

## Cytopathologic Diagnosis of Bile Obtained by Percutaneous Biliary Drainage

In Ae park, M. D., and Eui Keun Ham, M. D.

Department of Pathology, College of Medicine, Seoul National University

### = Abstracts =

From the one hundred forty eight patients with evidence of biliary tract obstruction, 275 bile samples were obtained from percutaneously placed biliary drainage catheters. Of the 148 patients, ova of *Clonorchis sinensis* were demonstrated in 17 patients (11.5%), with the epithelial cells. Among them, one case also demonstrated coexisting adenocarcinoma.

In 105 patients, the medical records were available for review and the clinical diagnoses were malignancy in 99 patients and benign lesion in 6 patients.

Of the 99 patients in which clinico-radiologic diagnosis were malignant, cytologic results were positive in 23.2%.

Dividing the patients into two groups, the ones with tumor of bile duct origin (group I) and the others with tumors producing extrinsic compression of bile duct, such as periampullary carcinoma, pancreas head carcinoma or metastatic carcinoma in lymph nodes from tumors of adjacent organs (group II), the cytologic results were positive in 37% and 11.6%, respectively.

In patients with histologic confirmation, the positive correlation was found in 50% and 20% in group I and group II, respectively, with remarkable difference between two groups. There were no false positives in cytologic diagnosis.

The overall concordance rate of cytologic diagnosis with diagnosis of clinical investigation in both benign and malignant lesions was 27.6% and the diagnostic specificity was 100%.

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**Key words:** Bile cytology, Percutaneous biliary drainage, Clonorchiasis, Diagnostic accuracy.

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\* This study is supported in part by a SNU Hospital research fund (EK Ham, 1987).

\* This paper was presented in 1988 at the 38th autumn meeting of Korean Society of Pathologist.

## Introduction

Carcinomas of the pancreatico-biliary tract and ampulla of Vater region are rare and early diagnosis of these tumors is difficult as there are no well defined localizing symptoms. When symptoms appear with these neoplasms, they are usually related to ductal obstruction, namely, obstructive jaundice.

Most of these tumors are found after neighboring structures are involved and already inoperable at the time of presentation, and even surgical exploration to obtain tissue for pathologic diagnosis is technically complex.

In these circumstances, cytologic diagnosis can spare patients who are not operative candidates an unnecessary operation.

A cytologic specimen for this purpose can be obtained from the duodenal intubation with aspiration<sup>1-3</sup>), and can be aspirated directly from the biliary tree during endoscopic retrograde cholangiopancreatography (ERCP)<sup>4-5</sup>) or percutaneous transhepatic cholangiography (PTC)<sup>6</sup>), or from T-tubes<sup>5,7-8</sup>) or biliary drainage catheters<sup>5,8-9</sup>).

Percutaneous biliary drainage is an effective alternative to biliary bypass surgery in patients with obstructive jaundice which can have numerous causes, and this procedure is indicated in various conditions<sup>10</sup>). This procedure also enables repeated cytologic examination with bile aspirated from percutaneously placed draining catheter.

This study was undertaken to evaluate the diagnostic results of bile obtained from percutaneous biliary drainage catheters or bile obtained at the time of PTC.

## Material and Method

Two hundred seventy five bile samples collected

between January 1984 and September 1986 from 148 patients with evidence of biliary tract obstruction were examined cytologically.

Most of the specimens were obtained through percutaneous biliary drain, but two specimens were obtained during PTC.

In patients with indwelling biliary drainage catheters, the cytologic examination was repeated two to ten times (Table 1).

**Table 1.** Frequency of examination in bile cytology.

1	81
2	35
3	20
4	5
5	3
6	1
7	2
8	0
9	0
10	1
Total	148

Each bile sample was centrifuged for 5 minutes at 2,000 rpm. The bile sediment was used to make four smears and the smears were immediately fixed in 95 % ethanol and were stained by Papanicolaou technique.

Those specimens were classified as inadequate, those devoid of epithelial cells, benign adenomatous hyperplasia, atypia or positive for malignancy, together with subclassification of cell type.

The specimens containing only inflammatory cells devoid of epithelial cells were also included to be inadequate specimen for cytologic interpretation.

