Correlation of endoscopic brush cytology with biopsy in diagnosis of upper gastrointestinal neoplasms

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ABSTRACT

Neoplasms of upper gastrointestinal tract, especially malignancy, are one of the leading causes of death worldwide. The advent of endoscopy has greatly facilitated the detection and diagnosis of gastrointestinal lesions. Although it has been shown that the combined use of cytology and biopsy renders the highest probability of defecting malignancy, the merit of routine brush cytology has been questioned since it appears to duplicate biopsy. This study is undertaken to correlate the findings of brush cytology with tissue biopsy and the feasibility of the procedure as an adjunct in diagnosis of upper gastrointestinal tract neoplasms. Seventy-five patients with upper gastrointestinal tract symptoms were subjected to endoscopy in a period of two years. Brushing was done before the biopsy was taken from the suspected lesions and cytological findings were compared with that of biopsy. Of the 75 cases, brush cytology was positive for malignancy in 65 cases (86.66%) and biopsy was positive in 58 cases (77.33%); the sensitivity of the study was 98.03%. Thus, brush cytology is a useful adjunct to biopsy in the diagnosis of upper gastrointestinal tract malignancy. With the inclusion of a "suspicious" category in the reporting of the smears, malignancy can be detected early, and if possible, patient management can be altered.

KEY WORDS: Brush cytology, endoscopy, upper gastrointestinal neoplasm

INTRODUCTION

Upper gastrointestinal tract is a common site for neoplasms, especially malignant tumors. Worldwide, gastric adenocarcinoma is the second most common cancer and carcinoma esophagus is the sixth leading cause of death.[1,2] In India, according to the National Cancer Registry, esophageal and gastric cancers are the most common cancers found in men, while esophageal cancer ranks third among women after the carcinoma of breast and cervix.[3] Early detection of malignancy greatly improves the survival rate of the patients. The 5-year survival rate of early esophageal cancer is 83.5% and early gastric cancer is more than 90%.[4]

Over the past 25 years, there has been a remarkable progress in the various techniques used in the diagnosis of gastrointestinal cancer. The advent of endoscopy and endoscopic biopsy has greatly facilitated the detection and diagnosis of gastrointestinal lesions. However, the diagnostic value of cytology has been less recognized in the evaluation of malignant lesions.

Various techniques for the collection of cytological samples have been described.[5] Endoscopic direct vision brush cytology is one among them. In 1964, Kameva *et al.*[6] introduced brushing cytology under direct vision using fiberoptic gastroscopy. This technique retrieves epithelial cells from a larger surface area of mucosa than that in a tissue biopsy. As malignant cells posses a lower level of intercellular cohesion than normal cells, brushing can selectively sample these dyshesive cells. This procedure is noninvasive, cost effective and has a rapid turn over time.

The use of cytology in addition to biopsy still remains controversial, as it appears to duplicate biopsy. Some of the studies have shown increased diagnostic accuracy with combined use of biopsy and cytology.[7,8] This study is undertaken to correlate endoscopic brush cytology with tissue biopsy of upper gastrointestinal neoplasms and to evaluate the utility of brush cytology in the diagnosis of upper gastrointestinal neoplasms, as an alternative to biopsy that is an invasive technique.

MATERIALS AND METHODS

Patients having upper gastrointestinal symptoms such as dysphagia, vomiting retrosternal pain, anorexia, loss of weight and mass abdomen were subjected to endoscopy. Endoscopy was done by using flexible video endoscope (Olympus 130 series). On endoscopy, patients with visible mucosal lesions such as ulcer, polypoid or ulcerative growth in the upper GIT were included in the study during a period of 2 years.

After visual examination of the lesion, a cytologic brush, which is made up of small nylon bristles at the tip with an outer protective sheath, is introduced through a separate channel in the endoscope. The brush is advanced up to the lesion and the exfoliated cells are obtained by leading the brush several times across the lesion until mucosal bleeding is observed. The brush is then withdrawn into its sheath and removed.

Six smears were made by directly smearing the brush onto a slide. Four slides were fixed with a spray fixative containing 95% ethyl alcohol in carbowax. These slides were stained by haematoxylin and eosin and Papanicolaou stain. Two slides were air-dried and stained with May-GrunWald-Giemsa stain. After brushing, multiple biopsies were taken from the surface and margins of the suspicious lesion. The tissue fragments were fixed in 10% buffered formalin and processed routinely. Histological sections were routinely stained by haematoxylin and eosin method. Special stains for demonstration of mucin were done with Periodic Acid-Schiff when required.

