Persistent Fever in a Patient with Polycystic Kidney and Liver Diseases and Bilateral Hip Prostheses

C. Gerry Kwok and I. Ross McDougall

Division of Nuclear Medicine, Department of Radiology, Stanford University School of Medicine, Stanford, California

Persistent fever in a 60-yr-old man with polycystic kidney and liver diseases and bilateral hip prostheses was presented in this study. Multiple diagnostic tests failed to localize a source of infection. Subsequently, a combination of a ^{111}In-oxine labeled WBC and ^{99m}Tc-sulfur colloid scans (and computer subtraction) demonstrated abnormally increased WBC activity in the left lobe of the liver, thus, diagnosis of an infected cyst (or cysts) was made. The patient responded to the treatment with antibiotics. This article discusses the clinical features of polycystic disease of the liver and kidneys. Infection in cysts are discussed as well as radiographic and scintigraphic investigations that can be used to diagnose and localize infection in a cyst.

Key Words: scintigraphy; infection; liver cyst; renal cyst; hip prosthesis

CASE HISTORY

A 60-yr-old man was admitted for work-up of fever. The patient had polycystic kidney and liver diseases, and renal failure, which was treated by a related donor renal transplantation 23 yr ago. He had a total of five hip replacements involving both hips. The last operation was 1 yr ago. The patient began having fevers and pain in the upper mid-abdomen 3 mo before this hospital admission. During his workup in another hospital, one of the liver cyst was aspirated, and there was no evidence of infection. A radiolabeled white blood cell (WBC) scan was performed but did not reveal the source of infection. A hepatobiliary scan (HIDA) and a right upper quadrant abdominal ultrasound were also negative for any source of infection. He was treated with 2 wk of intravenous antibiotics and was later discharged taking ciprofloxacin and clindamycin by mouth. The patient did well until the clindamycin was stopped, after 6 wk. Approximately 1 wk later, the fever and abdominal pain recurred. Symptoms persisted even after the clindamycin was restarted.

The patient was admitted to our institution for further evaluation. Initial work-up of the fever included blood and urine cultures. An infectious disease consultant recommended stopping all antibiotics with the objective of collecting blood and urine cultures, should the patient redevelop fever. MRI of the abdomen showed multiple cysts distributed throughout the liver and the native polycystic kidneys. One large cyst in the right lobe of the liver had a slightly different MR image than the other cysts (Fig. 1). That cyst was aspirated under ultrasound guidance and 50 cc of dark brown fluid were obtained. Grams' stain of the fluid did not show any organisms; the findings were attributed to an old hemorrhage. The patient redeveloped a fever 4 days after admission. A chest radiograph did not show any acute process. Grams' stain and culture of the cerebral spinal

fluid were also negative. CT of the head and sinuses were normal. An ^{111}In-oxine-labeled WBC scan was then performed. There was no abnormal focal accumulation of WBCs in the chest, the abdomen or the native polycystic kidneys (Fig. 2). There was irregular uptake of white cells in the liver with areas of increased uptake (Fig. 3, left). Radiolabeled WBC distribution in the left hip was more than the right hip (Fig. 3, right). A ^{99m}Tc-sulfur colloid study was performed 1 day later. Images of the liver and the hips were acquired in both the ^{111}In and ^{99m}Tc energy windows sequentially without moving the patient. Normalization and subtraction of the images in the two energy windows were performed on a digital computer. The image of the liver after subtraction demonstrates foci of increased activity in the left lobe highly suggestive of infection (Fig. 4). The subtraction image of the hips did not show any evidence of infection in the left hip (Fig. 5).

Due to the multiplicity and small size of the cysts in the left lobe of the liver, drainage or aspiration of the infected cysts was felt to be impossible. It was recommended that the patient be treated for 6 wk by intravenous antibiotics with close clinical follow-up. The patient responded to the therapy with resolution of fever and abdominal pain. The patient remained asymptomatic 5 mo after the therapy was finished. A follow-up ^{111}In WBC scan was not ordered.

DISCUSSION

Polycystic Kidney and Polycystic Liver Disease

Autosomal dominant polycystic kidney disease (ADPKD) is a systemic hereditary disorder characterized by renal cysts and commonly hepatic cysts. Reported prevalence varies between 1 in 500 and 1 in 1000 live births (*1*). Overall, approximately one-half million Americans have the disease, making ADPKD more common than sickle-cell disease and cystic fibrosis in the United States (*2*). ADPKD currently accounts for approximately 10% of all patients with end stage renal disease (*1,3*).

