acquisition time in the initial fast WO was about 28% in normal lungs, which is an acceptable value for the continuous repetitive rotating acquisition mode to produce nondistorted SPECT images without significant degrading resolution (*23–25*). The use of averaged projection data in both directional rotations during the acquisition time in this mode may reduce the artifacts of patient motion and change in ^{133}Xe activity in the lung (*23*).

This modality, thus, improves review and interpretation of ^{133}Xe SPECT, and it is practical due to computational efficiency and ease of implementation of a surface-rendering technique (*6,9,12*). However, it is not a complete substitute for multislice tomograms including the entire ^{133}Xe washout data, and image features heavily depend on the thresholds chosen (*3–6*). In the future, a three-dimensional display preserving the data from all ^{133}Xe washout process in voxel-by-voxel order should be developed to eliminate uncertainties associated with a threshold.

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Extraskeletal Uptake of Technetium-99m-MDP in Sites of Heparin Administration

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A 19-yr-old woman with juvenile diabetes and protein C deficiency was referred for a bone scan to rule out osteomyelitis of the right tibia. The bone scan did not reveal evidence of osteomyelitis. There was, however, extraskeletal uptake of the ^{99m}Tc bone tracer in the anterior abdominal wall confined to the sites of subcutaneous heparin administration. This case is presented because of its interesting scintigraphic findings and to discuss the association of protein C deficiency and heparin administration as a cause of extraskeletal ^{99m}Tc bone tracer accumulation.

Key Words: skeletal scintigraphy; extraosseous uptake; technetium-99m-methylene diphosphonate

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The causes of extraskeletal ^{99m}Tc skeletal tracer uptake are numerous, with heparin injection being cited as one of the causes (*1*). We present a case of 19-yr-old woman with juvenile diabetes, protein C deficiency disease and deep venous thromboses who was receiving systemic coumadin therapy and simultaneous subcutaneous heparin injections. The incidental findings of ^{99m}Tc skeletal tracer uptake in the abdominal wall posed a diagnostic enigma until further clinical review suggested the probable cause of these findings.

CASE REPORT

A 19-yr-old woman was admitted for superinfection of bilateral lower extremity skin manifestations (necrobiosis lipoidica diabeticorum) of her diabetes. She had been complaining of increasing pain in her right tibial area for several days.

She was diagnosed with insulin-dependent diabetes mellitus (IDDM) at 11 yr and protein C deficiency disease at 15 yr. Her past medical history revealed Legg-Calve Perthe disease on the left,

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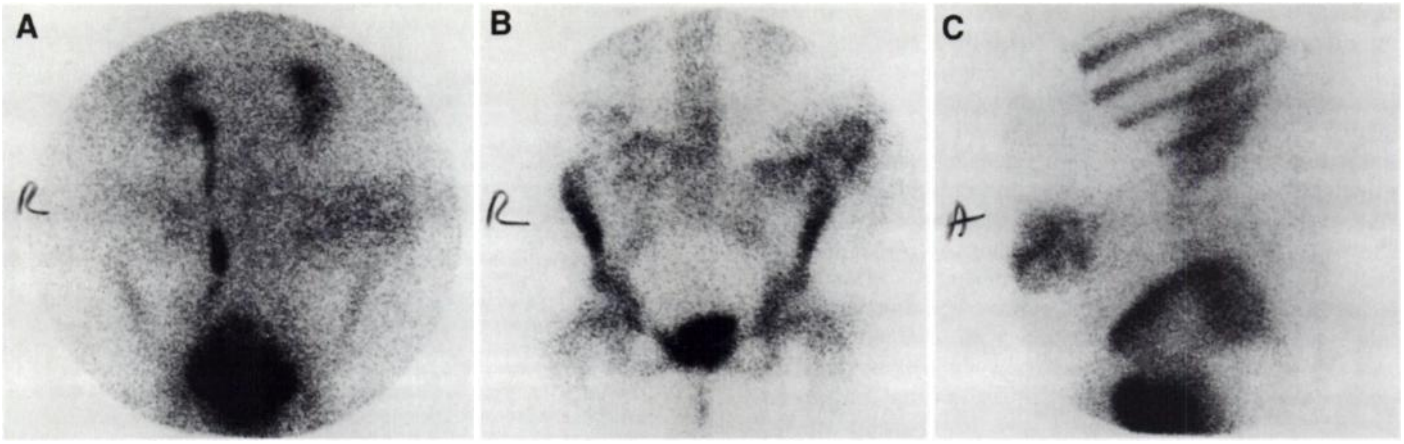

FIGURE 1. Anterior tissue phase ^{99m}Tc-MDP view of the (A) pelvis reveals bilateral abnormal tracer activity in the anterior abdominal wall. (B) Anterior and (C) lateral delayed ^{99m}Tc-MDP views of the abdomen reveal an anterior location of abnormal extraskeletal uptake of skeletal tracer within the abdominal wall.

multiple admissions for asthma, rupture of an ovarian cyst and multiple deep venous thromboses. Her most recent admission had been for right middle toe cellulitis and a large left groin hematoma.