The cytological and histopathological interpretations were derived according to WHO classification and criteria proposed by Takeda *et al.*[9] and Shu.[10] Smears were interpreted as negative for malignancy, suspicious for malignancy and positive for malignancy. For the purpose of statistical analysis, those smears reported as suspicious for malignancy with endoscopy showing frank growth were included in the positive group. False positive cytology reports were defined as malignant smears in the presence of a negative biopsy.

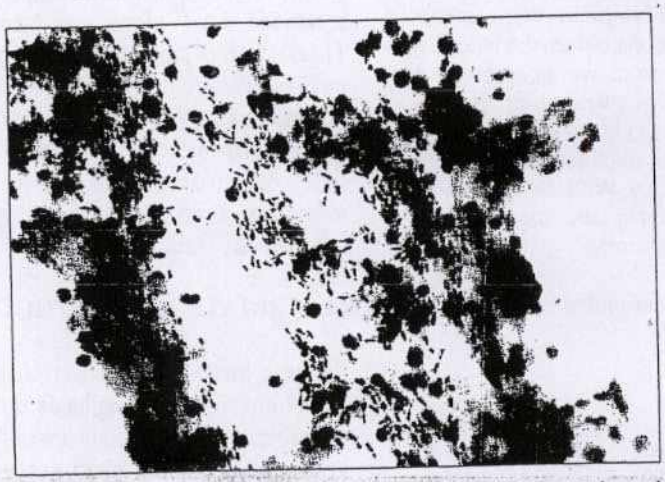

Figure 1: Smear showing malignant cells with candida in esophageal smear (H&E, x400)

RESULTS

A total of 75 patients presented with upper gastrointestinal tract symptoms and lesions suspicious of malignancy on endoscopy. The age of the patients ranged from 25–80 years. The highest number of patients was seen in the age group of 51–60 years. There were 48 (64%) males and 27 (36%) females. The male:female ratio was 1.7:1. Abdominal pain was the commonest symptom found in 29 patients (38.66%), followed by dysphagia in 27 patients (34.61%). Majority of the patients (97%) were nonvegetarians, and their diet included hot and spicy foods.

On endoscopy, 23 cases (30.66%) showed esophageal lesions, 48 cases (64%) showed gastric lesions and 4 cases (5.33%) showed duodenal lesions. In the esophagus, 22 cases (95.65%) showed a growth and one (4.34%) showed an ulcer. In the stomach, 37 (77.08%) cases showed a growth and 11 (22.9%) cases showed an ulcer. In the duodenum, all 4 cases had a growth.

On cytology, smears were cellular in 62 (82.66%) cases and scanty in 13 (17.33%) cases. Smears were positive for malignancy in 51 cases, suspicious for malignancy in 14 cases and negative in 10 cases.

Esophagus

The obtained brushing smears showed 14 (60.86%) positive cases. 8 (34.78%) cases were suspicious and 1 case (4.34%) was negative for malignancy. Two smears showed yeast forms of candida along with malignant cells as shown in Figure 1. Smears showed inflammatory background in 7 (30.43%) cases.

Biopsy of the lesions showed 18 (78.26%) positive cases, 2 (8.19%) atypical cases and 3 (13.04%) negative cases. Out of the 18 positive cases on biopsy, 16 (88.88%) were squamous cell carcinoma, one was adenocarcinoma (5.55%) and one, adenosquamous carcinoma (5.55%). Squamous cell carcinoma was well differentiated in 4 cases (23.52%), moderately differentiated in 11 cases (64.7%) and poorly differentiated in one case (5.88%).

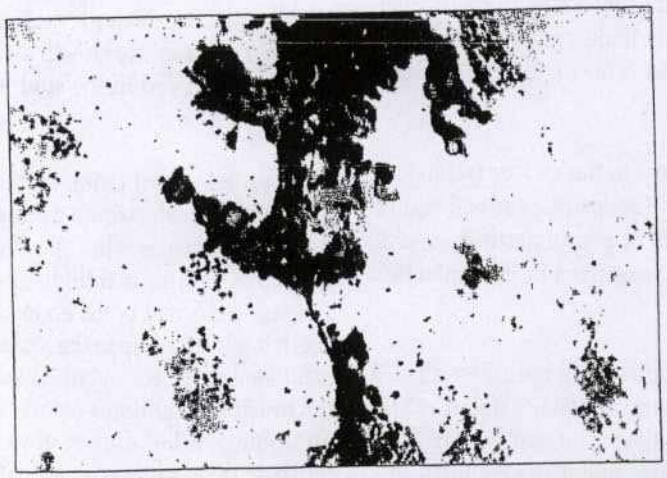

Figure 2: Smear from stomach showing clusters of malignant cells with frayed margins (H&E, x100)

