Indium-111 Autologous Leukocyte Imaging in Pancreatitis

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Thirty-nine patients with acute pancreatitis have been assessed using a prognostic factor grading system, abdominal ultrasound, and autologous leukocyte imaging. Both prognostic factor grading and leukocyte imaging can accurately assess the severity of the disease early in its course. All patients with a negative indium-labeled leukocyte image recovered without sequelae, whereas five of the 12 patients with a positive image developed complications, including two deaths. Abdominal ultrasound is of no value in assessing severity, but is a useful method of detecting those patients with gallstone-associated disease. In patients with suspected abscess formation following acute pancreatitis, indium leukocyte imaging does not differentiate between fat necrosis and abscess formation. In this situation, computerized tomography should be carried out before laparotomy is undertaken.

J Nucl Med 27:345–352, 1986

Acute pancreatitis and its sequelae remain a major challenge to the practicing clinician. Overall, the mortality in the United Kingdom ranges from 9–11% (*1,2*), but when the more serious hemorrhagic or necrotizing pancreatitis is encountered the mortality may rise to 90% (*3*). Many patients recover from the acute attack following a period of conservative management, but significant complications leading to death or requiring surgery develop in 16% of patients (*4*). Various parameters have been used to assess the severity of an attack of pancreatitis early in the course of the disease in order to predict which patients are liable to develop complications. Hypocalcemia (*5*), peritoneal lavage (*6*), an elevated fibrinogen level (*7*), complement activation (*8*), and serum trypsin (*7*) have all been shown to be of value in assessing severity. Pancreatic polypeptide levels may also be useful, but results in the literature are conflicting (*9,10*). Multiple prognostic factor grading based on the criteria of Imrie (*1*) or Ranson (*11*) has become widely accepted as a method of assessing severity. The major part of this study compares indium-111 (^{111}In) autologous leukocyte imaging with the prognostic criteria of Imrie and ultrasound examination as methods of assessing severity. Patients with chronic pancreatitis, pancreatic pseudocysts, and suspected pancreatic abscesses were also studied to determine the role of this investigation in these situations.

Received Nov. 19, 1984; revision accepted Nov. 26, 1985.

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PATIENTS AND METHODS

Fifty patients were studied, 39 presenting with acute pancreatitis, two with pseudocysts, three with chronic pancreatitis and an exacerbation of their pain, and six with suspected pancreatic abscesses following an acute attack.

Patients with Acute Pancreatitis

Thirty-nine consecutive patients presenting with their first attack of acute pancreatitis were studied prospectively. Twenty-one were men and 18 were women with a mean age of 49.8 yr (range 18–96 yr). The diagnosis of pancreatitis was based on clinical presentation and subsequent course of the illness, together with a serum amylase level on admission of >1,000 IU/l (mean value 3,219 IU/l; range 1,050–12,250). The severity of the disease was assessed using the prognostic factor grading system described by Imrie et al. (*1*). The patient was considered to have severe pancreatitis if three or more of the following factors were present within 48 hr of admission: (a) white cell count >15 × 10^9/l (normal range 4–11); (b) PaO_2 <8 kPa (normal

range 12.0–16.0); (c) plasma glucose >10 mmol/l (normal range 4.0–5.5); (d) blood urea >16 mmol/l (after correction of dehydration: normal range 2.5–8.0); (e) serum calcium <2 mmol/l (normal range 2.2–2.6); (f) serum albumin <32 g/l (normal range 35–55); (g) serum transaminases >100 u/l (normal range ALT 10–45, AST 10–40); (h) serum lactate dehydrogenase >600 u/l (normal range 130–270); (i) age over 55 yr.

When the pancreatitis was considered secondary to gallstones, the criteria were modified as suggested by Osborne et al. (*12*), the age factor was removed, and the serum transaminase level had to be >200 u/l.

Ultrasound examination of the upper abdomen was carried out within 6 days of admission in 36 patients. Indium-111 leukocyte imaging was undertaken within 5 days of admission in 38 patients, and on Day 7 after diagnosis in the remaining patient.

All patients were carefully observed throughout their hospital stay and for the following 3 mo, with any complications noted. Ultrasound-diagnosed cholelithiasis was confirmed in all patients by either endoscopic retrograde cholangiopancreatography and sphincterotomy or cholecystectomy during the same or at a subsequent admission.

