Case Report

Destructive Arthritis in a Patient with Haim-Munk Syndrome

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ABSTRACT. Haim-Munk and Papillon-Lefèvre are 2 closely related syndromes, inherited in an autosomal recessive pattern, manifested by palmoplantar keratoderma and early, destructive periodontitis. Recently, mutations in the cathepsin C gene have been recognized in both syndromes. We describe a patient with Haim-Munk syndrome (palmar plantar keratosis and periodontitis) and destructive arthritis of the wrists and shoulder joints, an association that has not been previously described. (J Rheumatol 2004;31:814–7)

Key Indexing Terms:
HAIM-MUNK SYNDROME
PALMOPLANTAR KERATODERMA
CATHEPSIN C
DESTRUCTIVE PERIODONTITIS

The Haim-Munk (HMS) MIM 245010 and Papillon-Lefèvre syndrome (PLS) MIM 245000 are rare autosomal recessive traits characterized by palmoplantar keratosis (PPK) and severe, early onset periodontitis, affecting both deciduous and permanent dentitions[1,2].

The periodontal disease associated with these syndromes is particularly aggressive and unresponsive to traditional periodontal therapies. As a result, most patients become edentulous by 20 years of age. In addition, some patients are reported to have an increased susceptibility to infections as well as a surplus of ectopic intracranial calcifications and mental retardation[3].

HMS shares the cardinal features of PLS yet includes a number of additional findings such as arachnodactyly, acro-osteolysis, atrophic changes of the nails, and radiographic changes of the fingers consisting of tapered, pointed phalangeal ends and a claw-like volar curve[1].

PLS cases have been described throughout the world at a frequency of roughly 1 to 4 per million people, with parental consanguinity reported in almost half of cases[4]. HMS has only been described among descendants of a Jewish religious isolate originally from Cochin, India, in which parental consanguinity is also characteristic[1].

Recently, mutations in the cathepsin C gene were identified as the underlying genetic defect in both PLS[5] and HMS[6]. The lysosomal protease cathepsin C gene (CTSC) message is expressed at high levels in a variety of immune cells including polymorphonuclear leukocytes, macrophages, and osteoclasts[7,8]. CTSC is also expressed in epithelial regions commonly affected by PLS and HMS, including the palms, soles, knees, and oral keratinized gingival[5]. All patients are homozygous for cathepsin C mutations, while heterozygous parents and siblings do not show any disease manifestations[6].

We report a novel association of a patient with HMS and symmetric destructive arthritis of the wrists and shoulders.

CASE REPORT

A 35-year-old woman was referred to the rheumatology division with symmetric oligoarticular arthritis involving the wrist and shoulder joints.

She was the product of an inbred marriage of Jewish immigrants from Cochin, India. She and a second sister out of 4 siblings were diagnosed with Haim-Munk syndrome at a young age due to keratosis palmoplantaris that became evident soon after birth, premature shedding of deciduous teeth beginning at 4 years of age, arachnodactyly, and acro-osteolysis. Both sisters were later found to carry 2 identical mutations of the cathepsin C gene[5]. Their parents and a healthy brother were found to be carriers of the same mutation, consistent with an autosomal recessive inheritance.

Her medical history consisted of conservative treatment for severe periodontitis, which eventually failed, necessitating the wearing of dentures since the age of 12. Palmoplantar hyperkeratosis was treated with topical emollients with partial improvement. Retinoic acid analogs provided better results but were only used briefly due to fear of side effects.

Rheumatic manifestations consisting of bilateral wrist and hand arthralgias first became evident in 1992, when the patient was in her early twenties, and were treated symptomatically. However, progressive pain and dysfunction ensued and she was first referred to an orthopedic assessment in 1994. Her medical records from that period indicate severe hyperker-

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atosis of the hands, arachnodactyly, and flexion contractures of the fingers. No significant hyperkeratosis was noted over her wrists, yet they were inflamed and painful with severe limitation of motion. Plain radiographs depicted severe joint space narrowing of the carpal bones with subchondral cysts. Bilateral wrist arthrodesis resulted in attenuation of pain at the cost of a severe handicap. Histological analysis revealed hyperplastic synovia with prominent chronic inflammation consisting mainly of plasma cell infiltrates. A year later, right shoulder pain developed insidiously. Examination disclosed no signs of inflammation or skin involvement over the shoulder joint. Plain radiographs were similarly unrevealing. However, range of motion continued to deteriorate over the next 3 years despite physiotherapy.

