

# Enthesopathy of the Patellar Tendon Insertion Associated with Isotretinoin Therapy

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A  $^{99m}\text{Tc}$ -MDP bone scan performed on a 34-yr-old female for suspected osteomyelitis of the proximal tibia revealed focally increased activity in both tibial tuberosities due to enthesopathies secondary to chronic isotretinoin therapy. Physicians should be aware that isotretinoin therapy can cause abnormal bone scans and not mistake these abnormalities for other diseases such as osteomyelitis. Second, bone scans may be helpful in diagnosing and following isotretinoin bone toxicity.

**J Nucl Med 1993; 34:455-457**

**I**rreversible skeletal changes have been described in patients with dermatologic disorders treated with isotretinoin (13-cis-retinoic acid) [Accutane<sup>®</sup>-US, Roaccutane<sup>®</sup>-UK], a synthetic vitamin A derivative (1-3). The earliest and most common changes occur in the axial skeleton and consist of premature osteophyte formation or hyperostosis of the cervical and thoracic spine and ossification of the anterior longitudinal ligament (4). Enthesopathy, a proliferation of bone at tendon insertions, has also been described as a later and less frequent manifestation of this disorder in the appendicular skeleton (2,5).

We report a patient who developed bilateral patellar tendon enthesopathy and skeletal hyperostoses as a result of chronic isotretinoin therapy for hydradenitis suppurativa. Skeletal changes involving both tibial tuberosities were found on a limited bone scan requested to exclude osteomyelitis of the left knee.

## CASE REPORT

A 33-yr-old female complained of a painful indolent mass on the anterior surface of the proximal left tibia that was unresponsive to a 6-mo course of nonsteroidal anti-inflammatory medication. Radiographs and CT showed calcification of the left patellar tendon at the tibial tuberosity insertion and mild bilateral

tibial tuberosity irregularities. An incisional biopsy and cultures of the left tibial tubercle mass revealed normal bone fragments without evidence of tumor or infection. Over the following year this painful mass recurred. She was referred for a bone scan in June 1992 to rule out osteomyelitis. She denied fevers, chills or a penetrating injury.

The patient had been treated with isotretinoin for hydradenitis suppurativa since 1986. An initial dose of 40 mg q.i.d. (2 mg/kg/day) was reduced after 2 yr because of a favorable response. She was taking 40 mg b.i.d. (1 mg/kg/day) at the time she presented to our department.

A firm, minimally tender mass was palpable on her left tibial tuberosity. There was no erythema, warmth, fluctuance or draining sinus in this area. She was afebrile and had a normal white blood cell count, sedimentation rate, calcium and phosphorous levels. A bone scan was ordered for possible osteomyelitis.

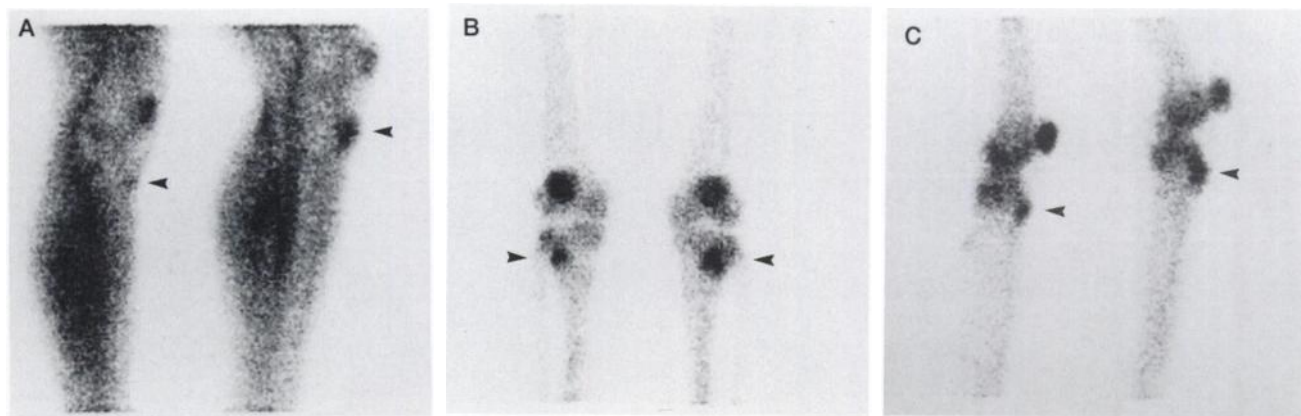
A limited three-phase bone scan was performed following the intravenous administration of 20 mCi (740 MBq)  $^{99m}\text{Tc}$ -MDP. Angiographic, blood-pool and delayed images at 2 hr were obtained of both knees in the anterior and lateral projections using a high-resolution parallel-hole collimator interfaced with a digital gamma camera. During the flow, blood-pool and delayed phases of the bone scan, there was focally increased activity related to both tibial tuberosities, although relatively more activity involved the symptomatic side (Fig. 1). The distal femurs and proximal tibial metaphyses were normal. We suspected that these abnormalities represented a process other than osteomyelitis because of absent contiguous metaphyseal involvement and the bilateral nature of this process.

