
Reflux Sign in Cholescintigraphy After Administration of a Gallbladder Contracting Agent

Hisao Itoh, Kenya Murase, and Ken Hamamoto

Department of Radiology, Matsunami General Hospital, Gifu and Department of Radiology, Ehime University School of Medicine, Ehime, Japan

This study reviewed 12 patients with the reflux sign in cholescintigraphy to assess its diagnostic usefulness in evaluating biliary passage. The reflux sign was determined by appearance or increase of the radioactivity in peripheral intrahepatic bile ducts after intramuscular injection of 10 μ g of ceruletide diethylamine (caerulein). Of the 12 patients, there were common bile duct (CBD) stone in four, chronic pancreatitis in two, biliary dyskinesia in two, papillary adenoma of the CBD, dilated CBD, papillitis, and juxtapapillary duodenal diverticulum in one each. Cholangiographically, dilated caliber of the CBD more than or equal to 12 mm was found in five and equivocal caliber of 8 to 11 mm was in the remaining seven. Apparent stenosis of the CBD was found in four with dilated CBD. There were two patients who had CBD stone with equivocal caliber of the CBD. The reflux sign seems to be a sensitive finding indicating the presence of biliary dysfunction, and would be helpful for the detection of incomplete obstruction of the CBD or CBD stone, especially in a patient with equivocal caliber of the CBD.

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Cholescintigraphy has been applied to jaundiced patients suspected of having incomplete obstruction of the common bile duct (CBD). Prolonged transit time, i.e., appearance of tracer to the duodenum later than 60 min, has been used as a index for cholestasis (1). However, prolonged transit time was not specific for incomplete obstruction of the CBD and ~20% of normal subjects showed prolonged transit time (2,3). The reflux of radioactive bile toward the hepatic ducts after administration of a gallbladder contracting agent has been reported to be a useful index suggesting incomplete obstruction of the CBD in chronic pancreatitis (CP) (4). We undertook a retrospective study of routine cholescintigrams demonstrating the reflux to assess its diagnostic value in the detection of incomplete obstruction of the CBD.

MATERIALS AND METHODS

A retrospective review of 239 consecutive studies of cholescintigraphy using technetium-99m (^{99m}Tc) n-pyridoxyl-5-

methyltryptophan (PMT) or ^{99m}Tc N-(p-butylphenylcarbamoylmethyl)iminodiacetic acid (BIDA) performed from 1983 till 1986 in Ehime University Hospital revealed 12 patients (5%) who were judged as positive reflux sign. Clinical records and direct and/or indirect x-ray cholangiograms were available in each patient (seven females and five males), ranging 35 to 77 yr in age; CBD stone in four, CP in two, biliary dyskinesia (BD) in two, papillary adenoma of the CBD, duodenal papillitis, dilated CBD, and juxtapapillary duodenal diverticulum (JDD) in one each (Table 1). The diagnosis was established by clinical symptoms, laboratory tests, upper gastrointestinal series, x-ray cholangiography including drip infusion cholangiography (DIC), percutaneous transhepatic cholangiography (PTC), and endoscopic retrograde cholangiography (ERC), operation, or histologic examination.

After at least 4-hr fasting, a patient lay under a large field-of-view gamma camera fitted with low-energy, all purpose collimator and 5 mCi of ^{99m}Tc PMT or BIDA was injected intravenously. Serial images were obtained at 5, 10, 20, 30, 45, and 60 min with a preset acquisition time. Then, 10 μ g of ceruletide diethylamine (caerulein) as a gallbladder contracting agent was injected intramuscularly and additional images were obtained at 1, 5, 10, 15, 20, and 30 min with the same acquisition time.

The reflux sign was determined by reading a series of scintigrams obtained before and after caerulein injection. When the radioactivity in the intrahepatic bile ducts (IHBD)

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For reprints contact: Hisao Itoh, MD, Dept. of Radiology, Matsunami General Hospital, 185-1 Dendai, Kasamatsu-cho, Hashima-gun, Gifu 501-06, Japan.