Polycystic liver disease (PLD) is often seen in association with ADPKD (*4*). The true prevalence of hepatic cysts in patients with ADPKD is not known. It is known, however, that the prevalence of PLD increases with age and with declining renal function. In a series of 158 patients with ADPKD, Milutinovic et al. (*4*) found 77% of patients over 59 yr had liver cysts.

Risk of Infection

Infection of both the upper and lower urinary tract is common among patients with ADPKD, but the overall frequency is not known. Several studies have demonstrated that infection of the lower urinary tract is present at any one time in 30–50% of the patients with ADPKD (*3*). When infection spreads to the upper urinary tract, besides parenchymal infection, cyst infection, perinephric abscess or sepsis can occur.

In general, it has been considered that complications from liver cysts are rare. This is not true, however, for patients with ADPKD and end-stage renal disease. In a group of 229 patients with ADPKD and end-stage renal disease, Grunfeld et al. (*5*)

FIGURE 1. Abdominal MRI demonstrates multiple structures of high signal throughout the liver (T2-weighted images) which correspond to the known cysts. There is a large cyst in the right lobe of the liver with a slightly different MR image appearance (higher signal) than the other cysts. That cyst was aspirated and found to be an old hemorrhage.

found up to 3% of the patient had liver cysts infection. It is possible that the progressive enlargement of liver cysts in these patients led to increased incidence of liver complications. Additionally, it is logical to expect that the incidence of infection of liver cysts would increase in proportion to the prolonged survival of these patients afforded by dialysis or renal transplantation.

Clinical Features

Renal infection is suspected in patients with high fever, and signs and symptoms referable to the kidney. Work-up includes microscopic study of urine for white cell casts, urine culture and blood culture. In a study of 26 patients with ADPKD and renal infection, Schwab et al. (1) found that patients who responded to the initial antibiotic therapy 100% had a positive urine culture, 55% had urinary white cell casts and 45% had positive blood cultures. The findings are comparable to that found in acute renal parenchymal infections in the general population. On the other hand, patients who did not respond to the initial antibiotic therapy, were characterized by the development of a discrete new palpable area of tenderness in the involved kidney (100%) and 93% had positive blood cultures. Urinary white cell casts were found only in 1 of 15 of those patients. From
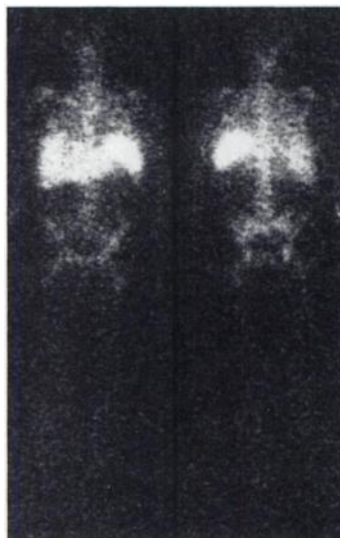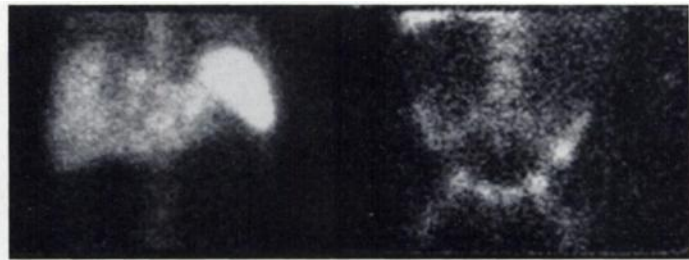
FIGURE 3. Static ^{111}In-WBC image of the upper abdomen demonstrates irregular distribution of radiolabeled WBCs in the liver with areas of increased focal uptake (left image). Static ^{111}In WBC image of the pelvis demonstrates increased radiolabeled WBC uptake in the superior and inferior regions of the left acetabulum (right image).
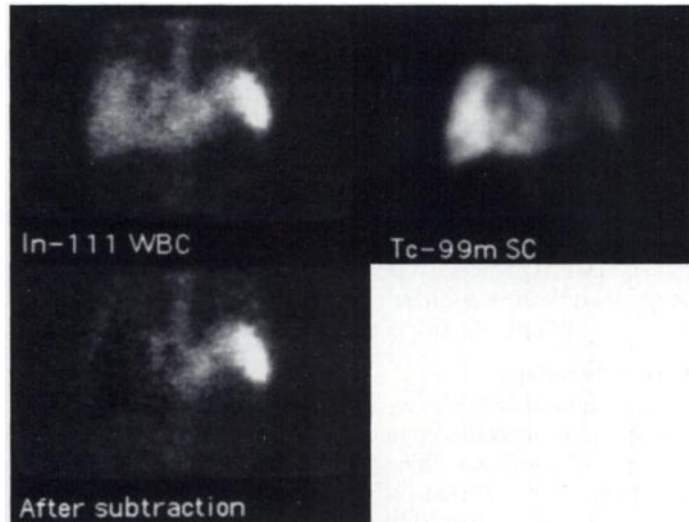
nephrectomized kidneys, the only evidence of active infection was in cysts and there was no parenchymal infection. Therefore, in patients with ADPKD and renal infection it should be accepted that a cyst is infected when appropriate antibiotics fail to eradicate the infection.