Physical examination revealed her to be a well-hydrated and well-nourished woman with a temperature of 37°C, a pulse of 110, respiratory rate of 20 and blood pressure of 120/75 mmHg. Examination of the head and neck, cardiovascular and respiratory systems and abdomen was unremarkable.

Both lower extremities had necrobiosis lipoidica diabeticorum. In addition, there was a 2-cm × 2-cm purulent ulcer on the right lower extremity. On the left anterior tibia, there was a small, 0.5-cm ulcerated lesion that was nonpurulent. There was tenderness to palpation around both pretibial ulcers. She had the following blood results: white blood cell count = 10.95, hemoglobin = 14.3, hematocrit = 41.7, platelets = 227, partial thromboplastin time = 93, prothrombin time = 15 (H), red blood cell count = 4.38 and erythrocyte sedimentation rate = 96. Her last protein C-antigen was 22% (normal range 65%–130%), and the total protein S was 42% (normal 60%–150%).

The patient's medication included coumadin (7 mg/day), heparin (10,400 U bid administered subcutaneously into the upper and lower anterior abdominal wall), insulin (10 U of regular and 20 U of NPH in the morning and 18 U of regular and 8 NPH in the evening, which was administered into the thighs), cimetidine (400 mg three times a day), albuterol nebulizers and ibuprofen (800 mg orally twice a day).

The bone scan performed with ^{99m}Tc-methylene diphosphonate (MDP) to rule out osteomyelitis in the patient's right tibia did not reveal any abnormality. However, it did reveal a serpiginous and circumscribed pattern of abnormal uptake in the anterior abdominal wall seen on both the tissue phase and the delayed images (Fig. 1). Clinical examination of the abdominal wall did not reveal any erythematous, purpuric or bullous lesions.

A subsequent ^{67}Ga study also revealed abnormal uptake at the same sites that was less intense and less extensive. A conventional recumbent frontal radiograph of the abdomen did not reveal any evidence of abnormal or dystrophic calcifications at the sites of abnormal skeletal tracer uptake.

DISCUSSION

Extraosseous localization of ^{99m}Tc-labeled skeletal tracers can occur as a physiological phenomenon (e.g., in the kidney or cartilage) or as a result of pathological changes. Dystrophic calcification, rhabdomyolysis, sites of myocardial, cerebral or splenic infarction and fluid collections all can accumulate ^{99m}Tc skeletal tracers. Technetium-99m-labeled tracers have been found to accumulate in benign conditions such as myositis ossificans and tumoral calcinosis and in malignant tumors such as sarcomas, adenocarcinomas and metastases (*1–3*). Sites of intramuscular injections of drugs such as meperidine, phenothiazines, heparin and iron dextran (*1–3*) also have been known to accumulate skeletal tracers.

The underlying pathophysiological mechanism of ^{99m}Tc skeletal tracer compound deposition appears to be related to several mechanisms, chief among which are extracellular fluid expansion, increased regional vascularity, vascular permeability, increased calcium content of tissue, binding of phosphate enzyme systems, altered calcium metabolism, ion exchange, presence of iron deposits, absorption into immature collagen and binding to denatured proteins or enzyme receptors (*2,3*).

In this patient, any one of three mechanisms was thought possible because of the history of protein C deficiency and juvenile diabetes associated with the long-term use of coumadin, heparin and subcutaneous insulin. Protein C and S deficiencies are associated with a high risk of venous thrombosis (*4–6*). Protein C is a vitamin K-dependent protein and is partly responsible for fibrinolysis. The gene for protein C is located in the q13–q14 region of chromosome 2 (*4*). Hereditary protein C deficiency is inherited in an autosomal dominant manner. Heterozygous protein C deficiency is associated with the development of recurrent episodes of deep venous thrombosis before the age of 40 yr but rarely with arterial thrombosis (*4,7*). The overall prevalence of heterozygous protein C deficiency in young people is 5%. The normal level of protein C ranges from 0.7 to 1.3 U/ml.

