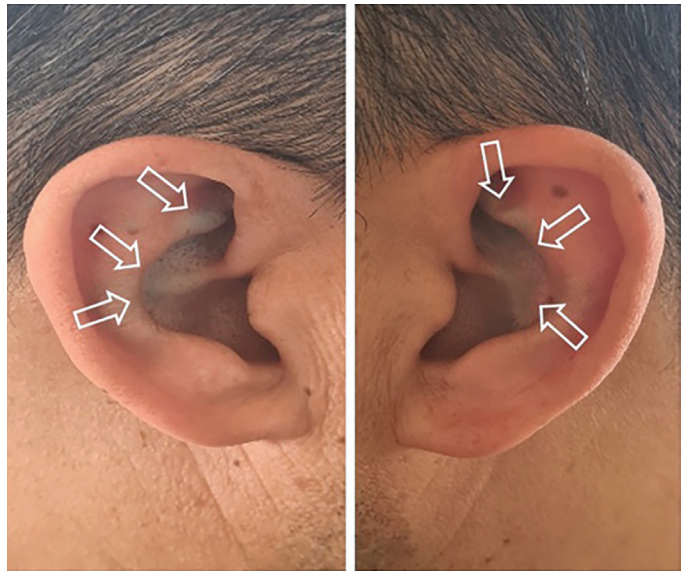

Figure 1. Bluish-grey pigmentation of the auricular cartilage (arrows)

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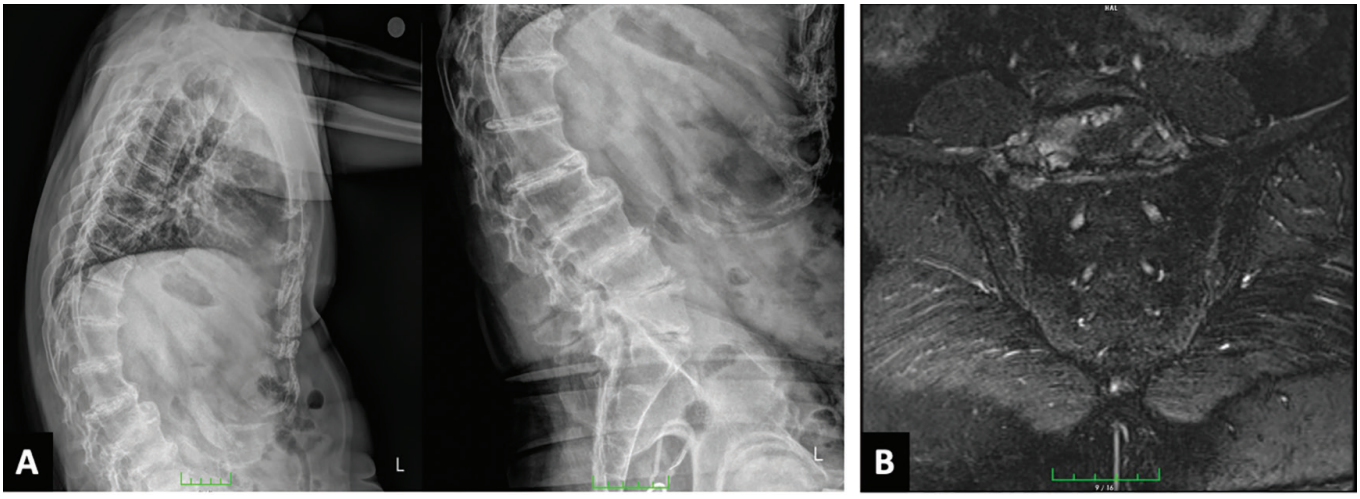

Figure 2. Radiographic and MRI assessment of the spine and sacroiliac joints. (**A**) Spinal radiographs demonstrating multilevel intervertebral disc space narrowing with characteristic "wafer-like" discal calcifications and subchondral sclerosis. (**B**) Contrast-enhanced fat-saturated T1-weighted MRI of the sacroiliac joints showing normal joint spaces and no evidence of active sacroiliitis (no pathological contrast enhancement or bone marrow edema)
MRI: Magnetic resonance imaging

Figure 3. Darkening of the patient's urine after standing for 24 hours, a bedside observation that strongly supported the clinical diagnosis of ochronosis. Measurement of urinary homogentisic acid and genetic testing were not performed

of urinary HGA and genetic testing were not performed; therefore, biochemical/genetic confirmation is unavailable, and the diagnosis relies on characteristic clinical, radiographic, and bedside findings.

This case highlights a critical diagnostic pitfall. Ochronosis can mimic the established features of inflammatory back pain and may even fulfill the classification criteria for axial spondyloarthritis (in this patient, the Assessment in SpondyloArthritis International Society criteria were met by inflammatory back pain, HLA-B27 positivity, and elevated CRP), which helps explain the original diagnosis and treatment. However, several clues should prompt consideration of ochronosis rather than axial spondyloarthritis: first, the radiographic pattern, as ochronosis commonly shows marked intradiscal calcification and degenerative changes with prominent "wafer-like" disc calcifications and absence of sacroiliitis; second, the presence of characteristic connective tissue pigmentation (e.g., auricular pigmentation); and third, the simple bedside urine darkening test, which strongly supports the clinical diagnosis when present.[1-5] Although inflammatory biomarkers are often normal in ochronosis, they may be elevated in some cases (as in our patient), making clinical vigilance and careful imaging interpretation essential. Diffuse idiopathic skeletal hyperostosis (DISH) was considered in the differential diagnosis; however, the absence of flowing anterior ligamentous ossifications and the presence of pathognomonic "wafer-like" intradiscal calcifications, together with early-onset auricular pigmentation, favored ochronosis over DISH.

Mislabeling ochronosis as AS exposes patients to ineffective or unnecessary immunomodulatory therapies and delays appropriate surveillance for systemic complications such as valvular disease, renal stones, and ocular involvement.[2-5] In our patient, there was no history of nephrolithiasis or cardiac valve disease; the ophthalmic examination revealed blepharitis but no scleral pigmentation or other ocular ochronotic signs. Targeted systemic screening was initiated, and the patient is being followed. Nitisinone therapy was not considered at the time of evaluation. Because biochemical or genetic confirmation was not obtained, we describe the diagnosis as strongly supported clinically rather than biochemically confirmed.

Ochronosis should be considered in the differential diagnosis of AS when imaging shows multilevel disc calcification without sacroiliitis, particularly when auricular or other connective-tissue pigmentation is present, and a urine darkening test is positive. Careful review of sacroiliac imaging, consideration of DISH in the differential, and targeted additional investigations (computed tomography spine and/or urinary HGA/genetic testing when available) can prevent premature diagnostic commitment and ensure timely evaluation for systemic involvement.

Footnotes

Authorship Contributions

Concept: H.A., M.T.Y., Design: H.A., S.K., Data Collection and Processing: H.A., M.T.Y., Analysis and Interpretation: S.K., Literature Search: H.A., S.K., Writing: H.A., M.T.Y.

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