Gallbladder Nonvisualization with Pericholecystic Rim Sign: Morphine-Augmentation Optimizes Diagnosis of Acute Cholecystitis

Elizabeth Oates, Donna-Lee G. Selland, Cynthia T. Chin and Dwight M. Achong
Division of Nuclear Medicine, Department of Radiology, New England Medical Center, and Tufts University School of Medicine, Boston, Massachusetts

This study investigated the value of morphine-augmentation in patients who demonstrated gallbladder nonvisualization with a pericholecystic rim sign at 1 hr, a cholescintigraphic pattern considered highly predictive of acute cholecystitis. **Methods:** Retrospectively, 170 consecutive morphine-augmented cholescintigrams were analyzed for the presence of a pericholecystic rim sign, marked or mild, associated with gallbladder nonvisualization at 1 hr (before morphine); those with a pericholecystic rim sign were further evaluated for persistent gallbladder nonvisualization versus gallbladder visualization after morphine. Scintigraphic interpretations were correlated with surgical pathology or clinical diagnosis. **Results:** Before morphine, 43/170 (25%) patients demonstrated gallbladder nonvisualization with a pericholecystic rim sign. Since only 31 had acute cholecystitis, a diagnosis based solely on that scintigraphic pattern would have resulted in 12 false-positives. After morphine, gallbladder visualization correctly excluded acute cholecystitis in seven; a single false-negative was encountered; five false-positives remained. Morphine-augmentation improved the positive predictive value from 72% (gallbladder nonvisualization with pericholecystic rim sign before morphine) to 86% (gallbladder nonvisualization after morphine). Of 24 patients with marked pericholecystic rim signs, 21 had acute cholecystitis. Of 31 with acute cholecystitis, however, 10 (32%) had a mild pericholecystic rim sign. **Conclusion:** Morphine-augmented cholescintigraphy optimizes the diagnosis of acute cholecystitis in patients with the suggestive, but not pathognomonic, cholescintigraphic pattern at 1 hr of gallbladder nonvisualization with a pericholecystic rim sign, regardless of its intensity.

Key Words: radionuclide imaging; gallbladder; cholecystitis; morphine sulfate

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Compared to conventional cholescintigraphy, morphine-augmentation improves specificity and shortens the imaging time for the diagnosis of acute cholecystitis (*1–4*). Described as a well-defined, sometimes broad, curvilinear or crescentic band of increased hepatic activity adjacent to the gallbladder fossa, a pericholecystic rim sign has been observed in 20%–60% of patients with gallbladder nonvisualization (*5–8*). As reported, the cholescintigraphic pattern of gallbladder nonvisualization with a pericholecystic rim sign at 1 hr predicts acute cholecystitis (positive predictive value >90%) and is strongly associated with advanced or complicated acute cholecystitis (perforation, gangrene, necrosis, abscess, ulceration, hemorrhage, fibrous exudate) (*5–9*).

Is gallbladder nonvisualization with a pericholecystic rim sign at 1 hr an appropriate and sufficient endpoint for diagnosis of acute cholecystitis, as advocated by many authors (*3,5–7,9*), or, should morphine augmentation be pursued regardless, as suggested by others (*10*)? To address this issue, we compared diagnostic success based on the pattern of gallbladder nonvisualization with a pericholecystic rim sign before morphine to gallbladder nonvisualization after morphine in a group of patients undergoing morphine-augmented cholescintigraphy.

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For correspondence contact: Elizabeth Oates, MD, New England Medical Center, 750 Washington St., Boston, MA 02111.

MATERIALS AND METHODS

Two experienced nuclear physicians blinded to the final diagnoses reviewed 170 consecutive morphine-augmented cholescintigrams completed over a 6-yr period (April 1988–June 1994). Each study was displayed on the computer and analyzed for a pericholecystic rim sign before morphine (all had gallbladder nonvisualization at about 1 hr as the reason for morphine augmentation). A pericholecystic rim sign was deemed present when it was noted independently by both observers; in six cases, a consensus was reached after initial disagreement. When present, each pericholecystic rim sign was graded as marked or mild. Marked referred to pericholecystic uptake much more intense than adjacent liver, while mild corresponded to less pronounced but definite pericholecystic uptake that was slightly greater than adjacent liver.

