Value of exfoliative cytology for investigating bile duct strictures

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Abstract

The cause of a biliary tract stricture may be difficult to determine radiologically. Exfoliative biliary cytology was evaluated in 62 patients (median age 65 years, range 30-94) with biliary tract strictures presenting to the Hepatobiliary Unit between January 1984 and December 1989. Bile samples were taken during endoscopic retrograde cholangiopancreatography (ERCP) in 42 patients, percutaneous cholangiography in 14, and both in six. The site of stricturing was upper third of the bile duct in 43% (n=27), middle third in 10% (n=six), and lower third in 47% (n=29). Of the 47 patients with radiological appearances of a malignant stricture, 22 (47%) had histological confirmation by biopsy either under computed tomography guidance, at endoscopy, at operation, or at necropsy. Fourteen of the 47 patients had positive cytology (30%). In seven patients cytology alone established the presence of malignancy (15%) and in the other seven positive cytology was confirmed by histology. The addition of cytology to tissue biopsy therefore allowed malignancy to be confirmed in 29 of the 47 patients (62%). None of the 15 patients subsequently shown to have benign disease had positive cytology. Sensitivity of the technique was 30% and specificity 100%. Samples for exfoliative cytology are simple to obtain, the results are highly specific and should be a routine part of the investigation of biliary strictures.

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Patients presenting with obstructive jaundice caused by a bile duct stricture may be managed by either surgery or stenting. Which treatment is most appropriate is dependent on the clinical state of the patient and whether the stricture is benign or malignant - information which may be difficult to obtain. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography allow visualisation of the site and give some information on the nature of the stricture but are not diagnostic. Imaging is able to define a mass lesion in about 40% of cases on ultrasound and 70% by computed tomography scanning in patients with extrahepatic biliary obstruction.¹ Percutaneous aspiration cytology has been reported as confirming malignancy in about two thirds of pancreatic cancers² and one half of bile duct tumours³ but cannot be done unless a mass lesion is established on imaging.

It is now over 40 years since exfoliative cytology was first used for the diagnosis of pancreatobiliary disease, Lemon and Byrne diagnosing pancreatic cancer from cells exfoli-

ated into the duodenum.⁴ Despite this initial success the popularity of exfoliative cytology declined because of occasional reporting of false positive results, caused by degenerative cellular changes in the duodenal juice.^{5,6} Since the early 1970s, however, it has been possible to collect bile samples at either endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography and a few small series of patients have been reported with good diagnostic yields and no falsely positive results.⁷⁻⁹ We have reviewed our experience of exfoliative cytology in the management of patients with biliary tract strictures.

Methods

PATIENTS

Over a six year period (January 1984 to December 1989) 62 patients with bile duct strictures had exfoliative cytology carried out. There were 33 men and 29 women with a median age of 65 years (range 30-94). The majority of patients presented with painless obstructive jaundice (Table I). Bile samples were collected at diagnostic or therapeutic endoscopic (ERCP, n=42) or percutaneous (n=14) biliary procedures or during both (ERCP and percutaneous transhepatic cholangiography, n=6).

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Endoscopic retrograde cholangiopancreatography was carried out under intravenous sedation using a side viewing endoscope (Olympus TJF-10 or JF-IT10) after intravenous administration of broad spectrum antibiotics and crystalloids. After visualisation of the stricture at cholangiography a guide wire was inserted across the stricture followed by an endoscopic transpapillary endoprosthesis (10 Fr (French gauge), Meadox Surgimed). Bile for cytology was aspirated through a catheter within or above the endoprosthesis by the endoscopist and sent on the day of sampling to the Cytology Department.

PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY

Percutaneous transhepatic cholangiography was carried out under intravenous sedation after intravenous administration of broad spectrum antibiotics and crystalloids. A Chiba needle cholangiogram was obtained and the biliary stricture shown. A further percutaneous puncture allowed the insertion of a sheath needle (Surgimed 5 Fr) into the dilated intrahepatic ducts under fluoroscopy. The needle was with-

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Figure 1: Sheets of benign ductal epithelial cells with regular arrangement and discrete cuboidal margin. Papanicolaou.

drawn and a guide wire passed into the biliary tree. After establishing external drainage (8.3 Fr catheter) a sample of bile was taken from the region of the stricture by the radiologist and sent on the same day to the Cytology Department. After a period of external biliary drainage (usually 48 hours) the guide wire was reinserted and advanced through the stricture to allow insertion of an endoprosthesis.

PROCESSING OF SAMPLES

Bile samples were processed on the day of sampling. After centrifuging the samples at 1500 rpm for five minutes the supernatant was discarded. The deposit was then resuspended and cytospin (a cell smear produced by centrifuging) preparations made. From each bile sample at least four slides were prepared, two for Papanicolaou (PAP) staining and two for May-Grunwald Giemsa (MGG). The slides from this entire series of patients were examined by a

TABLE I Presenting features of patients with bile duct strictures (n=62)

	n	%
Jaundice	56	90
Pruritus	35	56
Pain	16	26
Hepatomegaly	40	65
Cholangitis	3	5
Pyrexia	8	13

Figure 2: Neutrophilic exudate (pus) and granular yellow bile pigment together with a single irregular cluster of malignant epithelial cells exhibiting overlapped irregular nuclei. Papanicolaou.

single experienced cytologist (AD). The cytologist was provided with basic patient details such as name, age, sex, and unit number but only limited clinical information such as 'biliary stricture'.

FOLLOW UP INFORMATION

The results of imaging investigations, surgery and histological examination of tissue samples were reviewed by reference to the patients' notes. Follow up information was obtained from out patient clinical notes. In addition all patients in whom a histological diagnosis was not obtained at the initial admission to hospital had follow up information obtained by consultation with their general practitioners.

STATISTICAL ANALYSIS

Results were compared between groups using a χ^2 test.

Results

Red blood cells, white cells, granular bile pigment, and benign ductal epithelial cells were a common finding and are shown in Figure 1. Positive cytology was based on the presence of cells with established characteristics of malignancy as shown in Figure 2. Cholangiography (endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography) showed an upper third bile duct stricture in 27 patients, 18 being malignant and six having positive cytology (33%). There were six middle third strictures of which four were malignant and two had positive cytology (50%). Of the 29 lower third strictures 25 were malignant and six had positive cytology (24%). The final diagnosis and the results of cytology are given in Table II. One third of the patients with cholangiocarcinoma and a quarter of those with cancer of the pancreas had positive cytology. The results of cytology are compared with the method of sampling in Table III. Six patients, all with malignant strictures, had bile samples taken at both endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography. Two of these patients had positive cytology, in one at both endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography and in the other at percutaneous transhepatic cholangiography alone. Positive cytology was obtained more frequently in patients with malignant strictures undergoing endoscopic retrograde cholangiopancreatography (11 of 35, 31%) than in those undergoing percutaneous transhepatic cholangiography (four of 18, 22%) although this was not statistically significant ($\chi^2=0.50$).

Of the 15 patients with benign strictures five were caused by sclerosing cholangitis, five secondary to bile duct stones, and one each because of chronic pancreatitis, Mirizzi syndrome,¹⁰ Caroli's disease,¹¹ biliary cystadenoma, and polycystic liver. The clinical details, basis for the diagnosis and the follow up of this group of patients is shown in Table IV. Of the 15 patients with benign strictures follow up infor-

TABLE II Final diagnosis and results of cytology

Tumour site	n	Positive cytology (%)
Cholangiocarcinoma	12	4 (33)
Carcinoma pancreas	18	4 (22)
Periampullary cancer	4	1 (25)
Gall bladder cancer	4	2 (50)
Tumour metastases	5	1 (20)
Duodenal cancer	1	0
Lymphoma	1	0
Hepatocellular cancer	1	1
Cystadenocarcinoma	1	1

