INTRODUCTION

Reflex sympathetic dystrophy (RSD), also referred to as post-traumatic osteoporosis, Sudeck’s atrophy, reflex neurovascular dystrophy, traumatic angiopathy and others, is a rheumatic disorder of clinical concern and academic interest. Most of RSD are precipitated by trauma, burn, cancer and central nervous system diseases but some are not (1). Involvement is usually diffuse and the hand and foot are the two most common sites. Rarely, affection can be segmental (2). Symptoms include pain, edema, warmth, redness, atrophy and stiffness of the skin, limited articular motion, hyperhidrosis and hypertrichosis. Clinically, three stages can be distinguished in the course of RSD but with considerable overlap (1, 3). They are the hypertrophic or warm stage, the atrophic or vascular instability stage and the stabilized or cold stage.

Regarding the pathogenesis, the internuncial pool theory is currently accepted widely (1). It was first proposed by Leriche (4), advanced by Lorente (5) and recently reinforced by Marchettini et al. (6). However, another study by Veldman et al. (7) supported the Sudeck’s concept of an exaggerated regional inflammatory response. The identification of sympathetic vasoactive intestinal peptide (VIP)-containing nerve fibers innervated in cortex-periosteum zone has provided a biochemical basis for the reflex sympathetic theory (8). The VIP released from such sympathetic nerve fibers has been shown to cause regional hyperemia and dramatic bone resorption (8) that can be imaged using the three-phase bone scintigraphy (1, 3, 9-11). Radiography is useful for the detection of subperiosteal bone resorption (SBR) that is present in 69% of the subjects with RSD (12). Soft tissue swelling is an important radiographic finding (13). MRI has been shown to be valuable for the imaging of bone and periarticular edemas in RSD (14, 15).

We carried out this prospective study to establish pinhole SPECT (pSPECT) findings and to correlate them with radiographic findings including SBR which characterizes RSD (8-12). Three phase \(^{99m}\)Tc HDP bone scintigraphy and pSPECT were obtained in five patients with RSD of the foot. pSPECT findings were then correlated with those of radiography in all patients and with MRI in three. Based on the results, possible causative mechanism of SBR was speculated. In addition, diffuse osteoporosis that occurred in RSD was evaluated using pSPECT.
MATERIALS AND METHODS

Patients

Five patients (one man and four women with ages ranging from 29 to 62 yr) with RSD in the foot were investigated using the 99mTc-HDP three-phase scan and pSPECT. Clinically, RSD was considered to be in the atrophic stage in Cases 1, 2 and the hypertrophic stage in Cases 3-5. The diagnosis was based on clinical symptoms and signs, the duration of illness, precipitating factors and the results of imaging examinations. Bone radiographs were available in every patient and MRI in Cases 1, 3, 4.

Bone scans

All bone scans were performed in the Department of Nuclear Medicine of Kangnam St. Mary’s Hospital. The scans including three-phase bone scan and pSPECT were performed following the administration of 25-30 mCi (925-1,110 MBq) of 99mTc HDP. pSPECT was obtained as an extension of three-phase scan using 360°-rotation with a 4-mm pinhole collimator and 20-cm adapter cone (16). The gamma camera system used was a single-head Orbiter with a Digitrac 7500 detector (Siemens). It was connected to an Icon analogue data processor that permits reconstruction using the filtered back-projection algorithm and a Butterworth filter. The collimator-to-skin distance was 13-15 cm and 64 acquisitions were made. Scan time was 45 min (40 sec/ acquisition and 2 min for relocation), the radioactivities accumulated were 7.5-8 Kct/ acquisition and slice thickness was 2.4 mm. pSPECT images were reconstructed in all three planes, but the sagittal view was chosen for current analysis. The reason was that the identification of individual anatomical landmarks was easier and more accurate in the sagittal view in which objects were longitudinally arrayed so that dimension was larger and congruency with neighboring parts was better than in the other views.