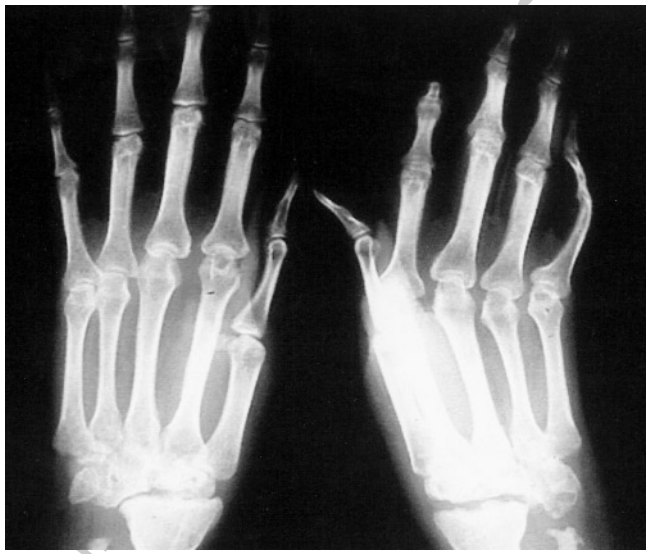
In 1999, magnetic resonance imaging with gadolinium enhancement depicted hypertrophied synovium of the right shoulder, and the patient was referred for evaluation at the rheumatology division (Figure 1). Examination revealed limited range of motion of the shoulder joints without obvious inflammation. There was no evidence of inflammation at the arthrodesed wrists. The skin overlying these painful joints was normal. The rest of the examination revealed the typical phenotype of the Haim-Munk syndrome[1] (Figure 2), but was otherwise noncontributory. Antinuclear antibodies, rheumatoid factor, C3, C4, and other serological tests were normal, as were a complete blood cell count, Chem-7 panel, and erythrocyte sedimentation rate. The patient was started on chronic nonsteroidal antiinflammatory therapy, with partial improvement in her symptoms. However, the clinical disability and the radiologic manifestations have progressed and she is on the brink of total shoulder arthroplasty.

DISCUSSION

The major manifestations of PLS and HMS are palmoplantar hyperkeratosis and periodontal disease, whereas arthritis has not been hitherto described in association with either syndrome.

In addition to the cardinal features of PLS-HMS, reports suggest that some patients have an increased susceptibility to infections[3], which may reflect a more deleterious effect of a specific cathepsin C mutation or the epigenetic effects of other gene loci. An infectious process followed by aseptic large joint synovitis is characteristic of reactive arthritis. However, there was no recognized triggering infection in our patient's history and neither she nor affected members of her family have an increased incidence of infections. Moreover, cultures of synovial tissue excised during the wrist operations were sterile with no evidence of an infectious process on histology or serology. Also, our HLA-B27-negative patient did not experience any of the associated manifestations of reactive arthritis such as enthesopathy, tenosynovitis, eye inflammation, or urethritis. Thus, it can be judiciously concluded that reactive arthritis was not the underlying mechanism in our patient, although it cannot be irrefutably ruled out. In addition, her clinical, radiographic, and serologic features are not compatible with a known rheumatic disease. The prominence of plasma cells in the synovia is not consistent with rheumatoid arthritis (RA), which might have otherwise been plausible. Other systemic diseases that might present with arthritis, such as solid and hematologic malignancies, sarcoidosis, and connective tissue diseases, were not evident on presentation and did not present over the 10 years of clinical followup. While the association of synovitis, skin lesions, and osteolysis is suggestive of SAPHO syndrome, a careful review of our patient's features allows for a clear distinction. Synovitis was limited to the shoulders and wrists, without sternoclavicular or spine involvement. There was no evidence of osteolysis or subsequent hyperostosis of the involved joints, although she has acro-osteolysis of her terminal phalanges, a typical feature of HMS. Histology of the shoulder joint depicted a plasma cell infiltrate rather than polymorphonuclear leukocytes and the skin lesions consisted of hyperkeratosis and not pustulosis.

Although our patient is the only one of her family known



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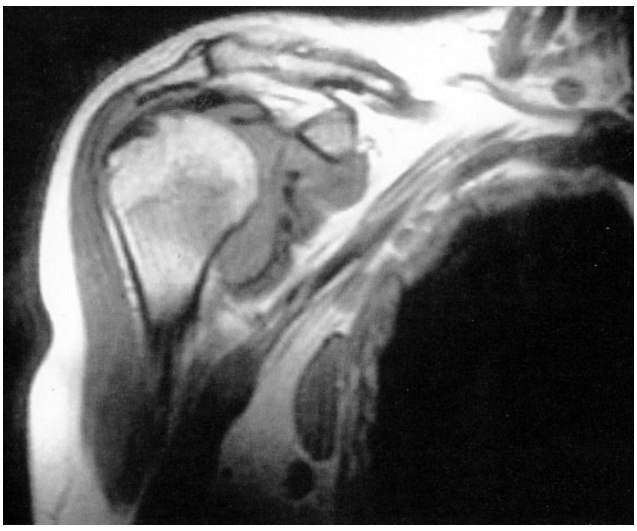

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Figure 1. A. Radiograph of terminal phalanges of the fingers showing marked thinning increasing towards the distal, tapering pointed ends and a claw-like volar bend. B. Magnetic resonance imaging with gadolinium enhancement depicted hypertrophied synovium of the right shoulder.

