RESEARCH COMMUNICATION

Biliary Brush Cytology in the Assessment of Biliary Strictures at a Tertiary Center in Iran

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Abstract

Background: Confirmation of cholangiocarcinoma and other malignant bile duct stenosis is challenging. The aim of the current study was to assess the accuracy of brush cytology for diagnosis of malignant biliary strictures. Methods: 105 patients with hepatic biliary strictures undergoing ERCP were included in this study. Prospectively collected data included symptoms, results of biochemical testing and imaging procedures, as well as details of ERCP. Exclusion criteria were: 1) strictures that would not permit passage of guidewire and brush accession; and 2) post-operative strictures. Brushings of the bile duct strictures were performed. All patients were followed for at least 6 months. The final diagnosis was confirmed following surgery, histopathological diagnosis of the lesion, radiological infiltration of adjacent organs or metastases, or after at least a 6-month follow-up. Results: 88 brush samples from 88 patients were of appropriate quality. The overall diagnostic sensitivity and specificity for malignant nature of biliary strictures were 40.7% and 100%, respectively. The sensitivity was 66.6 % for ampullary carcinomas, 36.3% for pancreatic cancer and 32.5% for cholangiocarcinomas. Conclusions: Despite the low sensitivity, due to the relative ease and safety, brush cytology should remain the first choice for diagnosis of causes of biliary strictures.

Key words: Biliary tract cancer - biliary brush cytology - biliary strictures - bile duct stenosis

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Introduction

Cytological sampling is best performed by brushing the bile duct stricture (biliary stricture) during ERCP or percutaneous transhepatic cholangiography (PTC). Under optimal conditions and using a variety of techniques, cytology sampling can provide a diagnosis in 75% and 50% of cholangiocarcinomas and of pancreatic carcinomas, respectively. The results in practice, however, are more disappointing (Mansfield et al., 1997).

Cytological brushing of bile duct strictures (biliary strictures) is usually performed with wire guidance across the stricture. A plastic brush collects the cytological specimen from the lining of the bile duct during an ERCP. There is little morbidity associated with brushing of the bile duct (Kipp et al., 2004). Histological sampling of a bile duct stricture is performed with an unguided biopsy forceps. This technique is particularly effective for exophytic lesions. The diagnostic specificity of biliary brush cytology is very high and few false positive diagnoses have been reported. The major limitation of the technique has been the relatively modest diagnostic sensitivity recorded in most studies to date.

Brush cytology during the endoscopic retrograde cholangiopancreatography (ERCP) is the most popular method for definite diagnosis of the nature of biliary strictures. Since its introduction, many studies have shown brush cytology during ERCP is not only a simple and useful diagnostic method without increasing the rate of complications and but also has potential of obtaining definitive diagnosis as well as aiding in further patient management. Its specificity is remarkably high but the main complaint about the method is its low sensitivity for the diagnosis of malignancy. Most of the studies report sensitivity 30–54% for bile duct brushings and 26–88% for overall brushings of pancreatobiliary tract. Low sensitivity is commonly attributed to the high rate of false negative diagnosis. Sampling errors and technical faults such as air-drying artifacts have been reported as main reasons for high rate of false negatives.

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Better communication and team-work approach have a positive impact on sensitivity also. Kocjan et al. (1997) found four main categories of reasons responsible for low sensitivity of biliary brushings including sampling error, dysplasia, special tumor types and smear background.

Extrahepatic bile duct strictures is caused by a variety of malignant and benign disorders. Confirmation of cholangiocarcinoma and other malignant bile duct stenosis is challenging. To managing optimally such patients, it is often essential to determine the etiology of the stricture. Although the radiological findings and clinical presentations are helpful for differentiating malignant from benign lesions, a definitive diagnosis of malignancy can only be established histocytopathology. Biliary brush cytology has been the most commonly used and studied technique at ERCP.

Considering this method as a well- known technique with feasibility and relative accuracy, re-establishing this technique in Iran was our aim. The current study was conducted to re-assess the accuracy of brush cytology for diagnosis of malignant biliary strictures.