TABLE 1
Biochemical, Cholangiographic, and Scintigraphic Characteristics of the Patients with Reflux*

Patient no.	Age/sex	Diagnosis	Chemistry		X-ray cholangiography				Scintigraphy		
			T. Bili (mg/dl)	AP (IU/l)	Method	Caliber* (mm)	Stenosis†	EF (%)	ICCHD	DAT (min)	Pooling
1	73/F	BD, JDD	0.4	157	DIC	8	no	0	yes	60<	-
2	35/F	BD	1.0	88	DIC	9	no	86.5	no	60<	-
3	77/F	JDD	0.8	123	DIC	9	no	46.4	yes	20	-
4	60/F	CBDS, CC	0.7	104	DIC, ERC	10	no	69.6	yes	60<	+
5	63/F	DP	0.9	98	DIC, ERC	10	no	72.6	yes	60<	-
6	64/F	CP	0.6	244	DIC	11	no	30.9	yes	60<	-
7	54/M	CBDS, JDD	0.6	134	DIC, ERC	11	no	35.3	yes	60<	+
8	45/M	CBDD, CC	1.0	129	DIC, PTC	12	no	2.5	no	60	-
9	58/F	CBDS, JDD	0.3	110	DIC, ERC	14	yes	10.2	yes	60<	+
10	60/M	CBDA, JDD	1.0	111	DIC, ERC, PTC	14	yes	ND	ND	60<	+
11	50/M	CP	1.3	112	DIC, ERC	15	yes	81.0	no	60<	+
12	56/M	CBDS, JDD	1.6	823	PTC	16	yes	ND	ND	30	+

T. Bili = Serum total bilirubin; AP = Alkaline phosphatase; EF = Ejection fraction of the gallbladder; ICCHD = Increase in caliber of the common hepatic duct; DAT = Duodenum appearance time; BD = Biliary dyskinesia; JDD = Juxtapapillary duodenal diverticulum; CBDS = Common bile duct stone; DP = Duodenal papillitis; CC = Chronic cholecystitis; CBDD = Dilated CBD; CP = Chronic pancreatitis; CBDA = Adenoma of the CBD; DIC = Drip infusion cholangiography; ERC = Endoscopic retrograde cholangiography; PTC = Percutaneous transhepatic cholangiography; and ND = Not done.

* Caliber of the CBD.
 † Stenosis of the CBD.

more peripheral than the right and left hepatic duct appeared or increased obviously on one or more scintigrams after caerulein injection, the patient was judged as having a positive reflux sign. When the increase was limited in the right and/or left hepatic ducts or the intensity of peripheral IHBD did not change, the patient was judged as negative.

The ejection fraction (EF) of the gallbladder was calculated by measurement of the areas of the gallbladder on cholecystograms obtained by DIC before (60 min image) and after caerulein injection (15 min image after injection) using the following formula:

$$EF (\%) = \frac{\text{Area of GB (before)} - \text{Area of GB (after)}}{\text{Area of GB (before)}} \times 100,$$

where GB is the gallbladder. The period between DIC and cholescintigraphy was in 3 wk in each patient.

The increase in caliber of the common hepatic duct (ICCHD) was determined by measurement of the caliber of the CHD on cholangiograms obtained by DIC before and after caerulein injection. When the caliber increased by 2 mm or more, the patient was judged as a positive ICCHD.

RESULTS

The level of serum total bilirubin (T. Bili) ranged from 0.3 to 1.6 mg/dl (0.3–1.1 mg/dl in normal) and two out of 12 patients showed hyperbilirubinemia. The level of alkaline phosphatase (AP) ranged from 88 to 823 IU/l (57–144 IU/l in normal adult) and it was high in three patients.

With measurement on indirect cholangiograms obtained by DIC, the CBD ranged from 8 mm to 16 mm in caliber (mean: 11.6 mm). Dilatation of the CBD equal to 12 mm or more was found in five and equivocal caliber of the CBD from 8 to 11 mm was in the remaining seven patients. Apparent stenosis of the CBD

was revealed in four patients by direct cholangiography such as ERC or PTC.