The etiology of the pancreatitis in the 39 patients was cholelithiasis in 18, alcohol in 13, paracetamol in one, and a mucinous cystadenoma in one. In six patients, no obvious cause for the pancreatitis could be found.

Patients with Post-Pancreatitis Sequelae and Chronic Pancreatitis

Eleven further patients were studied, two presenting with pseudocysts, three patients with chronic pancreatitis, and six patients with suspected abscesses following an attack of acute pancreatitis.

Two male patients with ultrasound-proven pseudocysts were referred from other hospitals, as they had developed pseudocysts 4 and 6 wk after the initial attack of pancreatitis. In one patient, the pseudocyst was confirmed at laparotomy, and in the other patient regression in size was followed by serial ultrasound examination.

Three male patients with alcohol-induced chronic pancreatitis were studied within 4 days of their admission with an acute exacerbation of abdominal pain. In these three patients, there was only moderate elevation of the serum amylase level (mean 547 IU/l; range 306–774).

Six further patients (three women and three men) with suspected postpancreatitis abscess formation were also studied. Four of these patients were transferred from other hospitals within 3 wk of their initial admission with acute pancreatitis. Three of the six patients were found at laparotomy to have abscesses.

Preparation of Indium-Labeled Leukocytes

For each patient in the study, a commercial [^{111}In]oxine solution* was used according to the manufacturer's protocol to label the leukocytes harvested from 50 ml of blood. The labeling dose of ^{111}In was in the range 270–540 μCi (10–20 MBq), and on average 79% of this was recovered from the labeling procedure attached to the leukocytes suitable for administration. The major source of loss of ^{111}In was due to leukocytes which became clumped during the labeling and had to be discarded. In a number of cases, the viability of the labeled leukocytes was assessed prior to administration using the Trypan Blue exclusion test, and this showed that, following the labeling procedure, >85% of the leukocytes remained viable.

Imaging Technique

In the majority of patients studied, imaging was performed at 6 and 24 hr following administration of the labeled leukocytes, and in the remainder a 24-hr image was obtained. The patients were positioned supine under a large field-of-view gamma camera fitted with a medium-energy, parallel hole collimator. Two analyzer windows were used to accept the 171 and 247 keV photons emitted by the ^{111}In, and for each image at least 400,000 count were collected. For the purposes of this study an [^{111}In]leukocyte image was considered positive whenever a collection of the radioisotope was noted outside the normal uptake by the liver, spleen, and bone marrow.

RESULTS

Patients with Acute Pancreatitis

Thirty of the 39 prospectively-studied patients had mild disease as judged by prognostic factor grading. The pancreatitis in 29 cases settled without complication and all were discharged from the hospital within 14 days. Twenty-seven of these patients did not show any abnormal collection of labeled leukocytes within the abdomen. During the follow-up period of 3 mo three patients with alcohol-induced pancreatitis developed a further attack of acute pancreatitis, but all settled without complication. None of the remaining 24 patients developed any complications during the follow-up period. Three of the 30 patients did have positive leukocyte studies, where areas of uptake were seen in the subhepatic and central parts of the abdomen (Fig. 1). One of these three patients subsequently developed a pseudocyst, which required surgical drainage. The remaining two patients settled without complication, and were discharged from the hospital within 12 days of admission. The etiology of the pancreatitis in these three patients was, respectively, gallstones in the patient who developed pseudocyst, paracetamol, and idiopathic.