Materials and Methods

In a prospective study at Taleghani university hospital in Tehran from December 2008 until December 2009, 105 patients with biliary strictures have undergone ERCP and 88 brushing samples from 88 patients who had inclusion criteria (confirmed dominant biliary stricture and suspected pancreaticobiliary neoplasia) were gathered. Exclusion criteria were: 1) Strictures that would not permit passage of guidewire and brush accessory 2) Post-operative strictures. The study was approved by the research and ethic committees of the Shaheed Beheshti University of Medical Sciences. Baseline data were collected prospectively at the time of presentation by face to face interviewing or from the recorded files, including demographics, clinical manifestations and previous medical history, results of biochemical testing and imaging procedures, as well as details of ERCP. Brushings were performed only in the CBD stricture with the GRBH-230-3-3.5 (size of brush device) (Wilson-Cook Medical Inc., Winston-Salem, NC). In patients with visible ampullary tumor, biopsy was also taken. Six cytology smears from each brushing sample were stained with Giemsa and Papanicolaou for routine diagnostic cytology. Cytology samples were classified as: negative for malignancy, presence of atypical cells, insufficient material, suspicious for malignancy or positive for malignancy. For the purpose of statistical analysis, we grouped samples with insufficient material, negative for malignancy and atypical cells as negative, while specimens being suspicious or positive for malignancy were considered as positive group. The final diagnosis was confirmed following surgery, histopathological diagnosis of the lesion, radiological infiltration of adjacent organs or metastases, or after at least a 6-month follow-up. In the absence of a tissue diagnosis, a clinical diagnosis was established based on clinical symptom, the results of imaging studies prior to the ERCP procedure, and particularly, the course of the disease. In 17 patients, the cause of the stricture remained unclear because of insufficient data during follow-up, and these patients were excluded from further analysis. Hence, 88 brushings from 88 patients were included in this study. For statistical analysis, the comparison of averages between the quantitative variables was done by means of the Mann Whitney-U and percentages by Ch-square test. Diagnostic sensitivity was calculated as true positive (TP)/TP + false negative (FN) results. Specificity was true negative (TN)/TN + false positive (FP) results. Positive predictive value (PPV) was TP/TP + FP, and negative predictive value (NPV) was TN/TN + FN results. For the purposes of analysis, atypical reports were considered to be negative. We considered 2-tailed P values ≤ 0.05 to be statistically significant. Analyses were performed using SPSS statistical software (version 16.0) for Windows.

Results

Of 105 patients with biliary strictures having

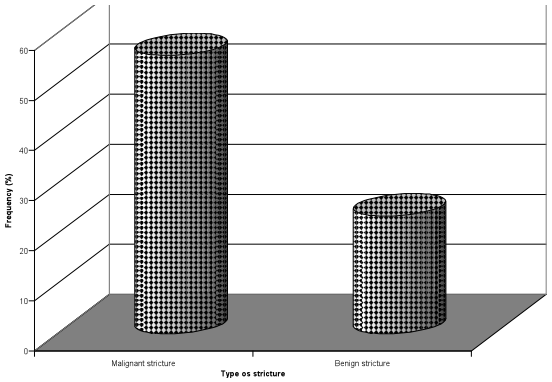

Figure 1. Main Benign and Malignancy Findings for Strictures of the Common Bile Duct

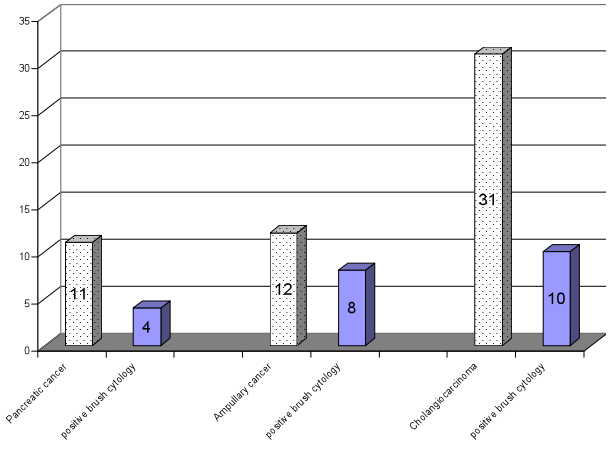

Figure 2. Distribution of the Positive Biliary Brush Cytology by Lesion Type

Table 1. Diagnostic Performance of Brush Biliary Cytology for Diagnosing Malignant Biliary Stricture

Malignancy	All	Pancreas	Ampulla	CC
Sensitivity	40.7%	36.3%	66.7%	32.5%
Specificity	100%	100%	100%	100%
Positive PV	100%	100%	100%	100%
Negative PV	51.5%	83%	89.5%	61.8%

CC, Cholangio-carcinoma; PV, predictive value

undergone ERCP, eighty-eight were included into the study with the mean age of 64.3 years and a male to female ratio 2.14. The final diagnosis in 54 patients (61.4%) was malignant strictures and in 51 patients was benign strictures. Two malignant and benign groups were nearly similar in terms of gender and mean age. Totally, common bile duct malignancies were detected in 56.8% of study participants, while common hepatic duct malignancies were revealed in 43.2% of them. No significant difference was found in the appearance of the CBD strictures in malignant group versus benign group (44.4% versus 76.5%, p = 0.128). However, stricture of common hepatic duct was slightly more common in the malignant group (55.6% versus 23.5%, p = 0.056) (Figure 1).