With respect to other scintigraphic findings, prolonged transit time with duodenum appearance time (DAT) over 60 min was found in nine patients and persistent pooling of radioactive bile in the CBD during before and after caerulein injection in six patients.

Four patients were diagnosed as CBD stone by direct cholangiography. In these patients, apparent stenosis of the CBD with dilated caliber was found in two patients (Fig. 1) and no stenosis with equivocal caliber was in two patients (Fig. 2). Of the two patients with CP, one with moderate change CP had equivocal caliber of the CBD (Fig. 3). The other with advanced change CP revealed stenosis at the intrapancreatic portion of the CBD by ERC. The calibers of the CBD in two patients with BD were equivocal and the findings of DIC in each suggested hypertonic sphincter of Oddi and hyperkinetic gallbladder, respectively. In one patient diagnosed as papillary adenoma of the CBD by operation, direct cholangiogram revealed dilated caliber of the CBD and irregular stenosis at the distal end of the CBD (Fig. 4). One patient with papillitis was diagnosed by duodenoscopy at ERC. Dilated CBD accompanied by chronic cholecystitis was found in one patient, however, PTC failed to depict its etiology. One patient with JDD which was located at the oral side of the papilla and 2 cm large showed the ICCHD, despite normal EF.

DISCUSSION

Accurate diagnosis of incomplete obstruction of the CBD, especially in early stages, remains formidable without direct x-ray cholangiography such as ERC or