Telenti et al. (6) retrospectively reviewed 14 cases of infected liver cyst and published detailed case reports. They found that the clinical and laboratory features of liver cyst infections are fever, new onset of right upper abdominal pain, leukocytosis and a high erythrocyte sedimentation rate. The features, however, are not exclusive or unique for liver cyst infection. Frequently, bacteremia has been found in patients with infected liver cysts but it is also not specific. Infection of a liver cyst is usually considered after other possible sources of infection have been excluded.

Radiographic Studies of Infected Cysts

Abscesses are hypoechoic with varying degrees of internal debris when studied by ultrasound. The appearance of abscess can be variable and if gas is present the abscess can be highly hyperechoic. According to Kuligowska et al. (7), the most consistent sonographic feature in their series of 22 patients with liver abscesses was distal acoustic enhancement. This was seen in all cases of solitary abscesses except an amebic abscess.

CT and MRI both provide highly detailed anatomic information of the organ in question and its surrounding structures. On

FIGURE 2. Whole-body ^{111}In-WBC scans demonstrates no abnormal focal accumulation of WBCs in the chest, abdomen or native polycystic kidneys.

FIGURE 4. A ^{99m}Tc-sulfur colloid study was performed 1 day after the ^{111}In-WBC scan. Static images of the upper abdomen were obtained in both the ^{111}In and ^{99m}Tc energy windows (top two images). The sulfur colloid image is then normalized to the ^{111}In-WBC image using the hottest liver region and subtracted from the ^{111}In-WBC image. The resultant image, after subtraction, demonstrates foci of increased WBC accumulation in the left lobe of the liver highly suggestive of infection.
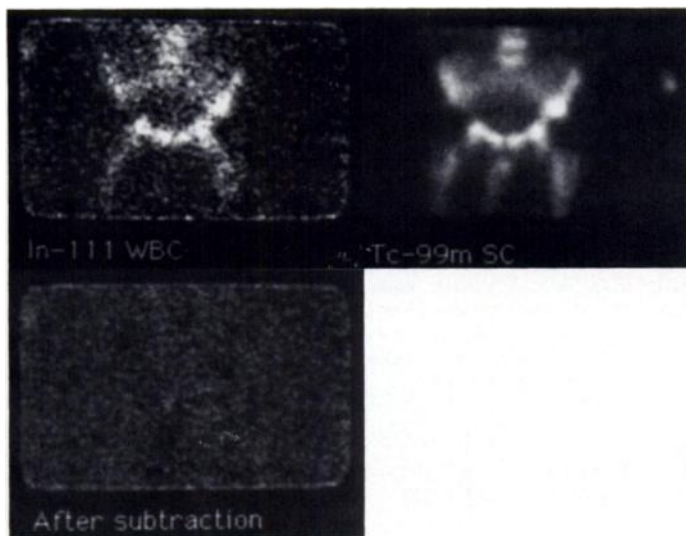
FIGURE 5. Static images of the pelvis in ^{111}In and ^{99m}Tc energy windows demonstrate similar increased tracer uptake in the superior and inferior regions of the left acetabulum. Subtraction image confirms the above impression and suggests no evidence of infection in the left hip.

CT, most abscesses are of low density and show rim enhancement when intravenous contrast is given. On MRI, rims of high and low intensity are seen on both T1- and T2-weighted pulse sequences. Overall, CT and MR image findings are not specific for infection (8).

