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Endoscopic cytology in biliary strictures. Personal experience

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SUMMARY: Endoscopic cytology in biliary strictures. Personal experience.

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Introduction. *The differential diagnosis between malignant and benign biliary strictures is the cornerstone of the management of jaundiced patients. The aim of our study is to define the role of cytology of the bile withdrawn during endoscopic retrograde cholangiopancreatography (ERCP), to reach a diagnosis of the nature of biliary stricture.*

Patients and methods. *This retrospective study was conducted on 67 consecutive patients affected of ingravescens obstructive jaundice who underwent ERCP±PTE (percutaneous transhepatic endoscopic) + bile withdrawn + stenting. We founded hilar stricture in 21 patients (31.3%), middle third the common duct stricture in 17 (25.3%), and lower third stricture in 28 patients (41.4%). In one patient (2%) the cholangiography did not show any stricture, but we continued with the withdrawn of bile after positioning a naso-biliary drainage.*

Results. *Diagnosis was made in only 40 of 65 patients (61.5%) and no epithelial lining cells of the biliary tree was found in the remaining 25 patients (38.5%). The presence of neoplasm in the pancreato-biliary tract was excluded (absence of malignant cells) in 25 of 40 diagnostic exams (62.5%). During follow-up only 7 of these 25 patients resulted in having a benign disease (true negatives 28%) while the remaining 18 cases were diagnosed with malignant neoplasm of the pancreato-biliary tract (false negatives 72%). Nine of 14 with positive cytology for carcinoma were diagnosed with cholangiocarcinoma (65%), 4 with pancreatic (28%) and 1 with ampullary carcinoma. Of 25 non-diagnostic samples, 5 (20%) resulted as benign, 20 (80%) as malignant. The statistical analysis by chi-square test allowed us to conclude that bile cytology, if diagnostic, is significantly valid in identifying carcinoma of the pancreato-biliary tract ($p < 0.05$) instead, considering the high rate of non diagnostic samples, its meaning is limited ($p = 0.09$).*

Discussion. *Exfoliative cytology of bile samples obtained during ERCP is easier and less invasive method to determine the diagnosis of biliary strictures, but due to its low sensibility, varying from 6 to 63%, it doesn't appear accurate to establish a definite diagnosis; the stricture dilatation before the withdrawal increases the diagnostic sensibility and accuracy of the cytological exam.*

Conclusion. *Bile withdrawn for cytology during ERCP is a safe*

RIASSUNTO: Citologia endoscopica perendoscopica nelle stenosi biliari. Esperienza personale.

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Introduzione. *La diagnosi differenziale tra stenosi biliari maligne e benigne costituisce il momento fondamentale per il trattamento dei pazienti itterici. Lo scopo del nostro studio è quello di definire il ruolo della citologia, utilizzando la bile prelevata durante la colangiopancreatografia retrograda per via endoscopica (CPRE), nel definire la diagnosi di natura di una stenosi biliare.*

Pazienti e metodi. *Questo studio retrospettivo è stato condotto su 67 pazienti consecutivi affetti da ittero ostruttivo ingravescens, sottoposti a ERCP ± PTE (endoscopia transepatica percutanea) + prelievo di bile + posizionamento di protesi biliare. Abbiamo identificato 21 stenosi ilari (31.3%), 17 stenosi della parte media della via principale (25.3%) e 28 stenosi del coledoco distale (41.4%). In un paziente (2%) la colangiografia non ha dimostrato alcuna stenosi ma abbiamo lo stesso prelevato la bile dopo il posizionamento di un sondino naso-biliare.*