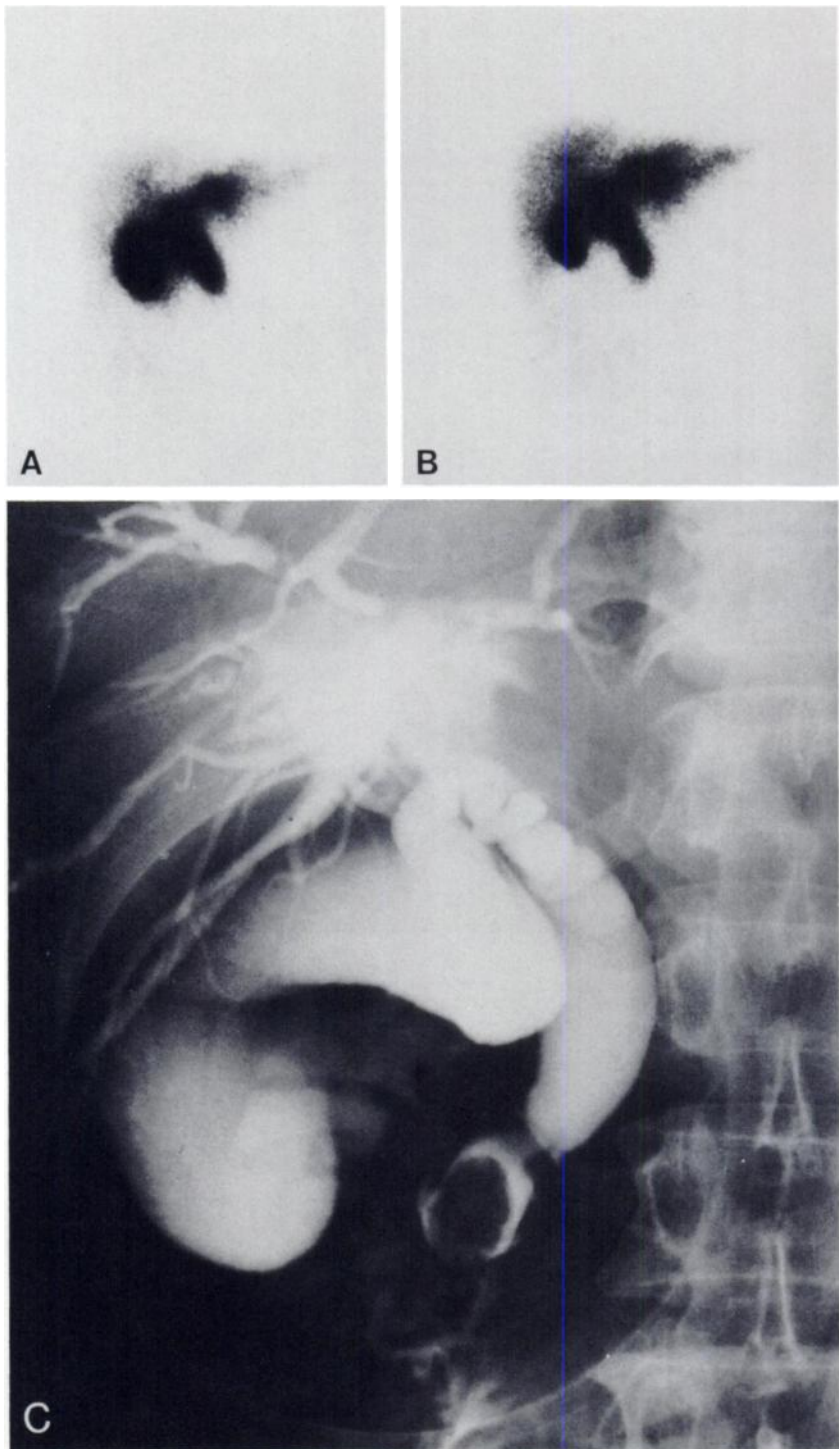


FIGURE 1
 Cholescintigrams at 60 min (A) and at 10 min after caerulein injection (B), and direct cholangiogram (C) by percutaneous transhepatic cholangiography (PTC) in a patient with common bile duct (CBD) stone (Patient 12). The radioactivity of the intrahepatic bile ducts (IHBD) increases; positive reflux sign, and persistent pooling of bile is found. PTC reveals a filling defect due to a stone and stenosis at the distal end of the CBD.

PTC. Although ultrasonography (US) is noninvasive and useful in detecting dilated or stenotic changes of the biliary system, it can hardly describe the distal end of the CBD because of the artifact from intestinal air. Furthermore, it must be realized that dilatation and obstruction do not necessarily represent the same entity and the absence of sonographically detectable dilatation does not exclude obstruction (5). Nuclear imaging using [^{99m}Tc]iminodiacetic acid derivatives have been applied

to jaundiced patients. It has been reported that detection and location of biliary obstruction scintigraphically should be based primarily on image pattern such as filling defects and segmental narrowing of the CBD, and bile pooling in the area and segmental ducts rather than appearance time of radionuclides (6). As an additional scintigraphic finding, we have reported previously that the reflux of bile to the hepatic ducts was helpful in detecting CBD stenosis (4).