Radiography and MRI

Plain radiographs of the foot in the anteroposterior, lateral and oblique positions were taken in every patient and MR images in the sagittal and coronal planes were taken in three patients (Cases 1, 4, 5). The MRI machines and technical factors used in three different hospitals were: GE Signa 1.5 Tesla (T1W: TR 350/TE 16) in Case 1, Philips Gyroscan T10-NT 1.0 Tesla (T2W/SPR/TSE: TR 3421/TE 70) in Case 3 and Shimadzu SMT 0.5 Tesla (T2W/SE /256: TR 2000/ TE 256) in Case 4.

Analytical intercorrelation of images

Sagittal pSPECT was correlated with the lateral radiograph to identify anatomical landmarks and to assess pSPECT alterations of affected bone and joint in all five cases. Then, pSPECT findings were correlated with and validated against sagittal MR image in Cases 1, 3, 4. All images were read by three experienced nuclear physicians who are radiology board certified.

RESULTS

Two patients with atrophic RSD

Case 1

A 29-yr-old man nine months ago sustained bimalleolar fracture of the right ankle that was healed well. In the recent months, however, the dorsum of the foot became diffusely swollen and tender with putty color change and limited articular motion. The diagnosis of RSD in the atrophic stage was entertained. 99mTc-HDP three-phase bone scan revealed increased blood flow and blood pool (Fig. 1A) as well as increased bone uptake in the ankle and calcaneus. pSPECT showed small, spotty, hot areas in the peripheries of ankle bones (Fig. 1B). Radiographic correlation showed individual hot areas to match in location with small, blotchy SBR (Fig. 1C) that, in turn, matched in location with the insertions of small, regional ligaments and tendons or entheses that were thickened and edematous on MRI (Fig. 1D). Tracer uptake was also increased in the retrocalcaneal, trochlear and subtalar surfaces that were radiographically normal.

Case 2

A 51-yr-old woman presented with the painful swelling of the dorsum of the right hindfoot with glossy skin change and motor weakness. Four months ago, she was treated for a bleeding cerebral artery aneurysm using endovascular coil embolization that was successful. The clinical diagnosis of RSD in the atrophic stage was entertained. 99mTc-HDP three-phase bone scan showed increased blood flow and blood pool in the right ankle (Fig. 2A) and pSPECT showed small, discrete, blotchy hot areas in the peripheries of ankle and tarsal bones including the medial malleolus, the dorsal aspects of the cuneonavicular and tarsometatarsal junctions and the posterior process of the talus (Fig. 2B). Radiographic correlation revealed the hot areas in tarsal bones to match in location with SBR (Fig. 2C). As in Case 1, the tracer uptake was increased also in the retrocalcaneal and subtalar surfaces that were radiographically normal.

Three patients with hypertrophic RSD

Case 3

A 58-yr-old woman with the clinical diagnosis of hypertrophic RSD of the right ankle was examined for prominent edema, warmth, coarsened skin, and morning stiffness of one month duration. She had lumbar spondylosis with symptoms...
of nerve root compression. \(^{99m}\)Tc-HDP three-phase bone scan showed increased blood flow and blood pool in the right ankle and hindfoot (Fig. 3A). pSPECT revealed discrete, spotty hot areas in the peripheries of the ankle and tarsal bones including the lateral malleolar tip, the dorsal aspects of the cuneonavicular and tarsometatarsal junctions and the posterior process of the talus (Fig. 3B). Tracer uptake was increased in the trochlear and subtalar surfaces but, interestingly, not in the retrotalar surface. Radiographic correlation revealed the spotty hot areas in the tarsal bones to match in location with cortical thinning and patchy SBR (Fig. 3C) that, in turn, matched in location with the insertions of the talonavicular, talotibial, and talofibular ligaments and the tibiotalar and posterior tendons as validated by MRI (Fig. 3D, E). MRI demonstrated altered signal intensities that were consistent with soft-tissue edema and peritendinitis.

