Delayed Skin Rash Following Administration of Technetium-99m Diphosphonate: A Case Report

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We report a case of a 48-yr-old woman who developed a delayed skin rash following intravenous (i.v.) administration of technetium-99m hydroxymethylene diphosphonate (^{99m}Tc-HDP). The rash was characterized by skin biopsy, and it was concluded that the reaction was due to the diphosphonate compound. The rash resolved spontaneously without treatment. With most ^{99m}Tc-based agents, adverse reactions are considered rare and are usually allergic in nature, but the delayed nature of this reaction is more common with diphosphonate compounds than with other radiopharmaceuticals. If a repeat examination is required, alternative agents (such as ^{99m}Tc-pyrophosphate) or any other diagnostic modality (magnetic resonance imaging) may be considered. An intradermal skin test may be helpful to determine the safest alternative bone agent.

Adverse reactions to radiopharmaceuticals are uncommon, and there is considerable variety in the nature of reported complaints. Technetium-99m-methylene diphosphonate (^{99m}Tc-MDP) is unusual in its reported association with a delayed skin rash (*1,2*). We report a case in which an apparent reaction to ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HDP) was further characterized by skin biopsy.

CASE REPORT

A 48-yr-old woman reported to clinic with abdominal and back pain with a lump in the left groin. The patient had a history of metastatic rhabdomyosarcoma, and had undergone intensive chemotherapy 18 mo earlier, at which time there was no evidence of disease related to her current complaints. A bone scan with ^{99m}Tc-HDP (Osteoscan®*) was ordered to evaluate for possible metastatic disease and was negative. The patient had one previous bone scan with ^{99m}Tc-MDP but no adverse reaction was reported. A rash, pruritic and erythematous, appeared two days (~ 48 hr) after injection of the radiopharmaceutical, first on her arms and then on here lower legs. The reaction peaked at the time of her next visit to clinic (around the seventh day) when maximum lesion size was reported to be 5–8 mm.

A 4-mm punch biopsy of a lesion on her right dorsal arm was ordered. Microscopic examination revealed dermatitic chronic infiltrate clearly around blood vessels and composed predominantly of lymphocytes, in a pattern consistent with persistent erythema (Fig. 1). Blood vessel walls displayed extreme swelling, and red cells were seen extravasating through the vessel walls. Lymphocytic vasculitis, probably drug related, was diagnosed. The rash cleared spontaneously without medication over the next week.

DISCUSSION

Reactions to ^{99m}Tc-HDP and other ^{99m}Tc-based diphosphonates are uncommon but are noteworthy in presenting a more consistent syndrome than other radiopharmaceuticals (*1*). Fifteen of 35 reactions to ^{99m}Tc-MDP reported in the United States over a seven-year period involved rash or itching beginning 2–24 hr or more after injection. Only seven reactions to ^{99m}Tc-HDP were reported in this series, and one in a four-year European series.

In general, it is difficult to firmly establish a radiopharmaceutical as the cause of an adverse reaction. Spicer, et al. reported a repeated reaction to ^{99m}Tc-MDP in a patient who was rechallenged by a second bone scan (*2*). The patient's sore throat and pruritic rash were more severe following the second scan. Fewer reactions have been reported following administration of ^{99m}Tc-HDP than ^{99m}Tc-MDP, but the nature of the reaction we report here is very similar, with a delayed skin rash. The histologic appearance of a lymphocytic vasculitis is typical of a drug reaction. In the absence of any other unusual exposures and no known allergies in this patient, we consider the clinical presentation and biopsy findings strong evidence of ^{99m}Tc-HDP as the cause of this woman's reaction.

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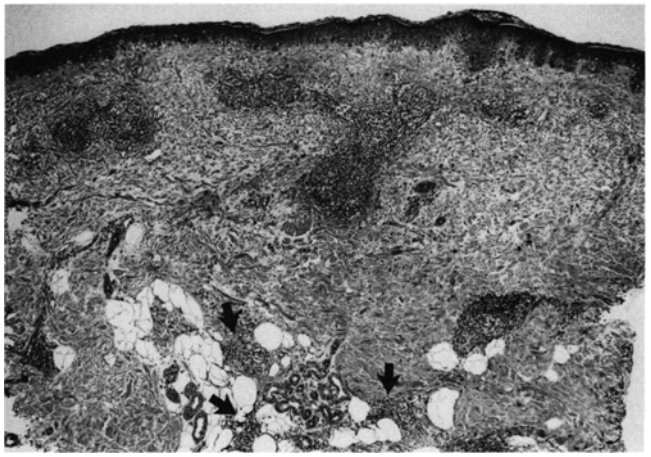

FIG. 1. Lymphocytic infiltrate surrounding blood vessels of the deep dermis (arrowheads) compatible with vasculitis.