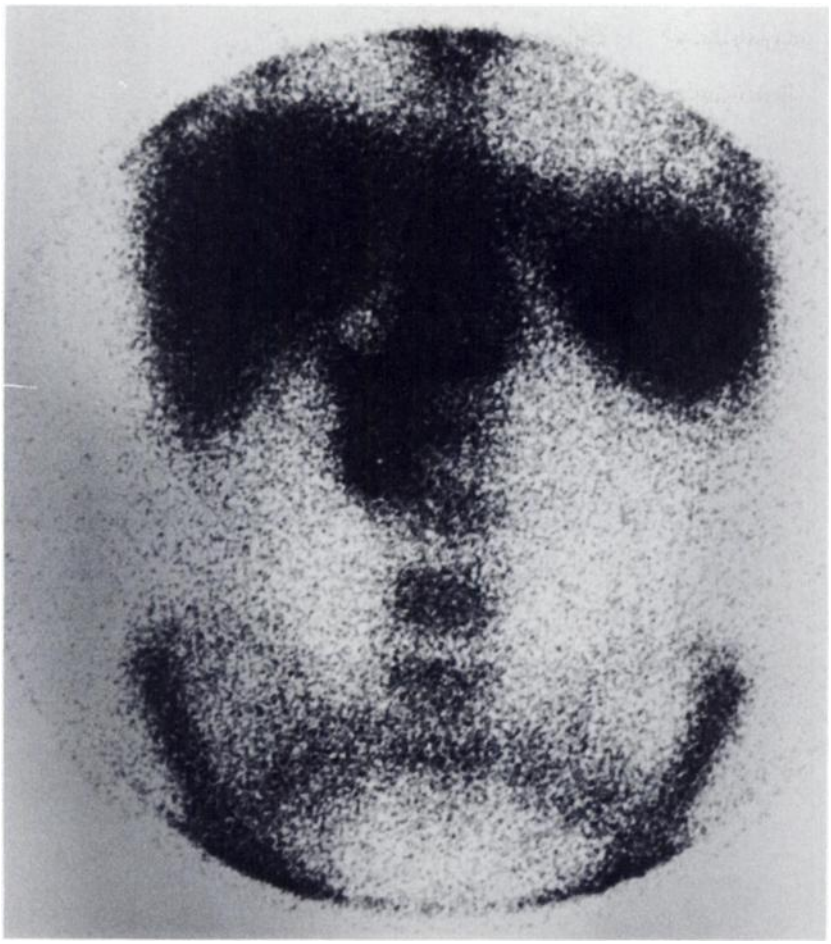

FIGURE 1
Indium leukocyte image showing normal distribution of activity in liver, spleen and bone marrow and abnormal accumulation in central and subhepatic areas

Nine of the 39 patients had severe pancreatitis after prognostic factor grading, and all nine had positive [^{111}In]leukocyte studies (Figs. 2 and 3). Six patients had gallstone-associated disease, two had alcohol-induced pancreatitis, and in the remaining patient the etiology was unknown. Two of these nine patients died, one as a result of extensive pancreatic necrosis and abscess, and the other following a perforated gallbladder. One patient developed acute renal failure and another, the adult respiratory distress syndrome; both patients recovered from these complications. Two of these patients underwent computerized axial tomography (CT) and this showed extensive fat necrosis corresponding to the areas of uptake of the ^{111}In.

Ultrasound examination was carried out in 36 of the patients. In 17, gallstones were identified, with none found in the remaining 19. Further investigation of these 19 patients (i.v. cholangiography and outpatient oral cholecystography) did not reveal any "missed" stones. Pancreatic examination by ultrasound was considered satisfactory in 31 of the 36 patients and the pancreas was not seen in five. Of the 31 patients with a satisfactory scan, a normal pancreas was seen in 19, a swollen pancreas in 11, and a cyst in one. This latter patient had a mucinous cystadenoma. The presence or absence of swelling did not differentiate between severe and mild disease, and did not distinguish between gallstone-related and alcohol-associated pancreatitis.

Patients with Chronic Pancreatitis and Pseudocysts

One of the three patients with alcohol-induced chronic pancreatitis had a positive [^{111}In]leukocyte image; two were normal. Ultrasound examination in all three patients was considered normal. None of the patients developed any complications throughout or following their hospital stay.

Both patients with pseudocysts had normal leukocyte images at the time of presentation with the cyst. In retrospect, both patients had severe disease based on prognostic factor grading at their initial presentation, but neither had an [^{111}In]leukocyte image carried out at that time.

Patients with Suspected Abscesses

Table 1 summarizes the results of the [^{111}In]leukocyte images in the six patients and compares the results with the findings at CT scanning and/or laparotomy. Three of the six patients were found to have abscesses at

FIGURE 2
Indium leukocyte image showing abnormal accumulation in central abdomen extending along line of pancreas towards spleen

laparotomy. Patients 3, 4, and 6 had marked fat necrosis in areas corresponding to the labeled white cell accumulation (Fig. 4).