Case 4
A 62-yr-old woman was evaluated for diffuse, painful, warm soft-tissue swelling and skin discoloration in the left ankle that had developed after a bimalleolar fracture sustained two months ago. Clinically, the diagnosis of hypertrophic RSD was entertained. \(^{99m}\)Tc-HDP three-phase bone scan showed increased blood flow and blood pool in the left ankle (Fig. 4A).
pSPECT demonstrated discrete, spotty hot areas in the peripheries of ankle and tarsal bones including the medial malleolar tip, the dorsal aspects of the cuneonavicular and tarsometatarsal junctions and tarsal sinus (Fig. 4B). Intense tracer uptake was seen in the malleolar fractures. As in Case 3, the calcaneus did not show increased tracer uptake. Radiographic correlation showed spotty hot areas in the tarsal bones to match in location with cortical thinning and patchy SBR (Fig. 4C) that, in turn, matched in location with the insertions of thickened, inflamed ligaments as MRI portrayed (Figs. 4D).

Case 5

A 59-yr-old woman was examined for painful swelling and discoloration of the dorsum of the left ankle and foot. The pain started after the removal of plaster cast that had been applied for seven weeks for a fracture in the fifth metatarsal base. The clinical diagnosis of hypertrophic RSD was entertained. 99mTc-HDP three-phase bone scan showed markedly increased blood flow and blood pool in the left ankle and tarsus and the fracture in the fifth metatarsal base (Fig. 5A). pSPECT showed small, spotty, hot areas in the tarsal sinus, the posterior talar process and the dorsal aspects of the talo-
As in Cases 3 and 4, the tracer uptake was increased in the trochlear and subtalar surfaces but not in the retrocalcaneal surface. Radiographic correlation showed spotty hot areas to match in location with patchy SBR that, in turn, well matched in location with the ligamentous insertions (Fig. 5C).

**DISCUSSION**

The clinical diagnosis of RSD is usually made on the basis of symptoms (1, 3) and bone radiography (12, 13) and scintigraphy (1, 3, 9-11). The diagnosis can also be assisted by MRI (14, 15). Synovial biopsy of symptomatic joint may demonstrate edema, hyperplasia, disarray of lining cells, fibrosis and capillary proliferation with perivascular lymphocytic infiltration (12, 17). Symptoms and signs may include pain, edema, redness, warmth, dusky discoloration, stiffness, hyperesthesia and atrophy of skin, stiffening and dysfunction of joint, hyperhidrosis, hypertrichosis and vasomotor disturbances (1, 7). Bone radiography is characterized by diffuse osteoporosis, patchy subperiosteal bone resorption (SBR), cortical erosions and soft tissue swelling (12, 13). The three-phase bone scan is useful in assessing vascular alterations in and, hence, the diagnosis of RSD (1, 3, 9-11). Three-phase bone scan demonstrates increased blood flow and blood pool in affected bones, joints and soft tissues, and delayed bone image portrays the tracer to characteristically accumulate in the peripheries of affected bones (9-11). $^{99m}$Tc-HDP psPECT is a recently introduced tomographic scan mode that can generate images of small bones and joints with remarkably improved spatial resolution that is comparable to that of CT and suitable for fine