Forty-three patients (28 women, 15 men, age range: 28–88 yr, average = 56 yr) had a pericholecystic rim sign. This group was further evaluated for persistent gallbladder nonvisualization versus gallbladder visualization after morphine.

All patients were fasting for at least 4 hr prior to cholescintigraphy. Nine were pretreated with intravenous sincalide (0.02 mcg/kg/3 min) (Kinevac, Squibb, Princeton, NJ) because of prolonged fasting (>48 hr) or hyperalimentation.

Following intravenous injection of 4.0 mCi (148 MBq) of ^{99m}Tc-mebrofenin, dynamic images were acquired for 30 min on a large field of view gamma camera equipped with a low-energy, all-purpose collimator and peaked at 140 keV with a symmetric 20% window. Serial sets of static 5-min views in the anterior, left anterior oblique and right lateral projections followed at 30, 45 and 60 min.

At approximately 1 hr (actual range: 40–150 min), intravenous morphine sulfate (0.04 mg/kg) was administered if gallbladder nonvisualization and small bowel activity were observed. Sets of 5-min static images were repeated at 20 and 40 min after morphine administration. Nine patients whose gallbladders failed to visualize promptly after morphine underwent delayed imaging between 2 and 24 hr (average = 7 hr). Five patients with minimal residual hepatic activity received a booster dose of ^{99m}Tc-mebrofenin (2 mCi, 74 MBq) 10–15 min before morphine augmentation (*4*).

Persistent gallbladder nonvisualization after morphine confirmed acute cholecystitis while gallbladder visualization indicated chronic cholecystitis. Cholescintigraphic diagnoses were correlated with surgical pathology in 33 patients (77%), 27 of whom were operated on within 1–3 days; in 6, surgery followed 7–43 days later. In 10 nonsurgical patients, correlation was made with clinical course and included ultrasonography in six.

Real-time ultrasonographic criteria for cholecystitis included:

TABLE 1
Clinicopathologic Profile

	Acute cholecystitis (n = 31)	Chronic cholecystitis (n = 11)
Surgical (n = 33*)	25	7
Complicated (n = 11)	11	0
Acalculous (n = 5)	3	2
Nonsurgical (n = 10)	6	4

*Table excludes 1 surgically absent gallbladder.

cholelithiasis, sludge, gallbladder wall thickening, pericholecystic fluid and direct tenderness.

Histopathologic criteria for acute cholecystitis were polymorphonuclear cellular infiltration and mural edema. Advanced (complicated) acute cholecystitis was defined as perforation, gangrene, necrosis, abscess, ulceration, hemorrhage or fibrin deposition. Chronic cholecystitis showed a predominant lymphocytic infiltration, fibrosis, glandular changes and, usually, gallstones.

RESULTS

Before morphine administration, gallbladder nonvisualization with a pericholecystic rim sign was observed in 43/170 (25%) patients. Acute cholecystitis was diagnosed in 31 (72%) and chronic cholecystitis in 11; one patient had a surgically absent gallbladder on reoperation for suspected acute cholecystitis (Table 1). Gallstones were present in all but five. Almost one-half (11/25) had complicated acute cholecystitis at surgery.

Gallbladder nonvisualization with a pericholecystic rim sign at 1 hr correctly predicted acute cholecystitis in 31/43 (72%), 30 of whom showed persistent gallbladder nonvisualization after morphine (Table 2) (Figs. 1, 2). Gallbladder visualization after morphine correctly identified seven patients without acute cholecystitis (Figs. 3, 4). There were five false-positives (Fig. 5) and a single false-negative after morphine (Table 2).

Pericholecystic rim signs were graded as marked in 24 (56%) and mild in 18 (Table 3). A marked pericholecystic rim sign correlated with acute cholecystitis in 21/24 (6 complicated); a mild pericholecystic rim sign correlated with acute cholecystitis in 10/18 (5 complicated). Of 31 patients with acute cholecystitis, 32% demonstrated mild pericholecystic rim signs.

TABLE 2
Correlation of Scintigraphic Patterns before and after Morphine with Diagnosis of Acute Cholecystitis

	TP	FP	PPV	TN	FN	NPV
Premorphine						
Pericholecystic rim sign	31	12	72%	–	–	–
Postmorphine						
Gallbladder nonvisualization	30*	5†	86%	–	–	–
Gallbladder visualization	–	–	–	7‡	1	88%

*Five sincalide pretreatment; five mebrotenin booster doses; seven delayed imaging.