TABLE III Results of cytology and method of sampling

Method	Malignant (n)	Positive cytology (%)
ERCP alone (n=42)	29	10 (35)
PTC alone (n=14)	12	2 (17)
Both (n=6)	6	2 (33)
Total ERCP (n=48)	35	11 (31)
Total PTC (n=20)	18	4 (22)

ERCP=endoscopic retrograde cholangiopancreatography.
PTC=percutaneous transhepatic cholangiography.

mation has been obtained in 13 (87%) with a follow up period of three to 10 years (median six years). Exfoliative cytology was negative in all 15 patients with benign disease resulting in no false positive results and a specificity of 100%.

Of the 47 patients diagnosed as having malignant bile duct strictures on radiological findings 29 (62%) had confirmation of this diagnosis by cytology and/or histology. The clinical details and follow up of the seven patients in whom the diagnosis was based on cytology alone are given in Table V. This group of patients all followed a clinical course suggestive of malignancy with progressive deterioration and death in two to six months from the time of discharge. Eighteen patients who were diagnosed on radiological grounds as having malignant bile duct strictures had negative cytology and no histological confirmation of malignancy. Insufficient follow up information was available in six of these patients (33%). Of the remaining 12 patients one died of

TABLE IV Clinical details of patients with benign bile duct strictures (n=15)

Patient	Age (yr)	Sex	Diagnosis	Based on	Follow up (yr)
AG	64	M	SC	ERCP, liver Bx, Op	7
PH	40	F	SC	ERCP, liver Bx, Op	6
NH	33	M	SC	ERCP, liver Bx	3
RS	56	M	SC	ERCP, liver Bx, PM	Died 2
LJ	35	M	SC	ERCP, liver Bx, Op	10
SP	68	F	Stones	ERCP, Liver Bx	5
HY	84	F	Stones	ERCP, FU ERCP normal	7
PM	42	M	Stones	ERCP, liver Bx	7
JB	83	M	Stones	ERCP, FU ERCP normal	Nil
SK	65	F	Stones	ERCP, FU ERCP normal	Nil
GB	71	M	Chr Panc	ERCP, Op Bx	3
BB	53	M	Mirizzi	ERCP, Op	7
AB	33	M	Caroli	ERCP, CT, Op Bx	6
LS	66	F	CystAd	ERCP, CT, Bx	4
SL	30	M	Polycystic liver	ERCP, CT	4

M=male; F=female; SC=sclerosing cholangitis; Stones=common bile duct calculi; Chr Panc=chronic pancreatitis; CystAd=biliary cystadenoma; Bx=biopsy; Op=operation; OpBx=operative biopsy; CT=computed tomography; Mirizzi=Mirizzi syndrome¹⁰; Caroli=Caroli's disease¹¹; FU=follow up.

TABLE V Malignancy confirmed by cytology alone

Patient	Age (yr)	Sex	Diagnosis	Based on	Follow up (months)
FW	84	M	Ca Panc	US, ERCP	Died 2/12
ST	84	F	Ca Panc	US, ERCP	Died 2/12
IS	47	M	Ca Panc	CT, ERCP	Died 3/12
PS	61	M	Ca Panc	CT, ERCP	Died 3/12
LW	69	M	CCA	ERCP, PTC, CT	Died 6/12
CW	86	F	Ca Panc	US, ERCP	Died 3/12
ES	62	F	Liver mets	CT, ERCP, PTC	Died 6/12

M=male; F=female; Ca=carcinoma; Panc=pancreatitis; CCA=cholangiocarcinoma; Mets=metastases; US=ultrasound; CT=computed tomography.

acute renal failure during the initial investigation and treatment and the remaining 11 patients died at a median period of four months (range one to 18 months) because of progressive caexia. The overall contribution of exfoliative bile cytology to the diagnosis of bile duct strictures is shown in Figure 3.