Plain radiographs of her left knee, cervical and thoracic spine were obtained. Enthesopathy at the patellar tendon insertion on the left tibial tuberosity were found which corresponded in location with the increased metabolic activity on bone scan (Fig. 2A). Anterior cervical and thoracic vertebral body osteophytes at multiple disc levels had the characteristic radiographic appearance of hyperostoses secondary to retinoid therapy (Figs. 2B and 2C).

## DISCUSSION

Isotretinoin belongs to a pharmacologic class of synthetic vitamin A derivatives collectively known as retinoids. Isotretinoin inhibits sebaceous gland function and keratinization and is primarily used for the treatment of severe recalcitrant cystic acne. Other applications for this drug include treatment of hydradenitis suppurativa and

Received Sept. 11, 1992; revision accepted Oct. 22, 1992.  
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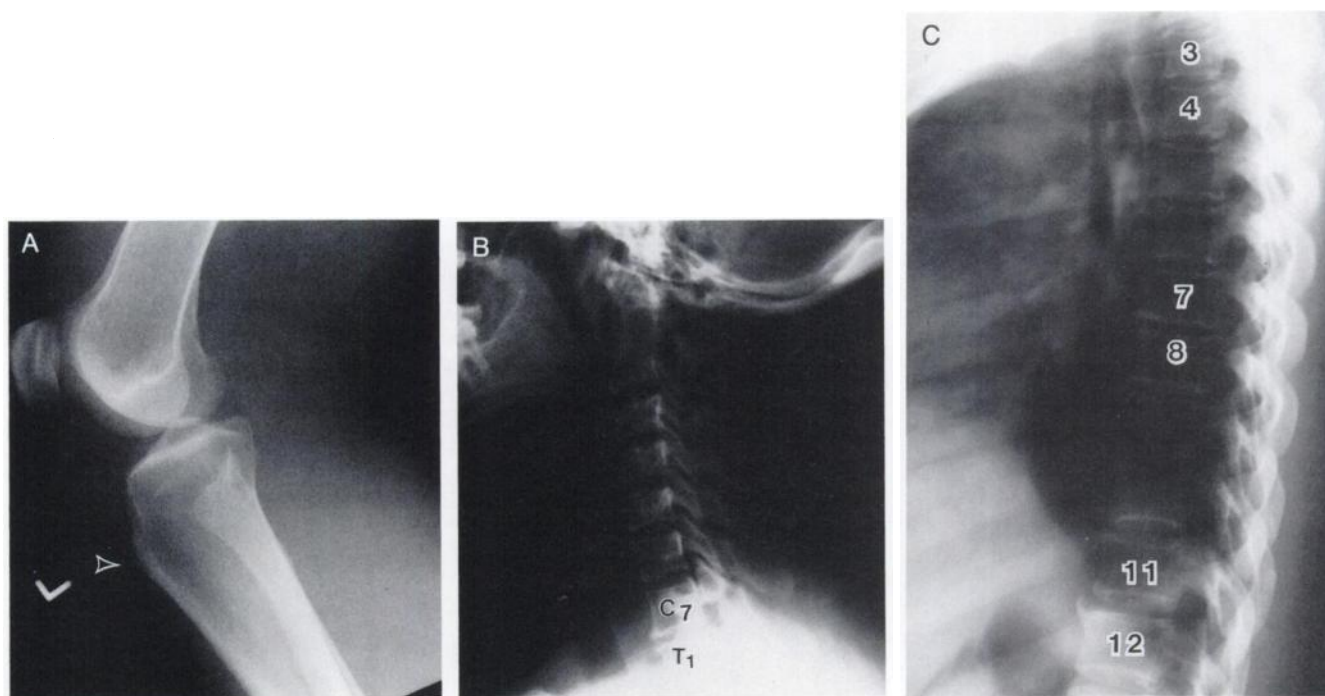
**FIGURE 1.** Bone scan shows increased activity in both anterior tibial tuberosities (arrowheads) on the lateral blood-pool images (A) and delayed images of the knees in the anterior (B) and lateral (C) projections.