†Three sincalide pretreatment; two delayed imaging.

‡One sincalide pretreatment.

TP = true-positive; FP = false-positive; PPV = positive predictive value; TN = true-negative; FN = false-negative; NPV = negative predictive value.

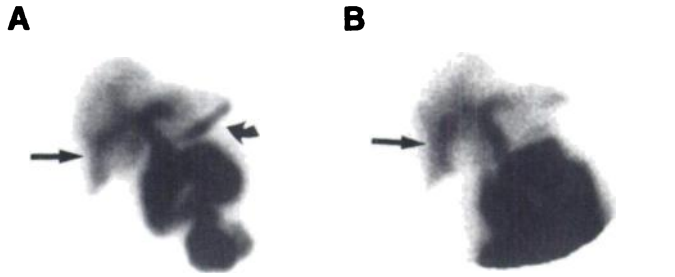

FIGURE 1. True-positive acute calculous cholecystitis. Marked pericholecystic rim sign (arrow) at 1 hr (A) with persistent gallbladder nonvisualization at 40 min after morphine administration (B). Spontaneous enterogastric reflux (curved arrow).

DISCUSSION

On conventional cholescintigraphy with delayed imaging, gallbladder nonvisualization suggests cystic duct obstruction due to acute cholecystitis. False-positives due to chronic cholecystitis and other conditions, such as prolonged or inadequate fasting, hyperalimentation and acute pancreatitis, may confound that diagnosis. Morphine augmentation is clearly superior to delayed imaging up to 24 hr (*11*). Patients, however, with severe intercurrent illness and hepatocellular dysfunction have a high incidence (60%) of false-positive morphine-augmented cholescintigraphy (*12*). In this study, an unequivocal pericholecystic rim sign was observed in a patient without a gallbladder.

Gallbladder nonvisualization with a pericholecystic rim sign at 1 hr has been considered virtually diagnostic of acute cholecystitis (*5–9*). This cholescintigraphic pattern is not pathognomonic and may be encountered in chronic cholecystitis (*7*). A pericholecystic rim sign has also been described with delayed gallbladder visualization in chronic cholecystitis (*10*) and with gallbladder visualization in acute cholecystitis (*13,14*).

Although pericholecystic rim signs are subjective, two experienced observers agreed on the presence and grading of

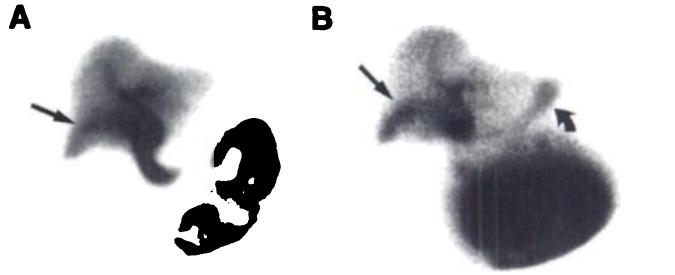

FIGURE 2. True-positive complicated acute cholecystitis. Marked pericholecystic rim sign (arrow) at 30 min (A) and gallbladder nonvisualization at 40 min after morphine administration (B). Enterogastric reflux after morphine (curved arrow).

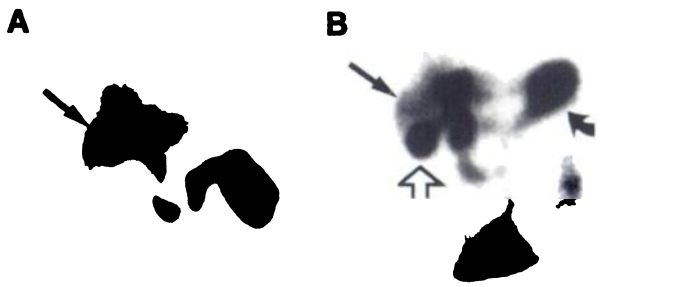

FIGURE 3. True-negative chronic calculous cholecystitis. Marked, broad pericholecystic rim sign (arrow) at 30 min (A) with gallbladder visualization (open arrow) at 20 min after morphine. Enterogastric reflux after morphine administration (curved arrow).