DISCUSSION

Indium-111 autologous leukocyte imaging has become an established method for locating sepsis within the abdomen (*13,14*). In a study of 163 patients with suspected intra-abdominal abscesses, Carroll et al. (*13*) showed that the technique had a sensitivity of 84% and a specificity of 95%. The test was particularly valuable when focal abdominal signs were absent. When used in conjunction with ultrasound examination, only one combined false-negative result occurred and there were no false-positives. Similarly, Ascher et al. (*14*) showed a test sensitivity of 87%, and a specificity of 92% in the detection of intra-abdominal abscesses. Indium-111 leukocyte imaging has also accurately assessed the extent of inflammatory bowel disease when compared with barium enema examination (*15*). Grading of the indium image before and after treatment correlated well with changes in the calculated disease activity index (*16*).

Our initial experience using this isotope on a small number of patients with acute pancreatitis suggested that it may be a useful method of differentiating severe from mild disease (*17*). One major problem with any study of this type is in defining what is mild and severe disease in the presence of a continuous spectrum of clinical manifestations. We have defined clinically severe disease as either the development of a significant complication or a protracted clinical course. McMahon et al. (*6*) suggested that any patient in a hospital more than 14 days has severe disease. We have used this time factor in the present study providing the hospital stay was related to the pancreatitis. Comparing the prognostic factor grading system with indium leukocyte imaging in the present prospective study has shown that both give an accurate assessment regarding the severity of the disease. There was agreement regarding the severity in 36 of the 39 patients studied. Of the three patients with a positive [^{111}In]leukocyte study and mild disease on factor grading, one developed a pseudocyst and, by definition, must be classified as having severe disease. There were two false positive results using the indium technique and one false-negative after prognostic factor grading when compared with the clinical criteria outlined above.

FIGURE 3
Abnormal distribution of [^{111}In]leukocyte activity centrally (within pancreas) and extending inferiorly towards pelvis and into both paracolic areas

TABLE 1
Patients with Suspected Pancreatic Abscesses

Patient	Sex	Age (yr)	Etiology	Site of ^{111}In collection	CT scan	Laparotomy findings	Outcome
1	M	20	Alcohol	Subhepatic, central L. paracolic	Swollen pancreas marked fat necrosis	—	Became diabetic-otherwise well
2	F	32	Gallstones	Central	Necrotic swollen pancreas	Pancreatic abscess	Well
3	F	23	Gallstones	Central R. paracolic L. subphrenic	Swollen pancreas, Marked fat necrosis, Pelvic abscess	Pelvic abscess	Well
4	M	62	Unknown	Central, subhepatic, R. paracolic	—	No abscess found	Well
5	F	42	Gallstones	Central	—	Pancreatic abscess	Died
6	M	54	Alcohol	Central R. paracolic	—	No abscess found	Well

FIGURE 4
Intense accumulation of radioisotope centrally and in right paracolic area in patient with suspected abscess, (Patient 4-Table 1). No abscess was found at laparotomy

The prognostic factor scoring system has been assessed prospectively in 347 patients presenting with 405 episodes of acute pancreatitis during a 7-yr period (*4*). One hundred thirty-one episodes were severe (more than three factors present) and of these, 31% had clinically severe disease defined as death of the patient, surgery during the same admission excluding elective surgery for gallstone associated pancreatitis, and the presence of complications. Of the 274 episodes considered mild, 8% were clinically severe. Prediction of severity in acute pancreatitis is only of value if it alters treatment and influences outcome. However, as the majority of patients with mild disease settle without complication and do not require therapeutic intervention it is important, when studying various treatment modalities, to exclude these cases. A negative leukocyte image excludes with confidence this group of patients.