The most common bile duct malignancy was cholangiocarcinoma that was reported in 58.0% of patients, followed by ampullary carcinoma (22.0%) and pancreatic head adenocarcinoma (20.0%). Our study showed that the positive biliary brush cytology was detected in 4 out of 11 patients with pancreatic cancer, 8 out of 12 patients with ampullary cancer and 10 out of 31 patients with cholangiocarcinoma (Figure 2). Our study showed that the positive biliary brush cytology had a perfect specificity (100%), but partially low sensitivity for diagnosis of malignancies (ranged 32.5 – 66.7%) particularly for pancreatic cancer and cholangiocarcinoma (Table 1). Furthermore, this diagnostic tool had perfect positive predictive value for diagnosing malignancies (100%); however, its negative predictive value was low (range 51.5 – 89.5%).

Discussion

The examination of brush cytology specimens has become an established diagnostic technique in the investigation of patients with suspected pancreatic, bile duct, gallbladder, and ampullary tumors. We have reviewed 88 consecutive brush samples obtained from 88 patients and correlated the findings with pathological and clinical outcomes. According to our knowledge, this is the largest series of pancreatico–biliary brush cytology specimens yet reported from Iran.

We found that brush cytology accurately identified CBD neoplasm in 56.8% and CHD neoplasm in 43.2% in our series, with a similar result to the most early and smaller studies reviewed by Kurzawinski (1993)or by Foutch (1994). Other more recent studies have reported somewhat lower diagnostic sensitivities ranging from 35% up to 48% (Lee et al., 1995; Ponchon et al., 1995; Kocjan and Smith, 1997; Sturm et al., 1999; Logrono et al., 2000; Štoos-Veić et al., 2010).

There are several possible explanations for the limited sensitivity of brush cytology in assessing pancreas and biliary carcinoma but these can be broadly separated into sampling and interpretation errors. The former may occur when tumors at these sites show a predominantly submucosal spread, with limited or absent surface epithelial abnormality (Sawada et al., 1989; Kurzawinski et al.,, 1993; Foutch, 1994; de Peralta-Venturina et al., 1996; McGuire et al., 1996). Similarly, strictures might be caused by external compression—for example, by lymph node metastasis—without directly involving the ductal epithelium.

The site of the tumor might also be important. Several studies have shown that diagnostic accuracy is the greatest for ampullary neoplasms, is intermediate for cholangiocarcinoma, and is the least for pancreatic carcinoma, particularly for tumors in the pancreatic tail (Kurzawinski et al., 1993; Foutch, 1994). However, we were unable to confirm this finding in our series. Interpretation errors are more likely to occur in well differentiated carcinomas with minimal cytological abnormality, or in specific tumor subtypes such as papillary or mucinous carcinomas not being recognized by pathologists (Mansfield et al., 1997). Kocjan and Smith (1997) re-examined cytological preparations from 20 confirmed false negative cases and found eight samples with features of carcinoma or dysplasia. A similar review by Logrono and colleagues (2000) found that interpretation and technical errors accounted for 12 of 36 false negative cyto-diagnoses and the remainder was the result of sampling error. These studies suggest that a considerable number of false negative errors is related to cytological underscoring and nowadays, the ancillary techniques based on tumour biology, such as the identification of p53 immunoreactivity or K-ras mutations can enhance diagnostic sensitivity in morphologically negative or equivocal cases (van Es et al., 1995; Ishimaru et al., 1996; Iwao et al., 1998; Sturm et al., 1999).

Previous studies have shown that a diagnosis of carcinoma on brush cytology is highly reliable and many have reported 100% diagnostic specificity that was similar to our report. On review, it was felt that the cytological appearances in each case should have been regarded as equivocal because of the degenerative changes in all specimens and the relatively scant atypical epithelial cells in two. False positive pancreatico– biliary brush cytology diagnoses have previously occurred as a result of the misinterpretation of low grade dysplasia, reactive papillary changes with epithelial atypia, intestinal metaplasia of biliary epithelium, and the effects of previous bile duct stenting (Rupp et al., 1990; de Peralta-Venturina et al., 1996). Sturm et al. (1999) also reported two false positive cytological diagnoses

among 74 patients with benign biliary strictures. Both patients were thought to have postsurgical bile duct stenoses and, interestingly, K-ras mutations were also identified in each case.

However, no patient had evidence of malignancy on clinical follow up. A further example of cytological misdiagnosis was described by Desa et al. (1991), who reported a case of pancreatic duct hyperplasia in which cytology had been reported as a highly suspicious carcinoma. Thus, It would appear from some recent large studies that atypical but reactive epithelial changes may closely mimic malignancy in occasional pancreatico–biliary brush cytology specimens.

There are many new methods for evaluating the pancreatico-biliary stricture such as EUS-guided FNA or spyglass cholangioscopy. These new technologies are not only expensive but also user-dependent devices and they are neither applicable nor present in every ERCP room particularly in developing countries. Easy feasibility, low cost, low complication rate and high specificity make brush cytology still essential as a baseline investigational procedure.

In conclusion, brush cytology, in conjunction with other clinical and radiological investigations, is a useful technique in the assessment of patients with suspected pancreatico–biliary neoplasia.

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