Scintigraphic Localization of Infection: Gallium-67

Sites of infection and inflammation can be localized and imaged using various nuclear medicine studies. The first widely used radionuclide was ^{67}Ga-citrate (9). Concentration of ^{67}Ga in infection is facilitated by leukocytes, but is not dependent on these cells. Because ^{67}Ga is normally distributed in the liver, spleen, and bone marrow and is excreted through the kidneys and gut, it is generally not preferred for abdominal infection. It should be recognized that ^{67}Ga has been used successfully to localize infection in renal cysts (10,11).

Labeled White Blood Cell Scan

Labeled WBC scans use the normal physiologic function of white cells to localize in sites of infection. WBC have been labeled with ^{111}In, usually as oxine, or ^{99m}Tc-HMPAO. Many have reported success in localizing infected cysts in polycystic kidneys and liver using ^{111}In-labeled WBC (12–15).

It is accepted that there is normal distribution of ^{111}In-labeled WBC in the liver, spleen and bone marrow. Normally there is no uptake or excretion of ^{111}In or ^{111}In WBCs by or through the kidneys or intestine. This contrasts with scintiscans using ^{99m}Tc-HMPAO labeled WBCs in which renal tract, bladder and large intestine are visualized. For this reason it is our preference to use ^{111}In WBC for suspected infection in the abdomen (16).

Other Techniques

Radiolabeled monoclonal antigranulocyte antibodies and radiolabeled nonspecific immunoglobulin have been investigated for localizing inflammation and infection (17,18). They have an advantage over labeled WBC for not needing white cells separation and labeling. However, there are still many problems needing further investigation. Another new technique under investigation is radiolabeled leukocyte chemoattractant peptide (19). The peptides, however, induce a profound transient reduction in peripheral leukocyte levels which is problematic. Currently, clinical data are not available concerning imaging infected cyst using these techniques.

Infection in the Liver

The drawback of ^{111}In-labeled WBC scan for the abdomen is uptake in liver and spleen. As a result, whenever the suspected abnormality is in or around these organs, it is advisable to obtain a ^{99m}Tc-sulfur colloid scan concurrently (20). The scans can be imaged side by side, or the ^{99m}Tc-sulfur colloid scan be subtracted from the ^{111}In white cell scan to "remove" normal liver and spleen. Any residual ^{111}In activity is likely due to an abscess. This technique was used in this patient, which demonstrated abnormal white cell uptake in the left lobe of liver at a site where there were multiple cysts on MR image.

Kidney Infections

There was no uptake of ^{111}In white cells in the region of the kidneys in our patient. However, if there had been abnormal activity in that region and the exact site was not clearly delineated, superimposition of an anatomic nuclear renal study such as ^{99m}Tc-DMSA or ^{99m}Tc-glucoheptonate would allow precise localization. SPECT imaging might be required. This approach has been used successfully and reported by Fortner et al. (15).

Infection in the Bones

Of the nuclear medicine techniques for diagnosing osteomyelitis, a three-phase bone scan has had the widest acceptance. In the case of suspected infected prosthesis, this procedure lacks specificity because it can be abnormal in loosened but uninfected prosthesis. A white cell scan is more specific. However, irregular uptake in or around the prosthesis can be related to bone and marrow, the irregularity being due to postoperative changes. In this situation, and in any patient where the distribution of ^{111}In white cells is irregular, comparison of the distribution of labeled white cells and colloid can resolve whether there is infection. When the findings are concordant, infection is unlikely, and when there is more white cell uptake, infection is likely. Achong et al. (21) found computerized subtraction produced 95% sensitivity, 93% specificity and 94% accuracy in 36 suspected sites of osteomyelitis. In our patient, the combined white cell scan and ^{99m}Tc-sulfur colloid scan allowed us to rule out infection in the hip prosthesis as well as demonstrate infection in the liver.

Because of the number and complexity of the hepatic lesions in our patient, a decision was made not to attempt aspiration or surgery but to treat with systemic antibiotics and re-evaluate his clinical condition. He has improved considerably.

CONCLUSION

Radionuclide studies offer more specific information for infection compared to ultrasound, CT and MR imaging. Indium-111-labeled WBC scintigraphy is recommended for possible intra-abdominal infection studies because there is normally no bowel or renal excretion as compared to ^{99m}Tc-HMPAO labeled WBC or ^{67}Ga. Indium-11-labeled WBCs normally accumulate in liver, spleen and bone marrow, which can make investigation of infection in those areas difficult. However, simultaneous use of ^{99m}Tc-sulfur colloid allows differentiation of infection from normal physiological activity.