Pathologically acute pancreatitis can broadly be divided into two groups: the so-called oedematous pancreatitis and the autodigestive tryptic form of the disease (*18*). Oedematous pancreatitis is associated with capillary dilatation together with interstitial and intralobular oedema without inflammatory cell infiltration in the initial stages (*19*). This explains why patients with clinically mild disease do not show evidence of uptake of labeled leukocytes. The main characteristic feature of the autodigestive form of pancreatitis is tryptic necrosis which initially involves the acinar tissue and the ducts but may extend to areas far beyond the anatomical confines of the pancreas (*19*). Again, this explains why, in patients with severe disease, the abnormal uptake of the labeled leukocytes may not be confined to the pancreas itself.

Gallium-67 (^{67}Ga) citrate has been widely used for the detection of inflammatory lesions for a number of years (*20*). However, excretion of this isotope into the gastrointestinal tract makes it difficult to evaluate areas close to the hepatic and splenic flexures and the pelvis. Tanaka et al. (*21*) in a retrospective report, showed that [^{67}Ga]citrate imaging in seven patients with acute pancreatitis all showed increased uptake of the isotope in the pancreas. They concluded that gallium imaging may be useful in confirming the diagnosis of acute pancreatitis. We have been unable to find any other reports of the use of either gallium- or indium-labeled leukocyte imaging in acute pancreatitis. In a comparison of these two radionuclide imaging techniques in the diagnosis of occult sepsis Sfakianakis et al.

(*22*) suggested that both methods were reliable in locating sepsis in patients with infection of short duration (<2 wk). Most patients with acute pancreatitis present within a few days of the onset of their symptoms. If further studies with [^{67}Ga]citrate in this condition confirm its usefulness as a diagnostic method, we believe ^{111}In will be more valued in predicting those patients with severe disease and liable to develop complications. The one limitation on the use of ^{111}In-labeled leukocytes is the presence of accessory splenic tissue which will cause intense uptake outside the normal spleen (*23*). Accessory splenic tissue frequently arises close to the pancreas, and may produce false-positive results. Indium-111 chloride imaging may also be of value in patients with acute pancreatitis, and does not suffer from the limitations of accessory splenic tissue or of excretion into the bowel. In a study of 258 patients with clinically suspected inflammatory processes, Sayle et al. (*24*) showed that the technique had an accuracy of 94%. This technique does not suffer from the disadvantage of requiring the long preparation time that is needed to label white cells. Its use in pancreatitis has, however, not been assessed.

Ultrasound examination has previously been shown to be of little value in the assessment of pancreatitis (*25*), an assessment with which we agree. In the present study, ultrasound examination was considered satisfactory in 31 of the 36 patients studied (86%), but was only considered abnormal in 12. However, ultrasound examination is useful in detecting those patients who have gallstone-associated disease and in the present study was 100% accurate. Ultrasound scanning also detects the formation of pseudocysts and serial examinations accurately chart their subsequent progress.

Although the numbers in the present study are small, we believe that patients with chronic pancreatitis may or may not have a positive image depending on the exact pathologic state of the chronically inflammed organ. We do not believe that this imaging technique is useful in this situation, as the main indication for surgery is the patients' symptomatology. Both patients with pseudocysts had negative indium leukocyte imaging, which we would expect through knowledge of the pathologic process involved.

Although we have only studied six patients with suspected abscesses, we have shown that a positive leukocyte image following pancreatitis does not always imply abscess formation. Two of the five patients undergoing laparotomy did not have abscesses present, merely extensive fat necrosis. We have found it impossible to differentiate by the leukocyte image alone between extensive fat necrosis and abscess formation. In this situation, we believe that CT scanning is useful in differentiating between the two processes.

We have shown that ^{111}In autologous leukocyte imaging is a useful technique to differentiate mild from severe pancreatitis. In the present study, a positive image was always present in those patients who developed significant complications, and a negative study excluded with confidence subsequent sequelae. Further studies using serial indium-labeled leukocytes in those patients with severe disease may produce useful information on the fate of fat necrosis.

FOOTNOTE

* Amersham International, Buckinghamshire, England.

ACKNOWLEDGMENTS

The authors thank all consultant surgeons in the Royal Victoria Hospital for allowing a study of their patients and Mrs. W. Hughes for typing the manuscript.