Risultati. *È stata possibile la diagnosi solo in 40 dei 65 pazienti (61.5%), mentre nei restanti 25 pazienti non è stata evidenziata cellularità nel prelievo di bile (38.5%). La presenza di neoplasia cefalopancreatica è stata esclusa (assenza di cellule atipiche) in 25 dei 40 esami diagnostici (62.5%) ma, durante il follow-up, solo 7 di questi 25 soggetti sono risultati affetti da stenosi benigna (veri negativi 28%), mentre i restanti 18 casi erano affetti da un tumore del distretto bilio-pancreatico (falsi negativi 72%). Nove su 14 pazienti con citologia positiva per carcinoma avevano un colangiocarcinoma (65%), 4 un cancro del pancreas (28%) e uno un carcinoma della papilla di Vater. Dei 25 campioni non diagnostici, 5 (20%) sono risultati benigni, 20 (80%) maligni. L'analisi statistica dei dati (test del chi-quadro) ci consente di affermare che la citologia biliare, se diagnostica, è significativamente valida nell'evidenziare una neoplasia del tratto bilio-pancreatico ($p < 0.05$) anche se, considerando l'alto tasso di campioni non diagnostici, il suo ruolo appare molto ridimensionato ($p = 0.09$).*

Discussione. *La citologia biliare esfoliativa di campioni ottenuti durante la CPRE è il metodo più facile e meno invasivo per la diagnosi di natura di una stenosi coledocica, ma per la sua bassa sensibilità (6-63%, secondo i dati della letteratura) non sembra particolarmente accurato; la dilatazione della stenosi prima del prelievo di bile sembra incrementare la sensibilità diagnostica e l'accuratezza dell'esame citologico.*

Conclusioni. *Il prelievo di bile durante CPRE è un metodo sicuro che non aumenta la morbilità procedura-correlata, consente un orientamento diagnostico nel 75% circa dei casi e la sua sensibilità ed accuratezza sono migliorate dal prelievo dopo dilatazione della stenosi. Benché un risultato negativo non escluda una diagnosi di mali-*

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method with no increasing in patient's morbidity. It allows a diagnostic orientation in 75% of the patients. Bile withdrawn after dilatation of stricture allows improves sensibility and accuracy. Negative results does not exclude malignant disease, however, if positive, it is considered diagnostic (positive predictive value 100%).

gnità, il risultato positivo va considerato diagnostico (valore predittivo positivo 100%).

KEY WORDS: ERCP - Stricture - Biliar cytology - Diagnosis.
CPRE - Stenosi - Citologia - Diagnosi.

Introduction

Management of biliary strictures remains a challenge for both surgeons and endoscopists. Obstructive jaundice could be solved by surgical, radiological or endoscopic techniques, according to the level and the nature of stricture and the clinical status of the patient.

The differential diagnosis between malignant and benign strictures is the cornerstone of the management of these patients, because it is often difficult to establish the malignant disease with radiologic imaging; this difficulty is due to both the frequent co-existence of proliferative and fibrotic phenomenons in the context of the mass and the possibility that the tumour doesn't infiltrate the ductal epithelium, therefore determining an extrinsic compression on the biliary tree (pancreatic carcinoma, enlarged lymph nodes, metastasis).

The aim of our study, starting from our experience, is to define the role of biliary cytology during ERCP, to reach a diagnosis of the nature of biliary strictures.

Patients and methods

This retrospective study was conducted in the Operative Unit of Surgical Endoscopy, part of the Section of General and Thoracic Surgery of Policlinico in University of Palermo, Italy, from January 2000 to January 2006.

We enrolled 67 consecutive patients affected by ingravescant obstructive jaundice with intra- and/or extra-hepatic biliary tree dilatation demonstrated with ultrasonography or CT. They underwent ERCP±PTE using Olympus® TJF-145 duodenoscopy (Olympus Ltd, Hamburg). We enrolled 39 male and 28 female, male:female ratio 1.39:1, aged 51-87 years, mean age 66 years.

After a selective cannulation of the biliary tree using sphincterotomy with hydrophilic guidewire, we proceeded with a withdrawal of pre-stricture (distal to stricture) bile; then we obtained a cholangiogram, and by-pass of the stricture with the insertion of biliary stent (Amsterdam type, 10 French, from 7 to 15 centimeters) after a withdrawal of the post-stricture (proximal to stricture) bile was done, using aspiration by the guide catheter. We have considered biliary stricture in case of reduction of $\geq 75\%$ of the normal biliary tree diameter. ERCP demonstrated a hilar stricture in 21 patients (31.3%), common bile duct middle third stricture in

17 (25.3%) and lower third stricture in 28 patients (41.4%). In one patient (2%), who underwent ERCP for recurrent cholangitis, the cholangiography did not show any stricture; we continued with the withdrawn of bile after positioning a naso-biliary tube.