Discussion

There are many well documented cases in which a seemingly benign stricture on radiological grounds has been subsequently shown to be malignant. A hilar stricture produced by sclerosing cholangitis may easily be confused with a cholangiocarcinoma¹² or a distal stricture from chronic pancreatitis with a carcinoma of the pancreas.^{13,14} These distinctions are often crucial to the management decision as treatment options vary from palliative stenting or radio/chemotherapy to curative resection or transplantation. Improved methods of obtaining a tissue diagnosis are therefore becoming essential to the management of biliary tract strictures. The 'no tissue diagnosis' rate of 38% reflects the difficulty of diagnosis in some patients, many of whom are not considered suitable for surgery and who do not have a mass on imaging. This high incidence of failing to establish a tissue diagnosis is due to reliance on imaging by some clinicians who are reticent, perhaps rightly, about invasive diagnostic techniques in a predominantly elderly and frail population. Although the possibility of this resulting in misdiagnosis is obviously

Figure 3: Tissue confirmation of biliary strictures.

present,^{12 13} follow up on this group of patients did not reveal any who had been falsely diagnosed as having malignancy.

In contrast with most other studies on exfoliative cytology for bile duct strictures this study has not focused on a particular primary site of tumour but rather the overall use of cytology with biliary strictures. Results by origin of tumour show that one third of patients with cholangiocarcinomas and one quarter of those with pancreatic cancer were positive on cytology. Most importantly in 15% of the patients suspected of malignancy on radiological grounds cytology was the only method of establishing a tissue diagnosis.

Suggested reasons for the high false negative rate on exfoliative cytology of pancreatic cancer include the enzymatic digestion of cells, pancreatic duct stenoses, intramural or extramural tumour growth and the distance between the sampling site and the tumour. Sampling directly from the pancreatic duct provides a more proximate sample for cytological diagnosis and may improve the diagnostic sensitivity.⁹ With cholangiocarcinomas the reported diagnostic sensitivity of exfoliative cytology varies from 44–100%¹⁵ and may depend on the method and site of sampling as well as its timing during the biliary manipulation. The high sensitivities obtained in some centres would suggest that it is technically feasible to obtain tissue confirmation by cytology in all patients with hilar strictures.

The positivity rate for samples collected at endoscopic retrograde cholangiopancreatography was 31% in comparison with 22% at percutaneous transhepatic cholangiography. This difference may be explained by the technique involved. At percutaneous transhepatic cholangiography bile is often sampled on initial puncture of the liver at a site distant from the stricture whereas at endoscopic retrograde cholangiopancreatography sampling is usually carried out at the site of the stricture after it has been disrupted by insertion of an endoprosthesis. An alternative explanation for the more favourable results at endoscopic retrograde cholangiopancreatography is that the type of stricture encountered by the two techniques is different, percutaneous transhepatic cholangiography being preferred when imaging suggests a high stricture and endoscopic retrograde cholangiopancreatography when it is low. This is not substantiated by analysis of the high strictures according to the method of diagnosis. Endoscopic retrograde cholangiopancreatography was carried out as often for high strictures (20 of 27 (74%)) as it was for the group as a whole (48 of 62 (77%)). These results would suggest that endoscopic retrograde cholangiopancreatography may be a better method of sampling for biliary cytology than percutaneous transhepatic cholangiography although larger numbers of patients within a randomised study would be required for conformation.

Methods are obviously required to improve the sensitivity of diagnostic biliary cytology. Multiple sampling for exfoliative cytology has been shown to improve the sensitivity of the technique but is time consuming.¹⁵ Of more practical value is the use of a cytology brush, either percutaneously or endoscopically which greatly improves the number of viable cells for analysis and may be carried out without removal of the guide wire used for stent insertion.^{15–17} A prospective study comparing exfoliative and brush cytology has not yet been reported. A satisfactory alternative or addition to biliary brush cytology is direct biopsy of the stricture using small forceps under fluoroscopic control. The results from this technique remain preliminary.¹⁸

We would conclude from this study that exfoliative cytology for biliary strictures is simple to perform, highly specific, able to provide a diagnosis when other methods fail and should, therefore, be carried out routinely.

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