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**Fig. 3.** (A) Three-phase bone scan shows increased blood pool in the right ankle and hindfoot (arrows). (B) Sagittal pSPECT shows spotty hot areas at insertions of dorsal tarsometatarsal (dtml), talonavicular (tnl), deltoid talotibial (d-ttl), tibialis posterior (tpt), tibialis anterior (tat) and tibiofibular ligaments (tfl). Hot areas are also in posterior talar process (pp), posterior malleolus (pm), trochlea (troc) and subtalar surfaces (stj). Calcaneus is not involved in this hypertrophic RSD (c). (C) Lateral radiograph shows SBR in the dorsal aspects of navicular bone and cuneiform (arrows), posterior talar process (pp), subtalar joint (stj), posterior trochlea (x) and malleolus (lig). SBR is also in medial cuneiform where tibialis tendons insert (*tts). Bones are porotic. (D) Sagittal T2 weighted MRI (TR 3421/TE 70) of right medial ankle shows soft-tissue swelling. Irregular bright edema signals are at insertions of ligament in the trochlea (upper central arrow) and tibialis tendon (left lower arrow). Tramline-like bright signals along extensor and flexor tendons in dorsum (white arrow) and bottom (right upper and lower arrows) reflect peritendinitis. (E) Mid-sagittal MRI shows bright signals at ligament insertions in talar head, navicular bone and cuneiform (small white arrows). There are synovial effusion and soft tissue edema about ankle (upper arrows) and in subtalar region (lower arrow). Calcaneus is normal accounting for absence of tracer uptake (See Fig. 3B).
We prospectively applied $^{99m}$Tc-HDP pSPECT to simultaneously assess metabolic feature and anatomic alterations of RSD in the foot. Interestingly, pSPECT showed multiple small spotty or blotchy hot areas to occur characteristically in the peripheries or corticoperiosteal zones of the affected bones of the ankle and hindfoot (Fig. 1B-5B). pSPECT and radiographic correlation showed the spotty hot areas to coincide in location with SBR in all five patients (Fig. 1C-5C). These findings were interpreted to suggest that blotchy areas of SBR with intense HDP uptake may represent focal bone resorption which characterizes RSD. Further cross correlation of pSPECT, radiography and MRI in Cases 1, 3 and 4 showed that both spotty hot areas and blotchy SBR were anatomically located at the same insertions of ligaments or tendons. And such results would warrant the speculation that the spotty hot areas and SBR in RSD are preferentially generated in the entheses where physical strain is more or less constantly applied to. Besides, increased tracer uptake was also seen in the trochlear, subtalar and retrocalcaneal surfaces that were radiographically preserved (Cases 1-3), and such uptake was also considered to be related with articular movement and calcaneal tendon insertion, respectively. In contrast, the osteoporosis noted in the cancellous bones of the hindfoot and tarsus did not accumulate tracer any more than normal bones that are free of physical stress and strain.

The pathogenesis of RSD is yet not fully clarified and there exist a number of theories and hypotheses. Of them, the inter-nuncial pool theory first proposed by Leriche in 1924 (4), later advanced by Lorente (5), and most recently reinforced by
Marchettini et al. (6) is most widely accepted. This theory assumes that an "excess" impulses originated from injured tissue travel via the afferent sympathetic fibers to the spinal cord where a series of reflexes are created. The reflexes then spread through multiple connecting circuits to give rise to a phenomenon of the after-discharge and hyperexcitation of the efferent sympathetic fibers leading to an abnormal sensitivity of the spinal nociceptive neurons of higher center and, finally, hypervascularity and "dramatic", cortex-periosteal bone resorption. The recent identification of the sympathetic VIP-containing nerve fibers innervated in the cortex-periosteum provided a biochemical basis favoring the reflex theory (7). The VIP released from such nerve fibers is known to cause hyperemia and dramatic SBR (7), and such alterations are imaged using three-phase bone scan aided with pinhole scan (1, 2, 7, 8). In contrast to the classic reflex theory, Roberts' hypothesis does not assume tissue or nerve lesion as prerequisite (17) and a most recent study by Veldman et al. (7) even supports Sudeck's concept of an exaggerated regional inflammatory response as a mechanism of RSD. It is worth to note that the radiographic investigation of bone in RSD by Genant et al. (12) showed characteristic mottled SBR. Our study has confirmed their observation and, in addition, our extended 99mTc-HDP pSPECT study demonstrated that SBR avidly accumulated the tracer. This observation seems to support the theory that VIP induces focal bone resorption in the subperiosteal zone (8) and, in turn,
activates osteogenesis in RSD. Furthermore, MRI correlation revealed SBR to occur in the enthesis onto which mooring or pulling forces of tendons or ligaments are constantly exerted.

Incidentally, it was of interest to observe that the tracer uptake was increased in the retrocalcaneal surface in two patients with atrophic RSD (Fig. 1B, 2B) but not in those with hypertrophic RSD (Fig. 3B-5B). The retrocalcaneal surface that was radiographically preserved in both groups is where the calcaneal tendon inserts. It was inferred that such retrocalcaneal uptake probably reflected activated bone turnover that is peculiar to RSD in the atrophic phase. For the validation and explanation of such an observation, future studies using a larger number of cases are necessary.

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