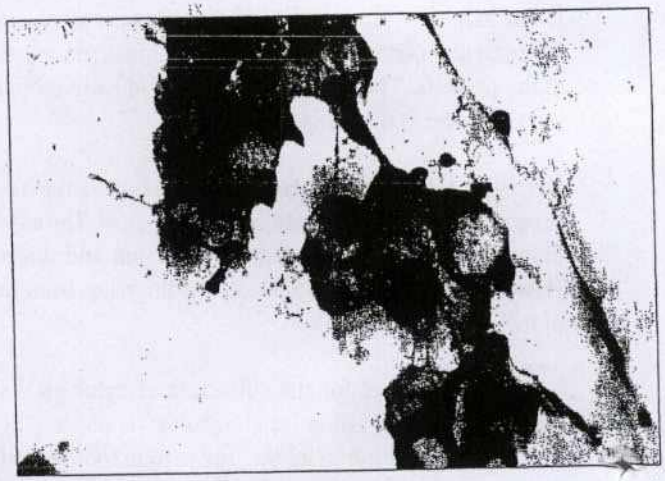

Figure 3: Smear showing signet ring adenocarcinoma from stomach (Pap, x400)

Cytology and biopsy were positive in 14 cases and negative in one case. There were 8 suspicious smears of which biopsy showed 1 negative, 1 inflammatory, 2 atypical and 4 positive cases. The correlation of these cases is given in Table 1.

Stomach

Majority of the lesions were found in the antrum 32 (66.66%), 13 (27.08%) in the body, and 3 (6.25%) in the fundus. In these cases, 4 of them showed lesions extending from the stomach to the esophagus.

Brushing smears were positive in 35 cases (72.91%), suspicious in 4 cases (8.33%) and negative in 9 (18.75%) cases. Smears showed an inflammatory background in 18 (37.5%) and were mucinous in 6 (12.5%); 11 cases (22.91%) were mucinous and also showed inflammatory background. Signet ring cells were observed in 3 cases. They were further demonstrated by Periodic acid-Schiff stain. Figures 2 and 3 show smears from adenocarcinoma arranged in small clusters with irregular frayed margins along with signet cells.

Out of 35 positive smears, all were confirmed by biopsy. Out of 9 negative smears, one false negative case was observed on biopsy. Of the 4 suspicious smears, 2 showed malignancy in biopsy. The correlation is shown in Table 2.

Duodenum

Smears were positive in 2 (50%) cases and suspicious in 2 cases (50%). Biopsy was positive in 3 cases and negative in 1 case. The correlation is given in Table 3.

DISCUSSION

The primary role of gastrointestinal tract cytology is cancer detection. Its potential, by using gastric washings, has been described even before the advent of endoscopes. Endoscopy allows the visualization of mucosal lesions, and at the same time, it permits the sampling of cytology and biopsy for a definitive diagnosis. In Kolar district of Karnataka state, carcinoma of the stomach is the third common cancer, followed by carcinoma of the esophagus in men. However, in women, carcinoma of the esophagus is the fifth common leading cancer with carcinoma of the stomach being only 1.5%.[3]

During the two-year study period, 75 cases were included in which both cytology and biopsy were performed. Majority of the patients were in the age group of 51–60 years, with 48 males (64%) and 27 females (36%). Brush cytology was positive for malignancy in 65 cases (86.66%), negative in 10 cases. Biopsy was positive in 58 cases (77.33%), inflammatory or dysplastic in 7 cases and negative in 10 cases.

The overall sensitivity of brush cytology in this study was 98.03% and the specificity was 81.11%. The sensitivity of this study is comparable to that in similar studies conducted earlier, as shown in Table 4. Significant discrepancies (suspicious cytology versus negative biopsy) were noted in 5 patients who had an exophytic growth (3 in the esophagus and 2 in the stomach). Since there was a strong clinical suspicion, these cases were taken for repeat endoscopy and biopsy and were found to be positive for malignancy.