REFERENCES

1. Imrie CW, Benjamin IS, Ferguson JC, et al: A single-centre double-blind trial of Trasylol in primary acute pancreatitis. *Br J Surg* 65:337-341, 1978
2. MRC multicentre trial: Death from acute pancreatitis. *Lancet* ii:632-635, 1977
3. Seligson U, Ihre T, Lundh G: Prognosis in acute haemorrhagic, necrotizing pancreatitis. *Acta Chir Scand* 148:432-429, 1982
4. Blamey SL, Imrie CW, O'Neill J, et al: Prognostic factors in acute pancreatitis. *Gut* 25:1340-1346, 1984
5. McMahon MJ, Woodhead JS, Hayward RD: The nature of hypocalcaemia in acute pancreatitis. *Br J Surg* 65:216-218, 1978
6. McMahon MJ, Playforth MJ, Pickford IR: A comparative study of methods for the prediction of severity of attacks of acute pancreatitis. *Br J Surg* 67:22-25, 1980
7. Berry AR, Taylor TV, Davies GC: Diagnostic tests and prognostic indicators in acute pancreatitis. *J R Coll Surg Edinb* 27:345-352, 1982
8. Foulis AK, Murray WR, Galloway D, et al: Endotoxaemia and complement activation in acute pancreatitis in man. *Gut* 23:656-661, 1981
9. Spence RAJ, Anderson JR, Alam JM, et al: Gastrointestinal hormones in acute pancreatitis. *J R Coll Surg Edinb* 28:160-163, 1983
10. Sive AA, Vinik AI, Barbezat GO, et al: Plasma pancreatic polypeptide concentrations in acute pancreatitis. *S Afr Med J* 21:1047-1049, 1980
11. Ranson JHC, Rifkind KM, Roses DF, et al: Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet* 139:69-81, 1974
12. Osborne DH, Imrie CW, Carter DC: Biliary surgery in the same admission for gallstone-associated pancreatitis. *Br J Surg* 68:758-761, 1981
13. Carrol B, Silverman PM, Goodwin DA, et al: Ultrasonography and indium-111 white cell scanning for the detection of intra-abdominal abscesses. *Radiology* 140:155-160, 1981
14. Ascher NL, Forstrom L, Simmons RL: Radiolabeled autologous leukocyte scanning in abscess detection. *World J Surg* 4:395-402, 1980
15. Saverymuttu SH, Peters AM, Hodgson HJ, et al: Indium-111 autologous leukocyte scanning: Comparison

with radiology for imaging the colon in inflammatory bowel disease. *Br Med J* 285:255-257, 1982
16. Saverymuttu SH, Lavender JP, Hodgson HJF, et al: Assessment of disease activity in inflammatory bowel disease; a new approach using ^{111}In granulocyte scanning. *Br Med J* 287:1751-1753, 1983
17. Anderson JR, Spence RAJ, Laird JD, et al: Initial experience with indium-111 autologous leukocyte imaging in patients with acute pancreatitis. *Br Med J* 287:637-638, 1983
18. Becker V: Pathological anatomy and pathogenesis of acute pancreatitis. *World J Surg* 5: 303-313, 1981
19. Beck IT: Histopathology of acute pancreatitis. In *The Exocrine Pancreas*, Beck IT, Sinclair DG, eds. London, Churchill-Livingstone, 1971, pp 105-118
20. Hoffer P: Gallium and infection. *J Nucl Med* 21:484-488, 1980
21. Tanaka T, Mishkin FS, Buozas DJ, et al: Pancreatic uptake of gallium-67 citrate in acute pancreatitis. *Appl Radiol* 71:163-164, 1978
22. Sfakianakis GN, Al-Sheikh W, Heal A, et al: Comparisons of scintigraphy with Indium-111 leukocytes and Gallium-67 in the diagnosis of occult sepsis. *J Nucl Med* 23:618-626, 1982
23. Coleman RE, Welch D: Possible pitfalls with clinical imaging of indium-111 leukocytes: Concise communication. *J Nucl Med* 21:122-125, 1980
24. Sayle BA, Balachandran S, Rogers CA: Indium-111 chloride imaging in patients with suspected abscesses: Concise communication. *J Nucl Med* 24:1114-1118, 1983
25. McKay AJ, Imrie CW, O'Neill J, et al: Is an early ultrasound scan of value in acute pancreatitis? *Br J Surg* 69:369-372, 1982