In cases with repeated cytologic examination, the most significant diagnosis was considered as the final cytologic diagnosis.

## Results

The cytologic presentation of all carcinoma of pancreatico-biliary area were very similar and the following criteria were used for cytologic diagnosis. Benign bile duct epithelial cells are cuboidal to columnar and are found in small clusters or sheets with honey-comb or pavement-like arrangement. The individual cells are rather small in size (Fig. 1).

Cytologic diagnosis of adenomatous hyperplasia was made in cases with rather large crowded clusters with a pseudopapillary arrangement (Fig. 2).

The clusters are found in quite large numbers, and show a honey-comb pattern with cohesiveness. In cases of atypical hyperplasia, the epithelial clusters are less cohesive and shows greater variation in size and shape with mild nuclear atypia (Fig. 3).

The adenocarcinoma cells are more likely found

in small clusters than large clusters or sheets of adenomatous or atypical hyperplasia. These cells are arranged in looser clusters than the tight clusters of benign or adenomatous hyperplasia. The cells show greater variation in size and shape with loss of polarity. The nuclei show prominent nucleoli and irregular crumping of chromatin (Fig. 4). These cells are similar to adenocarcinoma cells in other body fluids.

The ova of *Clonorchis sinensis* are oval in shape with golden-yellow distinct bilaminar wall and prominent shoulders (Fig. 5 & Fig. 6).

The cytologic diagnoses in 148 patients are summarized in Table 2. Squamous cell carcinoma was demonstrated in sample from patients with common bile duct carcinoma. Small cell carcinoma was demonstrated in sample from patients with lung carcinoma. Among 148 patients, clinical records were available in 105 patients, and clinical diagnoses are

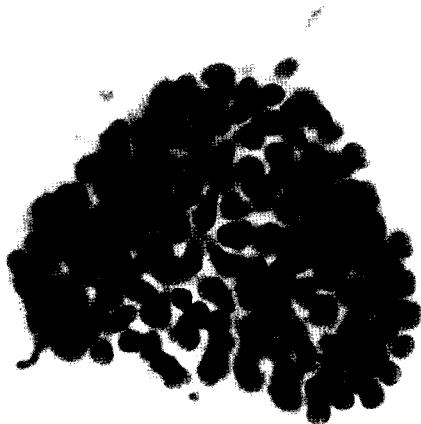
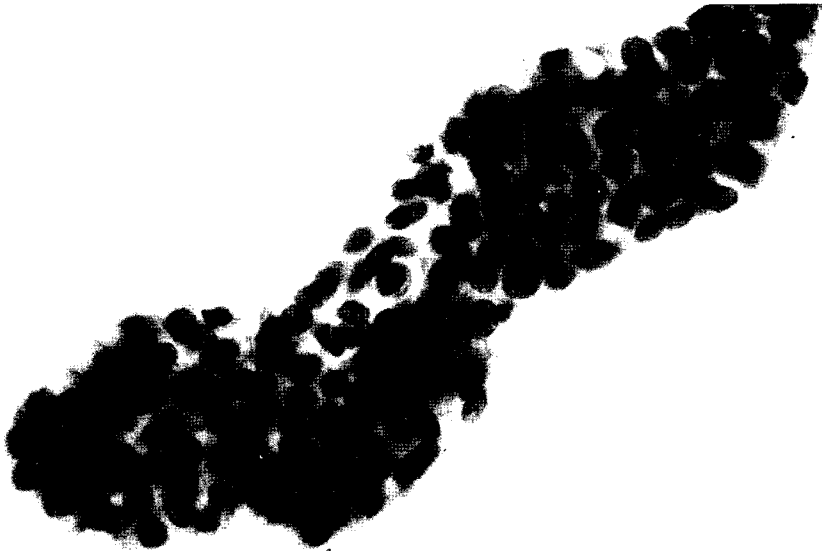


Fig. 1. Benign bile duct epithelial cells in small tight cluster (Papanicolaou,  $\times 400$ ).



**Fig. 2.** Large crowded epithelial clusters with pseudopapillary arrangement in adenomatous hyperplasia (Papanicolaou,  $\times 400$ ).