There was one false negative case that was because of scanty cell yield. A negative biopsy can also be due to the necrotic surface of the tumor or a fibrotic reaction caused by the tumor itself. Two false positive cases were obtained, and these cases were found to contain an ulcer on endoscopy. Regenerating epithelium from the ulcer edge shows marked nuclear hyperchromasia on cytology, and this could be the reason for the false positive case. In a study of 160 patients by Cook *et al.*, 5 false positive cases (3.1%) were obtained. Ricardo *et al.*[11] also obtained 5 false positive cases (1.3%) in their study. This has been attributed to cells regenerating from benign gastric ulcers, because morphologically the distinction between severe benign atypia and malignancy is difficult. In a study, Wang *et al.*[12] indicated that combining cytology with biopsy increases the false positive rates; however, it also increases the sensitivity of the procedure.

The sensitivity of this study is 98%, and this emphasizes the usefulness of brush cytology as a screening procedure. Although

Table 1: Comparison of biopsy and cytology in lesions of esophagus

Cytology	Histopathology			
	Negative	Inflammatory	Atypical	Positive
Negative (01)	01	-	-	-
Suspicious (08)	01	01	02	04
Positive (14)	-	-	-	14
Total (23)	02	01	02	18

Table 2: Comparison of biopsy and cytology in lesions of stomach

Cytology	Histopathology			
	Negative	Inflammatory	Atypical	Positive
Negative (09)	01	07	-	01
Suspicious (04)	01	01	-	02
Positive (35)		-	-	35
Total (48)	02	08	-	38

Table 3: Comparison of biopsy and cytology in lesions of duodenum

Cytology	Histopathology			
	Negative	Inflammatory	Atypical	Positive
Negative (0)	-	-	-	-
Suspicious (2)	1	-	-	1
Positive (2)	-	-	-	2
Total (4)	1	-	-	3

Table 4: Comparison of diagnostic sensitivity in various studies.[12]

Authors	Diagnostic sensitivity (%)
Cook *et al.*[13]	91
Donoghue *et al.*[7]	97
Qizilbash *et al.*[17]	95
Bita *et al.*[18]	100
Present study	98

definitive surgical treatment is rarely based on a positive or suspicious smear, the inclusion of the "suspicious" category alerts the clinician about the possibility of malignancy. Patient management is altered in these situations so that a repeat endoscopy and biopsy becomes mandatory.

Although multiple biopsies also increase the areas sampled, cytologic brushing seems to have the advantage of covering a relatively large area and tendency to selectively collect loose dyshesive cells. This may explain the superiority of cytology in detecting malignancy in the initial procedure itself. According to Cook *et al.*,[13] brush cytology could be reserved for situations in which difficulty is encountered in obtaining adequate tissue for histological examination. However, in a study, Donoghue *et al.*[7] found that with the additional use of cytology, the sensitivity increased from 88.3% to 97.5%. Therefore, cytology is a useful adjunct in patients with suspicious mucosal lesions.

We had 2 cases of fungal infection in esophagus identified both on cytology and biopsy. Fungal infection coexisting with cancer has been well documented and is because of the immunocompromised state of the patients. Shroff and Nanivadekar[14] also reported similar findings in their study. In the present study, there were 2 cases of multicentric carcinoma esophagus (8.5%). The reported rate of multicentric carcinoma esophagus varied between 8% and 26%. Pesko[15] *et al.* reported an incidence of 31%.

The limitation of cytology is its inability to distinguish between dysplasia/carcinoma in situ and invasive carcinoma. A tumor diathesis and a high cellularity in a smear may indicate invasion, but not with certainty. Another issue is whether the brushing should be performed before or after biopsies. Some of the authors prefer to perform the brushing after biopsy believing that it might decrease the yield of biopsy. However, studies have shown that the accuracy of brushing cytology in patients with carcinoma was significantly higher when the brushing was performed before biopsy than after biopsy.[16] In the present study, brushing was performed before biopsy; although some smears were reported to be hypocellular, no smears were categorized as unsatisfactory.

CONCLUSION

Although biopsy is used as a routine procedure in diagnosis of gastrointestinal tract lesions, cytology is useful because it is inexpensive, gives a rapid diagnosis and offers minimal discomfort to the patient. Cytology can be used as an adjunct to biopsy in the diagnosis of upper GIT neoplasms. With increased experience and adherence to strict criteria for malignancy and by using a "suspicious" category, malignancy can be effectively detected and treated.

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