Ifosfamide-Induced Alteration of Technetium-99m-DMSA Renal Parenchymal Imaging

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Renal cortical imaging with ^{99m}Tc-dimercaptosuccinic acid (DMSA) has become the imaging test of choice for the diagnosis of acute pyelonephritis. An unusual uptake pattern was observed in a child receiving chemotherapy for a bladder rhabdomyosarcoma. Chemotherapy from ifosfamide produces a specific pattern of injury to the renal tubule that alters uptake of DMSA.

Key Words: technetium-99m-DMSA; ifosfamide; renal tubular injury
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CASE REPORT

A 10-mo-old girl was diagnosed with embryonal rhabdomyosarcoma of the urinary bladder. The tumor (Stage III) was large and could only be incompletely surgically resected. Chemotherapy was started with the inner group rhabdomyosarcoma study IV (regimen 47). This consisted of vincristine, ifosfamide VP-16, adriamycin, cytoxan and actinomycin D. The patient never received radiation treatment. This multiple drug regimen was planned for 56 wk of treatment. The patient only received the prescribed doses for 38 wk because of multiple complications related to the chemotherapy.

The gastrointestinal problems included persistent nausea and vomiting with anorexia and poor oral intake. This necessitated hyperalimentation. Biopsy proof of gastritis and duodenitis and esophagitis was documented, but, after the biopsy, a traumatic duodenal hematoma further complicated the feeding problems.

Over the next 20 mo, recurrent multimicrobial urinary tract infections were documented, including candida cystitis. Because of citrobacter urinary tract infections, a ^{99m}Tc-dimercaptosuccinic acid (DMSA) scan was performed at 2.5 yr. An initial scan (Fig. 1) obtained at 1 hr demonstrated an abnormal pattern of uptake by the kidney more reminiscent of an agent undergoing glomerular filtration rather than a renal cortical image. A Fanconi-like syndrome of renal tubular damage had been documented earlier secondary to Ifosamide therapy. This renal tubular damage is proposed as the mechanism for the alteration in the uptake of the DMSA in the present case. The lack of uptake by the cortex of the kidney in comparison to the background and the high activity in the pelvocalyceal system was surprising but was confirmed on the 4-hr scan (Fig. 2). Increased liver and spleen activity, possibly indicative of reduced renal clearance, was not observed. Radiographs of the wrists and knees were obtained to determine elevated alkaline phosphatase and suspected rickets; however, they were normal. Recurrence of a tumor in the bladder necessitated a repeat partial cystectomy. The patient died of recurrent disease at 5 yr.

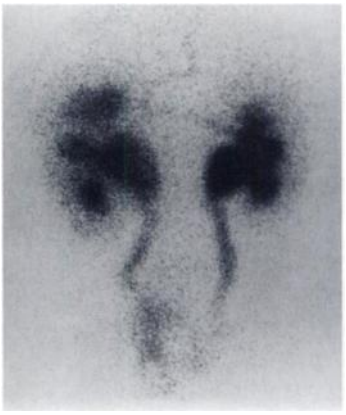

FIGURE 1. Posterior DMSA planar image of the kidneys after injection through central line. At 1 hr, there is little parenchymal uptake with DMSA already in the collecting systems.

FIGURE 2. DMSA image at 4 hr. Dilated collecting systems with minimal uptake in the renal parenchyma.

DISCUSSION

DMSA renal scanning has been demonstrated to be the imaging modality of choice for the diagnosis of both acute pyelonephritis and renal scars secondary to reflux nephropathy (*1*). In fact, it is the only imaging modality that has been proven in an animal model to be both sensitive and specific for the diagnosis of acute pyelonephritis (*2*). In this regard, it is has been shown to be far superior to other imaging modalities, including ultrasound examination (*3*).