The cytological exam executed by the same pathologist (blinded on clinical presentation, history and imaging studies) was done on slides prepared with the sample bile, centrifugation and elimination of super-natant, fixed according to Papanicolaou in 95% ethanol. When malignant neoplasm was suspected, the exam was repeated with the preparation of the monolayer slides with ThinPrep® (ThinPrep® 2000 direct-to-vial, Cytoc UK limited), on which was possible to do immunohistochemical assay. After ERCP, patients had clinical and serological follow-up for a period of 3 months to 5 years. In patients who underwent surgical treatment for adenocarcinoma, the definitive histological exam of the surgical specimen was executed to confirm the cytological report.

The results obtained from the bile's cytology, from clinical and laboratory follow-up and when possible from the definitive histological exam, were compared using a chi-square test, with significant results if $p < 0.05$. Two patients, a male and a female, were lost in the follow-up having denied their adhesion to the study.

Results

Diagnosis, reported as positive or negative for malignancy, was possible in only 42 of 65 patients (61.5%): in the remaining 25 patients (38.5%) no epithelial lining cells of the biliary tree were founded in the sample, so the exam was considered non diagnostic. In 25 of 40 diagnostic cytological exams (62.5%) the presence of neoplasm in the pancreato-biliary tract was excluded (absence of malignant cells). During follow-up, only 7 of these 25 patients resulted in having a benign disease (chronic pancreatitis, papilloedditis, iatrogenic stricture; true negatives 28%) while in the remaining 18 cases patients were diagnosed with malignant neoplasm of the pancreato-biliary tract (false negatives 72%).

In all 14 patients the bile cytology exam positive for malignant disease was confirmed with radiological imaging (not confirmed with histology) or with definitive histological exam after surgical resection (real positives, 100%). In particular, 9 of 14 with positive cytology for carcinoma were diagnosed with cholan-

giocarcinoma (65%), 4 with pancreatic (28%) and 1 with ampullary carcinoma. One patient, in which the cytological exam was done in two successive bile samples, the result was doubtful between neoplastic and inflammatory process; then successively, applying transabdominal US-guided biopsy, it was asserted as pancreatic cancer.

Of 25 non diagnostic samples, 5 (20%) resulted as benign, 20 (80%) as malignant, and in particular were assayed 8 cases of pancreatic cancer, 5 cases of cholangiocarcinoma, 3 cases of ampullary carcinoma and 4 cases of gallbladder carcinoma that infiltrated the primary biliary tree. In two patients in which the cytology of pre-stenotic bile resulted non diagnostic for the absence of cells, the post-stenotic bile after dilatation allowed to make diagnosis of malignancy. The sensibility was low (27%) but it reached 43.7% if calculated in patients with a specific diagnostic suspect. In this latter group, the negative predictive value reached 28%, with 54% of accuracy. Conversely, the cytological exam of the bile was highly specific (100%) therefore, when positive, it allowed us to do a specific diagnosis (positive predictable value 100%).

These data are reported in Table 1. The statistical analysis of our data was done using chi-square test, and allowed us to conclude that bile cytology exam, if diagnostic, is significantly valid in identifying carcinoma of the pancreatobiliary tract ($p < 0.05$), instead, considering the high rate of non diagnostic samples its meaning is limited ($p = 0.09$).

Discussion

Our experience was in agreement with previous report were a lot of biliary strictures seen with radiological imaging and initially considered benign, later revealed to be malignant: e.g., proximal choledochal stricture from Mirizzi's Syndrome can be confused with cholangiocarcinoma (1), hilar stricture due to sclerosing cholangitis can be confused with cholangiocarcinoma, and a distal choledochal stricture due to chronic pancreatitis can be confused with pancreatic carcinoma (2). It is crucial in these cases to make the differential diagnosis and choose the appropriate treatment.