disorders of keratinization, e.g., ichthyosis, epidermolytic hyperkeratosis.

Skeletal changes secondary to vitamin A toxicity were first reported in 1944 (6). Retinoids were developed in an attempt to avoid toxicity associated with vitamin A. However, these synthetic compounds also result in a high prevalence of untoward skeletal changes in patients treated for skin conditions not associated with proliferative skeletal lesions. In 1982, the first undesirable skeletal effect of isotretinoin was described as premature closure of the proximal tibial epiphysis (7). The following year bone changes similar to those induced by vitamin A,

including hyperostoses of the spine and ossification of both the anterior and posterior longitudinal ligaments, were reported with the use of isotretinoin (8). Since that time, multiple studies and several prospective trials have confirmed similar skeletal manifestations, including proliferative enthesopathies and diminished bone density, in patients treated with isotretinoin (2,4,5,9-11).

The mechanism of action of isotretinoin on the skeleton remains unknown. It is thought retinoids enhance production of interleukin-1 in bone, which in turn stimulates osteoblasts (1,12). Biochemical indices such as calcium and phosphorous are normal in patients treated with



**FIGURE 2.** Enthesopathy of the patellar tendon and hyperostoses of the spine. Lateral radiographs of the left knee (A), cervical (B) and thoracic (C) spine show calcification at the patellar tendon insertion (arrowhead) and anterior vertebral osteophytes at the following levels: C7-T1, T2-4, T7-8, and T11-12.

isotretinoin (13). There is no increased frequency of HLA B27 or any other HLA antigen (8,13).

The earliest and most frequent bone changes associated with isotretinoin therapy are small osteophytes occurring along the anterior margins of cervical and thoracic vertebrae and ossification of the anterior longitudinal ligament (4,14). Changes in the axial skeleton are similar to those reported in diffuse idiopathic skeletal hyperostosis (DISH), but they occur at a younger age and progress more rapidly (8,11,13,15). Anecdotal reports in other symptomatic individuals have described ossification of the posterior longitudinal ligament causing spinal cord compression (15,16). The resultant spinal stenosis increases the susceptibility to severe neurological consequences even following minor trauma.

The most prominent appendicular enthesopathies occur in the feet at the insertions of the gastrocnemius tendon and plantar fascia on the calcaneus. Enthesopathies occurring at sites other than the calcaneus that occur later in the course of therapy are initially unilateral and asymmetric and become bilateral with time (2). Bone changes have been reported as early as 5 wk and are associated with both short- and long-term uses of isotretinoin (17). In general, skeletal changes become progressively larger with continuation of retinoid therapy and the earliest bone changes become the largest hyperostoses over the period of therapy (2). They are independent of either the daily or cumulative dose (2,4).

In our patient, left patellar enthesopathy resulted in a painful mass in the proximal tibia that recurred within 1 yr following excision. Hyperostoses of her spine and enthesopathy of her knees were typical of skeletal changes secondary to chronic retinoid therapy.

While the majority of skeletal changes are asymptomatic and considered to be clinically insignificant, they are probably irreversible and it is unclear whether these changes cease once the retinoid is withdrawn (1-3). It is important for physicians to be aware that chronic isotretinoin therapy can result in bone scan abnormalities. Otherwise, diseases such as osteomyelitis, metastases, etcetera may be misdiagnosed.

Bone scanning may be useful in screening patients on retinoid therapy. Traditionally, skeletal changes follow-

ing retinoid therapy have been diagnosed and subsequently followed with radiographs. Bone scans, however, allow earlier detection of these skeletal changes and provide information about their metabolic activity. The bone scan's lower radiation exposure in comparison to skeletal survey is also beneficial.

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