DMSA is a renal cortical imaging agent that is a complex organic acid transported by a similar mechanism to other organic acids. This transport mechanism is an energy dependent pathway in both the proximal and distal tubular cells from the peritubular interstitial fluid into the cell (*4*). The DMSA then binds to the sulfhydryl groups inside the cell of the renal parenchyma and is not excreted. Glomerular filtration of DMSA has also been demonstrated with re-absorption (*5*), which allows delayed images to be obtained 2–4 hr after injection of the radiopharmaceutical. Forty to 50% of the DMSA remains in the cortex, allowing a higher target-to-background ratio than is possible in other renal radiopharmaceuticals such as glucoheptonate. DMSA does not accumulate in a dilated collecting system, which may obscure imaging of the renal parenchyma. The distribution of DMSA in the obstructed kidney has conflicting results. Some reports document excellent correlation with creatine clearance (*6*) without overestimation of function of an obstructed kidney (*7*). Increased cortical activity secondary to retention in obstructed tubules with activity remaining in dilated calyces and renal pelvis may also occur (*8*). Another possibility, as evidenced in the present report, is that recurrent

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rhabdomyosarcoma of the bladder could be causing the obstruction.

Ifosfamide is an ozazophosphorine derivative of cyclophosphamide. This chemotherapeutic agent is an attractive alternative for the treatment of cyclophosphamide-resistant tumors. It also has lower bone marrow toxicity. Specific damage to the proximal tubule results in a Fanconi-type renal tubular syndrome. This consists of diminished phosphate resorption from the proximal tubules and a hypophosphatemic state (*9*). Normal plasma calcium is maintained. Excess phosphate in the urine can lead to a radiographic pattern of rickets (*10*). In this report, the damage to the kidney, as shown by the decreased DMSA uptake, occurred before any radiographic evidence of rickets at the growth plate. Other renal tubular resorptive mechanisms are also damaged, resulting in glycosuria, renal tubular acidosis and abnormal vitamin D metabolism. This complication is more common in smaller children in the first decade of life and is described as producing rickets more commonly in children with a single kidney, such as after a nephrectomy for Wilms tumor (*11*). This complication is presumed to be dose-related, but there is a single case report of a child who developed Fanconi syndrome after the first dose of ifosfamide (*12*), which suggests that the nephrotoxicity of ifosfamide to the proximal renal tubules may not be completely dose-related. Earlier treatment with nephrotoxic drugs such as cisplatin or carboplatin exaggerates the damage from ifosfamide.

DMSA has been shown to be exquisitely sensitive in detection of renal tubular damage from ifosfamide. A quantitative serial study in children receiving ifosfamide documented a cumulative pattern of injury (*13*). This pattern showed decreased renal and background activity with increased bladder activity. None of the children showed activity in a dilated renal pelvis and ureters as our patient. The sensitivity to renal tubular damage was superior to laboratory measurements, including β_2 microglobulin values in the urine and renal tubular resorption of phosphate. DMSA was recommended as a suitable method to access ifosfamide-induced renal tubular damage. This case report also documents the superiority of the DMSA scan in detecting renal tubular damage over radiographic changes of rickets at the growth plate. This patient's radiographs of the wrists and knees were normal at the time of the DMSA scan.

In the present report, damage to the renal tubular cells from ifosfamide also interrupted the transport mechanism for binding DMSA. Without this binding to the renal tubular cells, DMSA was excreted by glomerular filtration, thereby accounting for the unusual pattern seen in Figures 1 and 2.

CONCLUSION

Ifosfamide may produce damage to the renal tubular transport mechanism, which is responsible for the binding of DMSA. We have described an altered uptake pattern on the DMSA scan that more closely resembles that of a glomerular filtration agent as seen, for example, with DTPA. This unusual uptake pattern can be recognized as a side effect of chemotherapy from ifosfamide.

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Lung Scintigraphy in Postpneumonectomy Dyspnea Due to a Right-to-Left Shunt

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We report the case of a 50-yr-old man who experienced exertional dyspnea 5 mo after a left pneumonectomy for carcinoma. As the clinical features pointed toward a pulmonary embolism, we performed a ventilation plus perfusion radionuclide lung scan. It showed no evidence of pulmonary embolism, but it did show a systemic uptake of the isotope, suggesting a right-to-left shunt that was confirmed by contrast echocardiography, which revealed an atrial septal defect. Right-to-left shunts after pneumonectomy have already been reported and can be diagnosed by lung scintigraphy. Usually, a patent foramen ovale is encountered, but the underlying physiopathology remains under discussion. Clinically, right-to-left shunts are often related to platypnea-orthodeoxia.

Key Words: ventilation; perfusion lung scan; pneumonectomy; dyspnea; platypnea-orthodeoxia

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