**Fig. 3.** Epithelial clusters in atypical hyperplasia show greater variation in size and shape of cells with mild nuclear atypism (Papanicolaou,  $\times 400$ ).



Fig. 4. Adenocarcinoma cells are found in smaller cluster with less cohesiveness (Papanicolaou,  $\times 400$ ).



Fig. 5. *Clonorchis sinensis* ova and epithelial cluster of adenomatous hyperplasia (Papanicolaou,  $\times 100$ ).

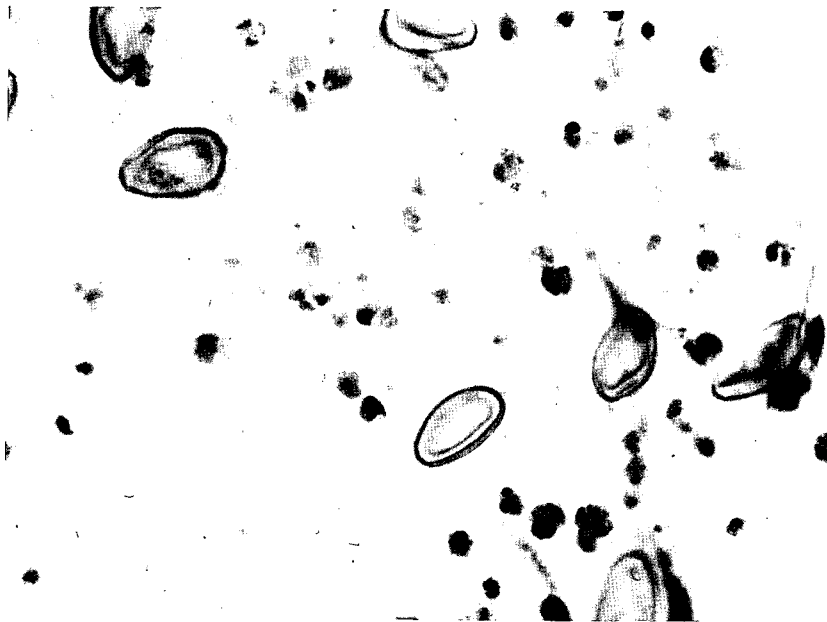


Fig. 6. Ova of *Clonorchis sinensis* with distinct bilaminar wall and shoulder (Papanicolaou,  $\times 400$ ).

Table 2. Classifications according to diagnosis of bile cytology.

	No.	%
Inadequate specimen	28	18.9
Negative	57	38.5
C.S. Infestation	17	11.5
(ova	16)	
(adult worm	1)	
Adenomatous hyperplasia	8	5.4
Atypical hyperplasia	6	4.1
Adenocarcinoma	30	20.3
(Adenocarcinoma with c.s infestation : 1)		
Squamous cell carcinoma	1	0.7
Small cell carcinoma, metastatic	1	0.7
<b>Total</b>	<b>148</b>	

Note : C.S. : *Clonorchis sinensis*

Table 3. Classifications according to clinical diagnosis (in patients with review of clinical records).

	No.	%
Benign lesion		
CBD stone	5	4.8
Stricture	1	1.0
Malignant lesion		
CBD ca.	45	42.9
Gallbladder ca.	3	2.9
Hepatic duct ca.	1	1.0
Klatskin tumor	5	4.8
Cholangiocarcinoma	2	1.9
Periampullary ca.	3	2.9
Pancreas head ca.	21	20.0
Metastatic ca.	19	18.1
<b>Total</b>	<b>105</b>	

Note : ca. : carcinoma

CBD : common bile duct

summarized in Table 3. The clinical diagnosis was malignancy in 99 patients and benignancy in 6.

In patients with clinical diagnosis of malignancy,

the results of bile cytology were analyzed according to clinical diagnosis (Table 4).

**Table 4.** Malignancy detection rate in bile cytology in each clinical diagnosis

Clinical diagnosis	No. of case	No. of malignancy	% of malignancy
CBD ca.	45	11	24.5
Gallbladder ca.	3	2	66.7
Hepatic duct ca.	1	0	0
Klatskin tumor	5	3	60
Cholangiocarcinoma	2	2	100
Periampullary ca.	3	0	0
Pancreas head ca.	21	2	9.5
Metastatic carcinoma	19	3	15.8
Total	99	23	

Malignancy detection rate : 23.2%

Of the 99 patients, cytologic results were positive in 23 and the malignancy detection rate of bile cytology was 23.2%. A cytologic diagnosis of "atypical hyperplasia" was not considered to be positive.