What recommendation should be made concerning additional nuclear medicine studies following an adverse reaction? There is little data available for making such decisions. Limited experience suggests that a similar reaction may occur with the same agent (*2*). If the reaction is mild and the diagnostic need for a second study is sufficiently high, the study could be performed recognizing the risk of a repeat reaction.

Another course would be to use a different agent. Whole-body scanning using ^{67}Ga-citrate was reported to be as sensitive as ^{99m}Tc-EHDP (another diphosphonate) for the detection of primary skeletal tumor sites in Ewing's sarcoma (*3*). However, the report also indicated that the sensitivity of a whole-body scan using the bone agent was clearly superior to ^{67}Ga-citrate for the detection of skeletal metastases.

Can a diphosphonate alternative to HDP be considered for this patient? We are not aware of any studies of cross-reactivity between commercially available diphosphonates, i.e. ^{99m}Tc-HDP and ^{99m}Tc-MDP. It appears that, due to the structural similarities of the compounds, reactions may occur in the same patient following administration of either agent. It has been suggested that cross-reactivity may be determined with the aid of an intradermal skin test using samples of alternative bone agents (*4*). It also was suggested that, because of the structural dissimilarities between polyphosphate and diphosphonate bone agents, ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) may be a safe alternative-bone agent in the case of suspected allergic reaction to a diphosphonate compound. This agent may be used with the knowledge that ^{99m}Tc-PYP typically demonstrates higher red blood cell binding, and hence slower whole blood clearance, than the commercially available diphosphonates. Image quality may therefore be less than ideal with ^{99m}Tc-PYP versus ^{99m}Tc-MDP or ^{99m}Tc-HDP.

A third option is pretreatment. Again, we are unaware of any information on prophylaxis for diphosphonates.

Finally, additional exposure could be avoided entirely. Alternative diagnostic methods can be used, although none combine the advantages of whole-body imaging, sensitivity, and modest cost which accompany radionuclide bone scans. For the detection of some types of metastatic disease, preliminary work indicates that magnetic resonance imaging (MRI) may have sensitivity similar to nuclear medicine procedures (*5*). However, cost in both money and time are dramatically different, and whole-body screening is impractical with MRI.

In summary, the occurrence of an allergic reaction to ^{99m}Tc-based diphosphonates is a rare event, and most frequently presents as, in this case, a delayed skin rash. The rash is expected to resolve without treatment. Since alternative ^{99m}Tc-based bone agents are available, they should be considered if repeat bone scanning is indicated. An intradermal skin test, as described elsewhere, may be helpful in the determination of the safest alternative (*3*).

NOTE

* Osteoscan®, Mallinckrodt, Inc., St. Louis, MO

REFERENCES

1. Cordova MA, Hladik WB, Rhodes BA, et al. Adverse reactions associated with radiopharmaceuticals. In: Hladik WB, Saha GB, Study KT, eds. *Essentials of Nuclear Medicine Science.* Los Angeles, CA: Williams & Wilkins; 1987:303–320.

2. Spicer JA, Preston DF, Stephen RL. Adverse allergic reaction to technetium-99m methylene diphosphonate. *J Nucl Med* 1985;26:373–374.

3. Ramos-Gabatin A, Orzel JA, Maloney TR, et al. Severe systemic reaction to diphosphonate bone imaging agents: Skin testing to predict allergic response and a safe alternative agent. *J Nucl Med* 1986;27:1432–1435.

4. Frankel RS, Jones AE, Cohen JA, et al. Clinical correlations of ^{67}Ga and skeletal whole-body radionuclide studies with radography in Ewing's sarcoma. *Radiology* 1974;110:597–603.

5. Kulkarni MV, Sandler MP, Shaff MI, et al. Clinical magnetic resonance imaging with nuclear medicine correlation. *J Nucl Med* 1985;26:944–957.