Efficacy of Bronchial Washing and Brushing Cytology in the Diagnosis of Non-Neoplastic Lung Diseases

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Received: 26 Aug. 2016; Accepted: 14 Apr. 2017

Abstract- Flexible fiberoptic bronchoscopy is often the initial technique for diagnosis of lung and bronchial tumors. Many studies have shown the high accuracy rate of bronchial washing and brushing cytology in the evaluation of neoplastic and non-neoplastic bronchopulmonary lesions. The aim of this study is to emphasize the value of the bronchial cytologic findings for diagnosis of non-neoplastic bronchopulmonary lesions. In a cross-sectional study, we retrieved all cases with bronchial washing and brushing cytology from 21 Mach 2014 to 21 December 2015. The slides of 100 patients with negative cytological reports were reviewed and concomitantly correlated with history, physical examination, clinical and pathologic documents. The cases with insufficient clinical and pathological diagnostic documents were rejected. The results classified in subgroups according to final diagnosis and cytological findings were discussed. We evaluated 100 cases that were previously had negative cytological reports.60 cases were male, and 40 cases were female with male to female ratio: 6/4. The age range was between 21 to 88 with the mean age of 57 years. Regarding lung cancer, 31% of cases were false negative. Causes of these falsely negative reports were been errors in screening, low cellularity, unsatisfactory smears and poor fixation. 23% were known cases of tuberculosis with some cytological findings including inflammation, necrotic calcified deposits, multinucleated giant cell and reserve cell hyperplasia. 19% were pneumonic patients with smears demonstrating inflammation, curschmann's spiral and reserve cell hyperplasia. Other non-neoplastic cases included in this study were asthma, granulomatous inflammation, rheumatoid arthritis, sarcoidosis, Wegener, SLE, heart failure, hydatid cyst, interstitial lung disease, and end stage renal disease. Cytological specimens from patients underwent bronchoscopic washing and brushing should be carefully examined. In situations with negative cytologic results, correlation with history, imaging and biopsy specimen is mandatory.

Acta Med Iran 2017;55(10):636-641.

Keywords: Bronchial washing and brushing; Cytology

Introduction

Bronchogenic carcinoma is one of the most frequent malignancies in the industrialized countries and the leading cause of cancer death in the world especially in males, but the incidence is on the rise in females (1,2).

For early diagnosis different diagnostic modalities are available, including sputum, washing, brushing cytology, biopsy and fine needle aspiration (3). Most of the lung cancers are un-resectable as patients present in advanced stages, and so respiratory tract cytology is frequently a primary diagnostic method performed in patients suspected of lung cancer or with respiratory symptoms (4,5).

Newly developed radiologic intervention and especially fiberoptic bronchoscopy and more use of fine needle aspiration (FNA) have high impacts on respiratory cytology practice (1,2,6).

Prior to the introduction of fiberoptic bronchoscopy in 1969 access to the tracheobronchial tree was limited to proximal large airways, but this technique revolutionized respiratory cytology as methods like bronchial brushing, washing and broncho-alveolar lavage (BAL) became more easily accessible and popular (1,2).

The sensitivity of bronchial washing and brushings are about 90% for central lesions and about 70% for peripheral lesions (1). Bronchial cytology also has a high accuracy rate for tumor subtyping especially for differentiating between small cell and no-small cell

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types (1,2,7,8). But while diagnosis of lung cancer has been the major focus of respiratory cytology, it is also variable useful in the investigation and management of a variety of benign and non-neoplastic lung lesions (1,2,9,10). Nevertheless, we have limited experience in the application of this technique in the management of non-neoplastic diseases of the lung.

So, in this study, we reviewed the cytologic findings in the patients with negative bronchial cytology report to illustrate the cytologic features of several non-neoplastic bronchopulmonary lesions.

Materials and Methods

To evaluate the value of bronchial cytology in the diagnosis of non-neoplastic lung diseases, in a retrospective study, all cytologic reports of bronchial washings and brushings in Faghihi Hospital during the time of 21 March 2014 to 21 December 2015 were reviewed. The reports with negative results were selected. Then we searched for patients that had definite diagnosis by history, physical examination, clinical and pathologic documents.

We didn't consider the cases without a definite clinical and pathological diagnostic document. Then we screened the slides of the 100 selected patients and searched for specific cytologic findings of lung diseases.

Specimens of bronchial washing sent to this laboratory are processed as below:

A: At first the specimens are centrifuged at 2500 g for 5 minutes.

B: At least 2 smears are prepared from the sediment and stained by PAP method.