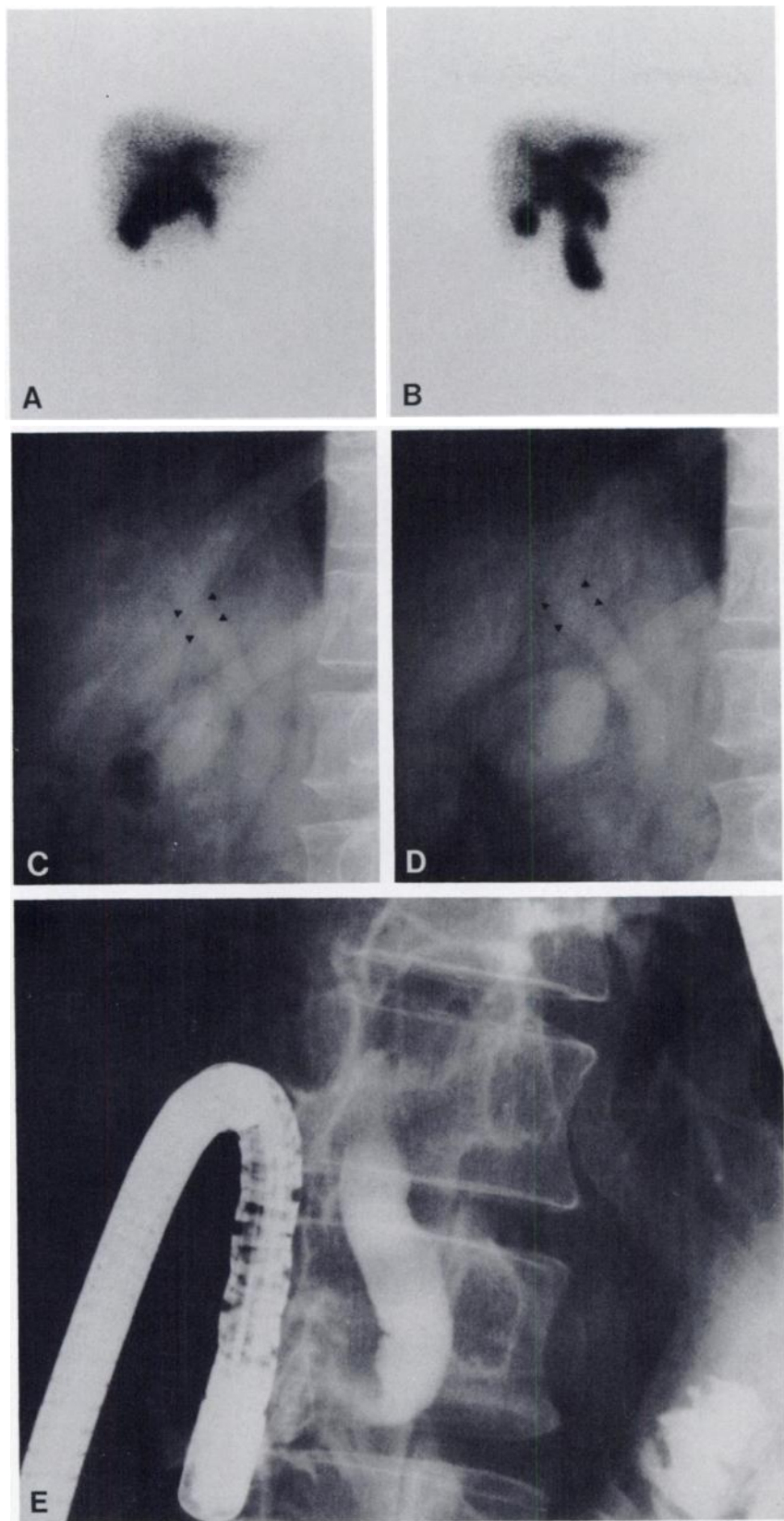


FIGURE 2
 Cholangiograms at 60 min (A) and at 10 min after caerulein injection (B), indirect cholangiograms by drip infusion cholangiography (DIC) at 60 min (C) and at 15 min after caerulein injection (D), and direct cholangiogram (E) by endoscopic retrograde cholangiography (ERC) in a patient with CBD stone (Patient 7). The radioactivity of the IHBD increases. Excretion of bile to the duodenum appears after caerulein injection. DIC demonstrates the increase in caliber of the common hepatic duct (ICCHD). The CHD changes in caliber from 9 mm to 11 mm (arrow head). ERC reveals CBD stone without stenosis.

The presence of the reflux sign in this study was based on the change of the radioactivity in peripheral IHBD. By reading a series of routine scintigrams, it seemed difficult to separate CHD image from the gall-

bladder image clearly and comparison of the radioactivities in the hepatic ducts at the hepatic portal would be unreliable. In peripheral IHBD, especially at the left lobe of the liver, the judgment of the reflux sign was