We analyzed the results dividing the patients into two groups, the ones with tumor of bile duct origin (group I) and the others with tumors producing extrinsic compression of bile duct (group II).

The results of bile cytology in group I are summarized in Table 5.

**Table 5.** Malignancy detection rate in bile cytology (I) (In patients with biliary origin tumor).

	No. of case	No. of malignancy
CBD ca.	45	11
Gallbladder ca.	3	2
Hepatic duct ca.	1	0
Klatskin tumor	3	5
Cholangiocarcinoma	2	2
Total	54	20

Malignancy detection rate : 37.0%

Of the 54 patients, cytologic results were positive in 20, and the malignancy detection rate of bile cytology was 37.0% in this group.

In group II, cytologic results were positive in 5 out of 43 patients (Table 6).

**Table 6.** Malignancy detection rate in bile cytology (II) (In patients with tumors producing extrinsic compression).

	No. of case	No. of malignancy
Periampullary ca.	3	0
Pancreas head ca.	21	2
Metastatic carcinoma	19	3
Total	43	5

Malignancy detection rate : 11.6%

In this group, the malignancy detection rate of bile cytology was 11.6%. The cytologic diagnoses were histologically confirmed in only 9 cases, because most of the patients in this study were not in a operative indication.

The results of this correlation are summarized in Table 7.

The positive correlation was in 50% and 20% in group I and group II respectively.

The results of overall diagnostic correlation of cytologic diagnosis with clinical diagnosis are summarized in Table 8.

**Table 7.** Correlation of cytologic diagnosis and histological diagnosis in bile cytology.

Clinical Dx	Cytologic Dx	Histologic Dx
1. CBD ca.	Adeno ca.	CBD, adeno ca.
2. CBD ca.	—	CBD, adeno ca.
3. CBD ca.	—	CBD, adeno ca.
4. GB ca.	Adeno ca.	GB, adeno ca.
5. Pancreas Head ca.	Adeno Ca.	LN, Metastatic adeno ca.
6. Pancreas Head ca.	Atypia	Endoscopic Bx : Adeno ca.
7. Pancreas Head ca.	Adenomatous hyperplasia	LN, Metastatic adeno ca.
8. Pancreas Head ca.	—	LN, Metastatic adeno ca.
9. Pancreas Head ca.	—	Pancreas, adeno ca.

Note : Ca. : carcinoma  
LN : Lymph node  
Bx : Biopsy

**Table 8.** Correlation of cytologic diagnosis and diagnosis of clinical investigation in bile cytology.

Cytologic diagnosis	Malignancy	Benignancy	Total
with (+) correlation	23	6	29
with (—) correlation	76	0	76
Total	99	6	105

Concordance rate : 27.6%  
sensitivity : 1  
specificity : 1  
predictive value for positive : 1  
predictive value for negative : 0.07

Of the 99 patients with clinical diagnosis of malignancy, 23 patients were in positive correlation. Of the 6 patients with clinical diagnosis of benignancy, all the cytologic results were benign, so the diagnostic accuracy in benign lesion was 100%. The overall diagnostic accuracy was 27.6%. The sensitivity and specificity were 1 in each. The predictive value for positive and negative were 1 and 0.07 respectively.

In Korea, the incidence of stomach carcinoma is high and there were many cases with evidence of common bile duct obstruction due to metastasis in porta hepatis or pericholedochal lymph node, or peri-

pancreatic lymph node, from stomach carcinoma. The results of bile cytology in patients with common bile duct obstruction together with primary tumor in another organ, are summarized in Table 9. Of the 19 patients, cytologic results were positive in 3 patients (15.8%).

Of the 17 patients with ova or adult worm of the *Clonorchis sinensis* in bile cytology, 10 patients were followed up with clinical records. The clinical diagnoses of these patients were ; common bile duct carcinoma in 4, hepatic duct carcinoma in 1, pancreas head carcinoma in 2, metastatic carcinoma in 1 and common bile duct stone in 2. In one patient, in which clinical diagnosis was common bile duct carcinoma, *Clonorchis ova* and adenocarcinoma cells are demonstrated in sequential bile cytology.