Warfarin-induced skin necrosis is a known complication, especially in people with protein C and S deficiencies, and women appear to be more susceptible, with the necrosis occurring in the breasts, thighs and buttocks. It typically occurs between the 3rd and 10th days of therapy and is unrelated to the drug dose. The lesions are sharply demarcated, indurated and erythematous. The warfarin inhibits synthesis of vitamin K-dependent coagulation factors, leading to a sharp fall in the protein C levels in patients who are heterozygous for protein C deficiency. This leads to a hypercoagulability and thrombosis in the cutaneous microvasculature, which can lead to skin necrosis. Skin necrosis also has been found with heparin administration (*8–10*). The incidence of heparin-induced skin reaction is approximately 1 in every 1000 patients (*10*).

In our patient, systemic coumadin administration could have been the likely source of the extraskeletal ^{99m}Tc-MDP deposition due to skin necrosis. However, the localized abdominal site of uptake mitigated against this hypothesis. Moreover, we did

not find any bullous or purpuric or necrotic lesions with eschar formation, which are known to occur with warfarin-induced skin necrosis. Because the patient also had been receiving long-term subcutaneous heparin therapy, especially in the anterior abdominal wall bilaterally, we felt that the most plausible explanation was skin necrosis or local changes in subcutaneous fat induced by the heparin administration, leading to the deposition of ^{99m}Tc-MDP. Lipoatrophy caused by long-term insulin therapy was excluded because the patient had been receiving the insulin predominantly in the thighs and the whole-body bone scan did not reveal soft-tissue uptake of ^{99m}Tc-MDP anywhere except in the abdomen.

In our patient, the incidental finding of extraskeletal uptake of ^{99m}Tc-MDP was thought to be most likely due to subcutaneous heparin injections. These caused either skin necrosis and microscopic dystrophic calcification in the anterior abdominal wall or an altered biochemical milieu in subcutaneous fat, leading to dissociation of the technetium from the radiopharmaceutical.

CONCLUSION

Interpretation of the soft-tissue uptake of bone scanning agents is always an interesting academic exercise, presenting the nuclear medicine physician and radiologist with a wide range of possibilities. Although in most instances the cause is straightforward, physicians are sometimes confronted with a more complex clinical situation in which any one of many agents might have caused the extraskeletal uptake of the bone scanning agent in a patient. In our patient, the incidental finding of the extraskeletal uptake of ^{99m}Tc-MDP was thought to be most likely attributable to subcutaneous heparin injections, causing either skin necrosis and microscopic dystrophic calcification in the anterior abdominal wall.

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Transferrin-Dependent Uptake and Dosimetry of Auger-Emitting Diagnostic Radionuclides in Human Spermatozoa

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Localization of Auger-emitting radionuclides within spermatozoa could lead to the induction of transmissible genetic damage. We have quantified in vitro uptake of the widely used diagnostic Auger-emitters, ^{111}In and ^{99m}Tc, by ejaculated human spermatozoa and investigated the role of transferrin in their cellular localization. The resultant dose to sperm heads, including cellular dosimetry for Auger emissions, has been calculated for each radionuclide and compared with that achieved using conventional macrodosimetry. **Methods:** Freshly isolated human spermatozoa were incubated in a physiological salt solution containing ^{111}In-chloride, ^{99m}Tc-pertechnetate or the transferrin-binding isotope ^{59}Fe-citrate as a positive control. Cellular uptake mechanisms were investigated with transferrin competition and temperature dependence studies. The percentage uptake of each radionuclide was determined, and the dose to individual sperm heads was calculated using both conventional macrodosimetric methods and by consideration of radionuclide localization and energy deposition at the cellular level, including Auger electron emissions from ^{111}In and ^{99m}Tc. **Results:** On in vitro incubation, human spermatozoa were found to accumulate ^{111}In and ^{59}Fe but not ^{99m}Tc. Cell uptake of ^{111}In and ^{59}Fe was transferrin-mediated; however, an alternative transferrin-independent uptake pathway was also present for ^{111}In. The dose to sperm heads from ^{111}In, calculated using measured uptake and cellular dosimetry, was found to be larger than that calculated using conventional dosimetry by a factor of more than 100. In contrast, conventional dosimetry was adequate for ^{99m}Tc and ^{59}Fe. **Conclusion:** Isolated human spermatozoa appear to accumulate transferrin-binding isotopes, such as the Auger-emitter ^{111}In. If this uptake mechanism operates in the male reproductive tract, the resultant high dose to the sperm head could indicate that contraception may be advisable after large diagnostic doses of ^{111}In and, possibly, other transferrin-binding radionuclides. Such precautions could prevent transmission of any genetic damage from irradiated spermatozoa.

Key Words: spermatozoa; transferrin; radionuclides; Auger emissions; dosimetry

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Transferrin-binding radionuclides, such as ^{59}Fe and ^{111}In, are commonly used in diagnostic nuclear medicine. Laboratory and