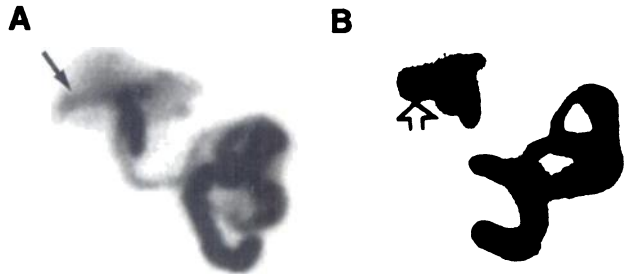

FIGURE 4. True-negative chronic calculous cholecystitis. At 1 hr (A), gallbladder nonvisualization with mild pericholecystic rim sign (arrow); at 20 min after morphine (B), gallbladder visualization (open arrow) excluding acute cholecystitis.

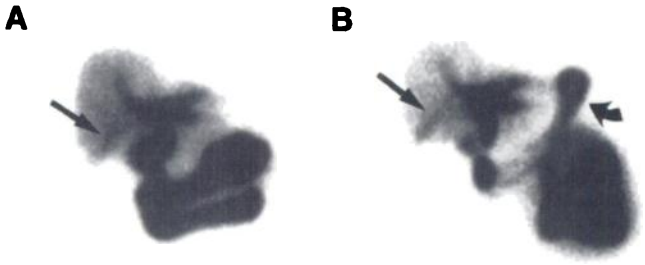

FIGURE 5. False-positive chronic calculous cholecystitis. Mild pericholecystic rim sign (arrow) at 1 hr (A) with gallbladder nonvisualization at 40 min after morphine (B). Enterogastric reflux after morphine (curved arrow).

pericholecystic rim signs in almost all patients. In this morphine-augmented population, 25% demonstrated a pericholecystic rim sign. Obvious (marked) pericholecystic rim signs may predict more severe (complicated) gallbladder disease (*8*). Similarly, in this study, marked pericholecystic rim signs more often signaled acute cholecystitis (positive predictive value = 88%) than did mild pericholecystic rim signs (positive predictive value = 56%) (Table 3). One-third (10/31) of patients with acute cholecystitis demonstrated mild pericholecystic rim signs. Unexpectedly, only 32% of marked pericholecystic rim signs were associated with complicated acute cholecystitis in contradistinction to 83% of mild pericholecystic rim signs.

In this study, terminating cholescintigraphy at 1 hr based solely on gallbladder nonvisualization with a pericholecystic rim sign—without morphine augmentation—would have resulted in 12 (28%) misinterpretations (Table 2). Morphine augmentation sharply reduced the number of false-positives from 12 to 5 and improved the positive predictive value for acute cholecystitis from 72% to 86% without adding significantly to time or effort.

For five patients with false-positive results (gallbladder nonvisualization after morphine), chronic calculous cholecystitis was diagnosed surgically 3–10 days later in four; each had a mild pericholecystic rim sign. Concomitant patient conditions, such as liver disease, intercurrent illness, or hyperalimentation did not contribute to these false-positive studies. There was a surgically absent gallbladder in one patient with a marked pericholecystic rim sign.

Of seven patients with true-negative results (gallbladder visualization after morphine) for chronic cholecystitis, five were calculous and two acalculous. In three of these patients, surgery was performed 1 day, 7 days and 43 days later. Interestingly, three had conditions (one hepatocellular dysfunction, two serious intercurrent illness) that could have led to false-positive studies. Except for one patient with chronic calculous cholecystitis, all had mild pericholecystic rim signs.

TABLE 3
Correlation of Pericholecystic Rim Sign Grade with Final Diagnosis

Grade	Acute cholecystitis	Chronic cholecystitis
Marked (n = 24)	21*	3
Mild (n = 18)	10†	8

*6/19 (32%) complicated at surgery.
†5/6 (83%) complicated at surgery.

The single false-negative was encountered in a patient with acute calculous cholecystitis in whom surgery occurred 25 days later (such that morphine-augmented scintigraphy may have been true-negative when performed). False-negative morphine-augmented cholescintigraphy is a recognized but unusual phenomenon; morphine may raise biliary pressure sufficiently to overcome an incomplete cystic duct occlusion (*15–18*).

CONCLUSION

Morphine-augmentation should be considered in any patient with the cholescintigraphic pattern of gallbladder nonvisualization with a pericholecystic rim sign. Safe and readily accomplished, this pharmacologic maneuver optimizes the diagnosis of acute cholecystitis and is of particular value in those with a mild pericholecystic rim sign.

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