REFERENCES

1. Schwab SJ, Bander SJ, Klahr S. Renal infection in autosomal dominant polycystic kidney disease. Am J Med 1987;82:714–718.
2. Gabow PA, Grantham JJ. Polycystic Kidney Disease. In: Schrier RW, Gottschalk CW, eds. Diseases of the kidney, 5th ed. Boston: Little, Brown; 1993:535–569.
3. Gardner KD, Evan AP. Cystic kidneys: an enigma evolves. Am J Kidney Dis 1984;3:403–413.
4. Milutinovic J, Fialkow PJ, Rudd TG, Afodoa LY, Phillips LA, Bryant JI. Liver cysts in patients with autosomal dominant polycystic kidney disease. Am J Med 1980;68: 741–744.

5. Grunfeld J-P, Albouze G, Jungers P, et al. Liver changes and complications in adult polycystic kidney disease. *Adv Nephrol* 1985;14:1–20.

6. Telenti A, Torres VE, Gross JB, Van Scoy RE, Brown ML, Hattery RR. Hepatic cyst infection in autosomal dominant polycystic kidney disease. *Mayo Clinic Proc* 1990;65:933–942.

7. Kuligowska E, Connors SK, Shapiro JH. Liver abscess: sonography in diagnosis and treatment. *Am J Roentgenol* 1982;138:253–257.

8. Bennett WF, Bova JG. Review of hepatic imaging and a problem-oriented approach to liver masses. *Hepatology* 1990;12:761–775.

9. Lavender JP, Lowe J, Barker JR, Burn JI, Chaudri MA. Gallium-67-citrate scanning in neoplastic and inflammatory lesions. *Br J Radiol* 1971;44:361–366.

10. Tsang V, Lui S, Hilson A, Moorhead J, Fernando O, Sweny P. Gallium-67 scintigraphy in the detection of infected polycystic kidneys in renal transplant recipients. *Nucl Med Commun* 1989;10:167–170.

11. Amesur P, Castronuovo JJ, Chandramouly B. Infected cyst localization with gallium SPECT imaging in polycystic kidney disease. *Clin Nucl Med* 1988;13:35–37.

12. Gesundheit N, Kent DL, Fawcett HD, Effron MK, Maffly RH. Infected liver cyst in a patient with polycystic kidney disease. *West J Med* 1982;136:246–249.

13. London RD, Malik AA, Train JS. Infection in a patient with polycystic kidney and liver disease: noninvasive localization and treatment. *Am J Med* 1988;84:1082–1085.

14. Gilbert BR, Cerqueira MD, Eary JF, Simmons MC, Nabi HA, Nelp WB. Indium-111 white blood cell scan for infectious complications of polycystic renal disease. *J Nucl Med* 1985;26:1283–1286.

15. Fortner A, Taylor A Jr, Alazraki N, Datz FL. Advantage of indium-111 leukocytes over ultrasound in imaging an infected renal cyst. *J Nucl Med* 1986;27:1147–1149.

16. McDougall IR, Baumert JE, Lantieri RL. Evaluation of indium-111 leukocyte whole-body scanning. *Am J Roentgenol* 1979;133:849–854.

17. Becker W, Goldenberg DM, Wolf F. The use of monoclonal antibodies and antibody fragments in the imaging of infectious lesions. *Semin Nucl Med* 1994;24:142–153.

18. Rubin RH, Fischman AJ. The use of radiolabeled nonspecific immunoglobulin in the detection of focal inflammation. *Semin Nucl Med* 1994;24:169–179.

19. Fischman AJ, Babich JW, Rubin RH. Infection imaging with technetium-99m-labeled chemotactic peptide analogs. *Semin Nucl Med* 1994;24:154–168.

20. Fawcett HD, Lantieri RL, Frankel A, McDougall IR. Differentiating hepatic abscess from tumor: combined indium-111 white blood cell and technetium-99m liver scans. *Am J Roentgenol* 1980;135:53–56.

21. Achong DM, Oates E. The computer-generated bone marrow subtraction image: a valuable adjunct to combined ^{111}In WBC/^{99m}Tc in sulfur colloid scintigraphy for musculoskeletal infection. *Clin Nucl Med* 1994;19:188–193.