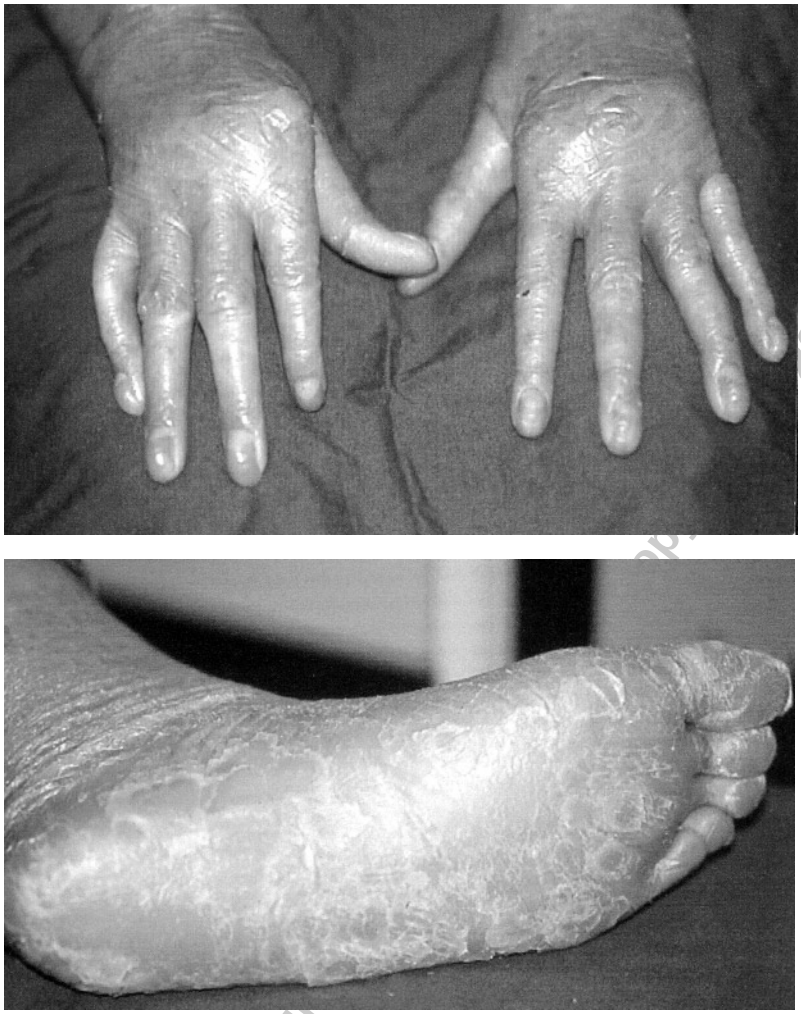

Figure 2. Clinical findings in the patient with HMS. A. Dermal involvement of the fingers. B. Plantar keratosis.

to have the combination of HMS and arthritis, we presume that the 2 conditions are not coincidental. While she carries an identical mutation, in codon 286 of exon 6 (2127A→G) of the cathepsin C gene, to that carried by other members of the Cochin kindred[6], variable clinical expression and pleiotropic effects of identical and allelic mutations have been previously recognized in numerous other conditions, such as craniosynostoses[7]. Also, cathepsin C is present in large amounts in osteoclasts, in addition to being expressed in the skin. It has been postulated that the additional osseous findings in patients with HMS, in contrast to PLS, including arachnodactyly, acro-osteolysis, pes planus, and nail deformities, are the result of the specific cathepsin C mutation present in HMS[6].

The pivotal role of osteoclasts in the pathogenesis of arthritic bone erosions has been recently elucidated in several animal models. Receptor activator of nuclear factor-κB ligand (RANKL) is an essential factor for osteoclast differentiation and also functions to augment T cell-dendritic cell cooperative interactions. When arthritis was generated in a RANKL knockout mouse model, using a serum transfer model, the degree of bone erosions was dramatically reduced compared to that seen in arthritic control mice[10]. Further evidence for the role of osteoclasts in bone erosion in arthritis comes from a recent study using the tumor necrosis factor-α transgenic mouse model, in which mice develop a spontaneous, destructive polyarthritis at an early age. When these mice were treated with pamidronate plus osteoprotegerin (OPG), a decoy receptor for RANKL, they exhibited an 81% reduction in the size of bone erosions[11]. There may be synergistic effects between osteoclasts and other cell types in the process of bone erosions in arthritis. Synovial macrophages, fibroblasts, and osteoclasts are all sources of cathepsin K, an important proteinase released by the latter in states of physiological bone remodeling, and which has also been identified at sites of cartilage

erosion in RA[12]. All in all, the rapidly destructive arthritis noted in our patient may also be the result of increased osteoclastic activity within joints.

Additionally, the synovial lining may share some characteristics of the junctional epithelium, a thin, permeable, nonkeratinized epithelium to which teeth attach and which is the site of gingival inflammation and destruction in HMS-PLS[13]. Interestingly, when teeth are exfoliated, junctional epithelium no longer exists and inflammation subsides. This may serve as a rationale for future synovectomies in our patient.

Finally, in addition to presenting a novel association and increasing the rheumatologist's awareness to these 2 unique syndromes with their various dermatologic and skeletal manifestations, this case poses a major therapeutic enigma that has yet to be resolved.

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