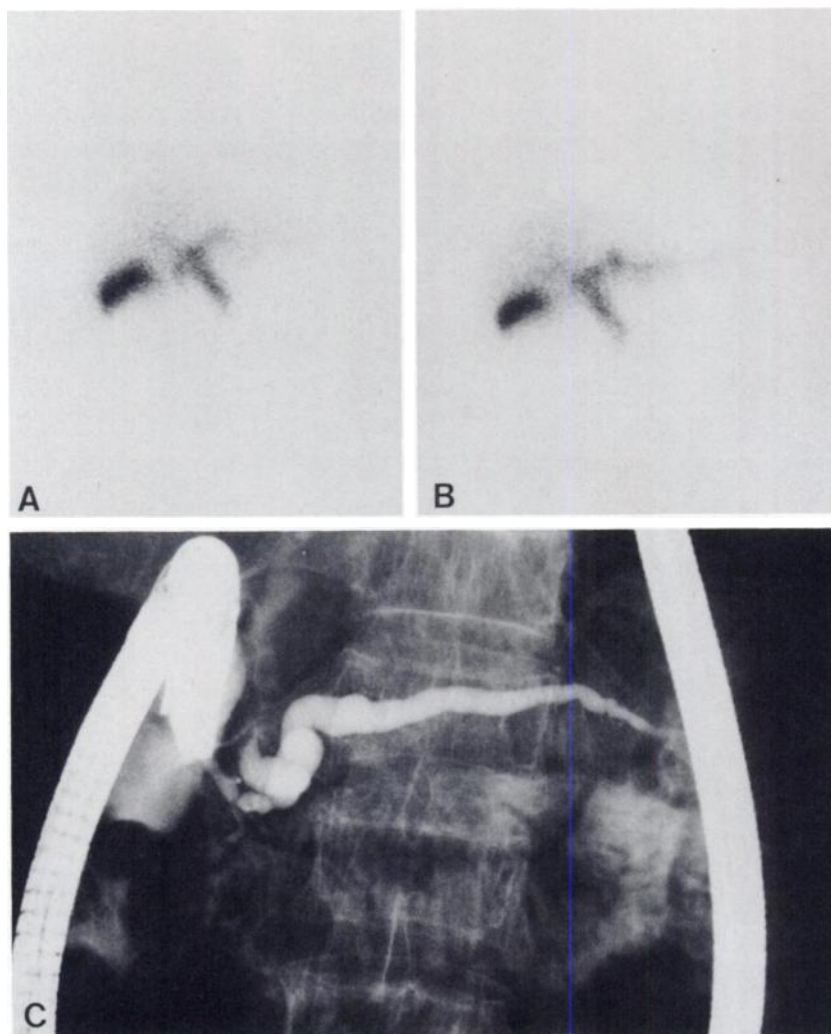


FIGURE 3
 Cholescintigrams at 60 min (A) and at 5 min after caerulein injection (B), and pancreatogram (C) by endoscopic retrograde pancreatography (ERP) in a patient with chronic pancreatitis (CP) (Patient 6). The radioactivity of the IHBD increases. The main pancreatic duct is smoothly dilated to 8 mm in caliber. The patient is diagnosed as moderate change CP.

quite simple because of the distance from the gallbladder and the lowered background.

The reflux sign is not frequent; only about 5 percent of reviewed patients show this finding. According to cholangiographic findings, these patients are able to be divided into two groups; one is patients who have equivocal caliber of the CBD without stenosis, and the other having dilated caliber with apparent stenosis. In the former group including BD, JDD, CP, CBD stone, and papillitis, although morphological changes of the CBD is trivial, the presence of biliary dysfunction to some degree would be expected in each patient. CP may produce periductal fibrosis at the intrapancreatic portion of the CBD and is usually associated with a stenotic change of the CBD in a severe case (7). CBD stone itself would become a cause of passage disturbance of bile without CBD stenosis. In case of JDD, compression of the CBD by a diverticulum close to the papilla or insufficient papillary sphincter with or without bacterial infection would be a cause of biliary dysfunction (8). In the latter group which includes CBD stone, adenoma of the CBD, and CP, apparent stenosis

at the distal end of the CBD is proved by direct x-ray cholangiography and the presence of passage disturbance of bile is undoubted. Scintigraphically, pooling of bile above a stenosis was obvious in each patient.