Exfoliative cytology of bile samples obtained during ERCP is the easiest and less invasive method to determine the stricture nature (Table 2), but due to its low sensibility, varying from 6 to 63%, it doesn't appear accurate to establish a definite diagnosis (3). The limited sensibility of this method is mainly determined by the lower or absence of cells in the sample; theoretically, the manipulation of the stricture could favour the epithelial exfoliation, increasing the number

TABLE 1 - PERSONAL EXPERIENCE: DIAGNOSTIC VERSUS DIAGNOSTIC AND NON DIAGNOSTIC REPORTS.

	Diagnostic	Diagnostic and non diagnostic
Sensibility	43,7%	27%
Specificity	100%	100%
Positive predictive value	100%	100%
Negative predictive value	28%	24%
Accuracy	54%	32%

TABLE 2 - LITERATURE REVIEW OF BILE CYTOLOGY (modified from ref. 9).

Authors, year	Patients (n)	Sensibility (%)	Specificity (%)
Foutch, 1991	30	6	100
Davidson, 1992	62	30	100
Kurzawinski, 1993	47	33	100
Mohandas, 1994	49	63	100
Sugiyama, 1996	52	32	100
Lo, 1996	36*	19	100
Sciumè, 2005	40	43	100
Total (mean)	316	32	100

* biliary stricture was dilated up to 10 Fr before doing withdrawal of bile for cytology.

of cells in the bile withdrawn after dilatation of the stricture and therefore the diagnostic sensibility.

Mohandas et al. affirm that the stricture dilatation before the withdrawal increases the diagnostic sensibility and accuracy of the cytological exam; in their experience, indeed, only 27% of the pre-stenotic bile cytology exams resulted positive for malignant neoplasm, instead, in the same patients, the post-stricture bile cytology exam was able to do diagnosis of malignant tumour in 67% of the cases ($p < 0.03$) (4). In another experience the sensibility of cytological exam withdrawn after stricture dilatation reached 50% (5). This data confirms the hypothesis that traumatism on the lining cells of the biliary tree with dilatation of stricture increases the number of exfoliated cells in the bile. Instead, analogous study demonstrated that the sensibility of pre-stenotic bile reaches 34% while it is lower in samples of bile taken after dilatation (31%) and the difference is not statistically significant ($p < 0.56$) (6).

The sensibility and accuracy of the method are greatly influenced by both the experience of the pathologist in assaying the slides and the collaboration of a multidisciplinary équipe. The manoeuvres during ERCP can alter the lining epithelium of the biliary

tract and if the pathologist is not notified, the accuracy of the exam is reduced with probability to fail the diagnosis (7).

The level of the stricture is another important variable that influences the accuracy of the cytological exam: as reported by Mansfield's group (8), the sensitivity of this method is higher for cholangiocarcinoma rather than for cephalopancreatic tumours (9), probably due to more cellularity in the sample.

Conclusion

Patients with obstructive jaundice due to biliary stricture and with malignancy suspect, based on the anamnestic-clinical evaluation and imaging (abdominal ultrasonography, TC), need to be confirmed by

histo-cytological exam. In our opinion ERCP is a safe method to withdraw a sample of bile for cytology, without increasing the morbidity of the exam and allows to a diagnostic orientation in about 75% of the patients. Bile withdrawn after dilatation of stricture allows to reach more sensitive and accurate data. In case of negative results, it does not allow to exclude a malignant disease, however, if positive it is considered diagnostic (positive predictive value 100%).

In all patients with stricture and suspect of malignancy, if bile cytology is done routinely it could be useful to make the diagnosis.

The multidisciplinary treatment of malignant biliary stricture necessitates a wide collaboration of gastroenterologist, radiologist, endoscopist, surgeons, pathologist in order to optimize the quality and timing of the treatment.

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