## Discussion

Obstructive jaundice due to partial or complete biliary obstruction may sometimes be produced by intrinsic lesion of the bile ducts or by extrinsic compression of the ducts. The most common causes of extrinsic compression are carcinoma of the head of the pancreas, acute or chronic pancreatitis or invol-



**Table 9.** Cytologic diagnosis of bile cytology in tumors with metastatic lesion compressing bile ducts.

Clinical diagnosis	Cytologic diagnosis
1. Stomach ca. with meta.	—
2. Stomach ca. with meta.	Inadequate
3. Stomach ca. with meta.	Inadequate
4. Stomach ca. with meta.	—
5. Advanced stomach ca.	—
6. Stomach ca. with CBD obs	—
7. Stomach ca. with liver meta.	—
8. Stomach ca. with liver meta.	Adeno ca.
9. Stomach ca. with CBD obstruction	Adenomatous hyperplasia
10. Stomach ca. with meta. to porta hepatis	Atypia
11. Stomach ca.	—
12. Stomach ca. with obstruction	—
13. Stomach ca.	—
14. Colon ca. with CBD meta.	—
15. Lung ca. with pancreas meta.	Small cell ca.
16. Lung ca. with meta.	Adeno ca.
17. Lung ca. with pericholedochal LN meta.	—
18. Cx. ca. with peripancreatic meta.	Adenomatous hyperplasia
19. Meta. carcinoma of unknown primary.	c.s. ova

Note : meta. : metastasis  
 Ca. : carcinoma  
 Cx. : uterine cervix

vements of the lymph nodes in the porta hepatis by lymphoma or metastatic carcinoma. Cytologic examination is very useful in evaluating the causes of extrahepatic biliary obstruction, but there is a significant false-negative rate. Extrahepatic biliary obstruction, secondary to extrinsic compression from metastatic disease or lymphomas also yields negative results because of the absence of mucosal involvement<sup>11)</sup>. The cells found in biliary drainage fluid may be from extrahepatic and intrahepatic radicles of the biliary tracts, the gallbladder or, from pancreas and other adjacent organ when the bile duct mucosa is involved by carcinoma of the head of pancreas or any other metastatic carcinoma. A variety of methods for obtaining bile for cytodiagnosis have been reported. These include duodenal drainage with or without secretin stimulation<sup>2)</sup>,

operative choledochoscopy<sup>12)</sup>, minilaparotomy<sup>13)</sup>, aspiration during ERCP<sup>14)</sup> or PTC<sup>6)</sup>, or through T-tube drainage, or percutaneous biliary drainage. The duodenal aspiration procedure gives the patients discomfort and cell morphology deteriorates rapidly in duodenal juice due to mixing of gastroduodenal juice and pancreatic juice, making cytologic diagnosis difficult. ERCP enables more accurate collection of pure pancreatic fluids directly from the pancreatic duct or bile by selective cannulation of the representative ducts. In this way origin of the examined cells can be defined more precisely. An even more accurate and early diagnosis can be obtained by passing a brush into the ducts during this procedure.

Although the results of bile cytology obtained through percutaneous biliary drainage catheter

are not so satisfactory the procedure gives two possibilities ; firstly, the relief of symptoms caused by obstruction and secondly, the possible confirmation of malignant neoplasm, however, neoplastic tissue of origin cannot be identified with certainty solely from its morphologic base.

There was a difference in results of bile cytology in this study, between the group with tumors of bile ducts origin and another group with tumors producing extrinsic compression of bile ducts, giving the better results in former. Our results gives lower detection rate compared to direct aspiration cytology during ERCP<sup>14)</sup> and not effective in detection of tumors of pancreas, periampullary region and metastatic carcinomas from tumors of adjacent organs, but this bile juice cytology adjunct to percutaneous biliary drainage is a simple non-invasive method for confirmation of malignant neoplasm of the biliary tracts.