The finding of ICCHD in DIC has a close relationship to reflux in cholescintigraphy. The flooding of bile from contracting gallbladder to the CBD may cause elevation of endopressure under certain circumstances of impaired drainage of bile, producing both the reflux of bile toward the hepatic ducts and the increase in caliber of the bile duct with some elasticity simultaneously. The same finding of the ICCHD has been studied using US with a fatty meal ingestion (9,10). It has been reported that the response of the normal extrahepatic duct to ingestion of a fatty meal is to remain the same or decrease in size. If the common duct is of normal caliber or slightly dilated before administration of a fatty meal and increases in caliber after fat ingestion, this is a strong indicator of bile duct pathology and further procedures are warranted. To observe the response of bile duct caliber, US is preferable to DIC, US is noninvasive and is able to observe it continuously,

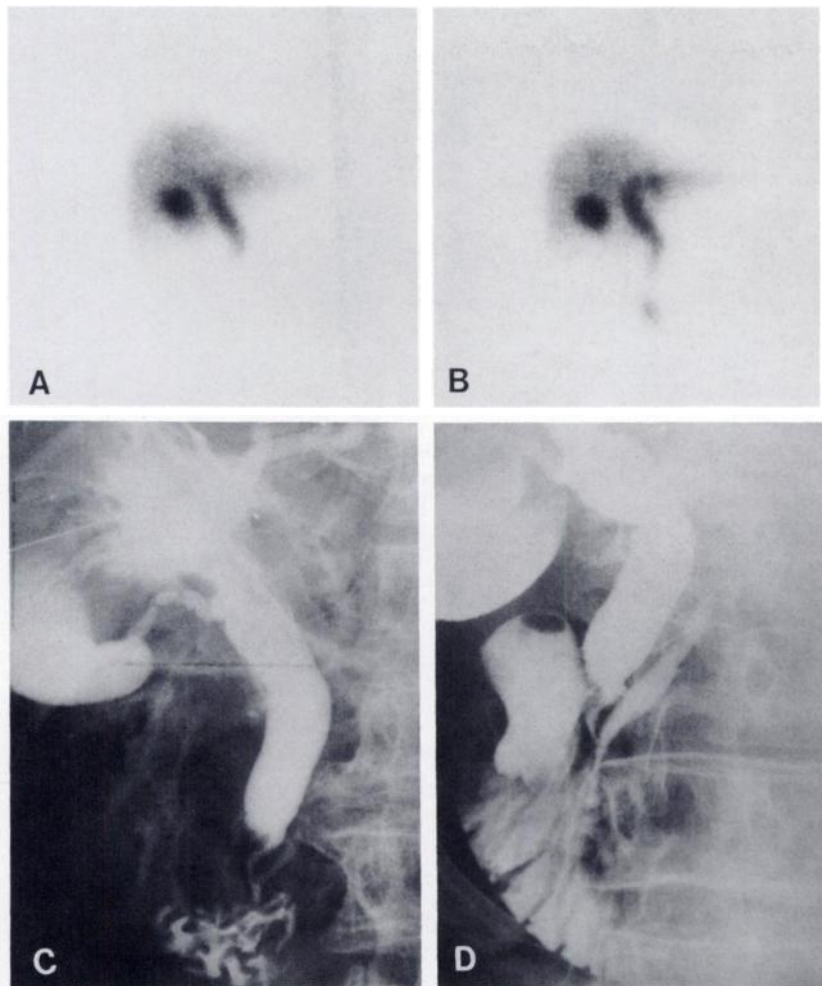


FIGURE 4
 Cholescintigrams at 60 min (A) and at 5 min after caerulein injection (B), and direct cholangiograms by PTC (C) and ERC (D) in a patient with papillary adenoma of the CBD (Patient 10). The radioactivity of the IHBD increases. Irregular segmental stenosis at the distal end of the CBD is revealed by PTC or ERC.

whereas DIC has high rate of serious adverse reactions to the contrast material and exposure is limited one time or two after gallbladder contraction. Therefore, these studies should be performed by US.

To summarize the application of the reflux sign in cholescintigraphy, it suggests the presence of biliary dysfunction caused by various diseases and would become a useful scintigraphic sign in detecting incomplete obstruction of the CBD or CBD stone, especially in a patient with equivocal caliber of the CBD. However, in a patient with markedly dilated CBD, the reflux sign seems to be complementary to the other scintigraphic findings such as pooling of bile or filling defect.

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