Bile cytology generally gives a low false-positive rate and the same finding is found in our results of cytology from percutaneous biliary drainage. In countries of Far East, the clonorchiasis is a frequently occurring disease and the most common documented cause of cholangiocarcinoma<sup>6)</sup>. In this study, the bile cytology of one patient whose clinical diagnosis was common bile duct carcinoma, adenocarcinoma cells and coexistent ova of *Clonorchis sinensis* were demonstrated. Except for this case, bile cytology in the other cases only demonstrated ova of *Clonorchis sinensis* although the clinical diagnosis was malignancy, and failed to reveal any evidence of "cause and effect" of *Clonorchiasis*, and cholangiocarcinoma and any other carcinoma of bile duct origin.

If the cases of where the clinical diagnosis was malignancy but, only ova of *Clonorchis sinensis* were found in bile cytology, cases therefore of *Clonorchiasis* and not malignancy, then our res-

ults from bile cytology in detection of malignancy could be higher than those showing in this paper. If some cases of these were truly malignant, then this finding may be indirect evidence that clonorchiasis is a causal factor in the development of cholangiocarcinoma.

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= 국문초록 =

### 담즙의 세포병리학적 진단에 관한 연구

서울대학교 의과대학 병리학교실

박인애 · 함의근

췌-담도 및 배터 팽대부 주위의 암은 조기진단이 어려워 처음 발견시 질병이 상당히 진행되어 있어, 근치술은 물론 생검진단도 수행하기가 어려운 경우가 흔히 있다. 과거 이런 환자들의 진단 방법의 하나로 십이지장에서 담즙을 얻어 세포병리 검사가 시도 되었었으나, 이 경우 얻어진 담즙에 위액 및 혈액이 섞여 있어 변성을 쉽게 초래하고, 염증세포들이 많이 섞여 있을 뿐만 아니라 주위의 염증으로 비정형 세포변화를 초래하여 진단이 어려운 경우가 흔히 있었다. 최근 이런 환자들에 있어 수반되는 증상인 폐색성 황달의 완화와 방사선학적 진단을 위해 경피 경간 담도 조영술 및 담즙배출술이 시행되고 있는데, 이때 비교적 세포형태가 잘 유지된 담즙을 반복 채취하여 세포 병리검사가 시행된다. 저자들은 이 방법으로 얻어진 담즙의 세포 병리학적 진단 성적을 검토하여 다음과 같은 결과를 얻었다. 총 검체는 148명 환자의 275 검체로 이들의 세포 병리학적 진단은 선암 30예 (20.3%) 편평상피 세포암 1예 (0.75%), 전이성 소 세포암 1예 (0.7%), 선조성 비후 8예 (5.4%) 비정형 6예 (4.1%), 간 흡충증 17예 (11.5), 양성질환 57예 (38.5%)였고 28명 (18.9%)에서는 부적합 검체가 의뢰 되었었다. 그중 105명에서 의무기록의 확인이 가능하였는데 이들의 임상진단은 99명에서는 악성 질환 이었고 6명에서는 총 담관 결석과 협착과 같은 양성 질환 이었다. 담즙 세포 병리검사에서의 이들 악성 진단율은 23.2% 이었다. 이들 악성 질환을 담도 유래의 종양과(1군) 부근 림프질의 전이성암, 췌장암, 배터 팽대부 주위암 등의 외인성으로 담도를 압박하는 종양(2군)으로 나누어 보면 악성 진단율은 각각 37%와 11.6%로 현저한 차이가 있었다. 이들중 조직학적 진단이 가능 하였던 9예의 경우 세포 병리 진단율은 각각 50% (1군)와 20% (2군)로 역시 현저한 차이가 있었다. 임상진단이 양성 질환 이었던 예들은 전예에서 세포 병리학적으로 양성으로 진단되어 담즙 세포 병리검사의 임상진단과의 일치율은 27.6%, 특이도는 100%이었다. 이상으로 이 담즙세포 검사의 악성 진단율은 그리 높지 않으나, 경피 경간 담즙 배출술로 환자의 증상을 완화 시키면서 부수적으로 진단도 얻을 수 있는 유용한 방법이라 하겠고, 그중 담도유래의 종양군에서 외인성으로 담도를 압박하게 되는 종양군에 비해 현저히 높은 진단율을 보였다.