The brushing specimens are immediately fixed with 70% ethanol by the pulmonologist and sent to the cytology laboratory where they are stained with PAP method

Results

One hundred cases were included in this study who had negative bronchial cytology report and definite clinical or pathologic diagnosis.60 cases were male, and 40 cases were female with male to female ratio of 6/4. The age range was between 21 to 88 years with the mean age of 57.05 years.

False negative cases

Thirty one of 100 cases (31%) were known cases of lung cancer (false negative cases). 25 cases were male, and 6 cases were female. 10 cases were squamous cell carcinoma, 4 cases were small cell carcinoma, 3 cases of adenocarcinoma and 2 cases were poorly differentiated non-small cell carcinoma and 2 cases were metastasis to lung. About the other 9 cases, we didn't have the pathologic reports, but they were definite cases of lung cancer.

Causes of falsely negative reports were:

- ✓ 8 cases were due to screening error and by reviewing these slides, we found single or clusters of malignant cells. Of these 8 cases, 2 of them were adenocarcinoma, 2 cases were squamous cell carcinoma, and one of them was small cell carcinoma. One case was metastatic breast cancer and 2 cases were poorly differentiated non-small cell carcinoma.
- ✓ 3 cases were due to poor fixation.
- ✓ 4 cases had unsatisfactory smears. These smears were considered unsatisfactory because of having no bronchial epithelial cells/alveolar macrophages or obscured cellular morphology due to excessive hemorrhage.
- ✓ 5 cases were low cellular
- ✓ Some atypical cells were found in 3 smears, but they were not definitely malignant.
- ✓ In the remaining 8 smears that were adequate and satisfactory, there was not cytologic sign of malignancy.

Cases of tuberculosis

Twenty three of 100 smears were of tuberculosis patients that 16 of them show acute and chronic inflammation. 6 smears showed caseation and calcification, 4 of them had degenerated back ground. 4 cases had giant cells in smear, and 4 cases showed reserve cell hyperplasia and the other 2 cases showed normal bronchial cytologic findings.

Four cases in this study had pathologic report of chronic granulomatous inflammation and negative PCR for TB bacilli that one of them in bronchial cytology showed caseation and calcification. 2 of them showed only mild inflammation. One case showed increased number of macrophages and the other one had no specific finding.

Pneumonia cases

All 19 pneumonic patients in this study had severe acute and chronic inflammation in their bronchial smears, but in one of them we find Curschmann's spiral, in one another reserve cell hyperplasia, and one case showed calcified necrotic material.

Rheumatoid arthritis (RA) cases

We had 3 cases of rheumatoid arthritis that only in one case showed necrotic calcified deposits.

Sarcoidosis cases

Out of 3 cases of sarcoidosis, 2 of them showed reserve cell hyperplasia and one of them had multinucleated giant cells in bronchial cytology smears.

Asthma cases

All asthmatic patients had mucin back ground and mucus threads in their bronchial cytology smears, and 3 of them had curshmann's spiral, and one of them had reserve cell hyperplasia.

Other cases

The single case of Wegener's in this study showed multinucleated giant cells in bronchial cytology smears. We found 2 cases of lung hydatid cyst with smears demonstrating many macrophages, mucus threads, and inflammation. 2 cases of heart failure had no specific finding in their bronchial cytology smears. In bronchial cytology of a case of pulmonary emboli, necrotic background and inflammation were the only significant findings. We found curschmann's spiral in cytology of a patient with ESRD (end stage renal disease). The last 2 cases of interstitial lung diseases had normal bronchial cytology features.

Table 1. Distribution of various diagnosis of all cases

Total cases: 100	
Cancer	31%
Squamous cell carcinoma	10
Small cell carcinoma	4
Adenocarcinoma	3
Bronchoalveolar carcinoma	1
Poorly differentiated non-small cell carcinoma	2
Metastasis to lung	2
No tissue diagnosis	9
Tuberculosis	23%
Pneumonia	19%
Asthma	7%
Granulomatous inflammation in biopsy	4%
Sarcoidosis	3%
Rheumatoid arthritis	3%
Hydatid cyst	3%
Interstitial lung disease	2%
Heart failure	2%
Systemic lupus erythematosus	1%
Pulmonary emboli	1%
ESRD	1%

Table 2. Causes of false negative reports

	No of cases	Percentage
Inadequate screening	8	(25.8%)
No sign of malignancy in cytology	8	(25.8%)
Low cellularity	5	(16.1%)
Unsatisfactory specimen	4	(12.9%)
Poor fixation	3	(9.67%)
Some atypical cells were seen	3	(9.67%)
Total	31	100%

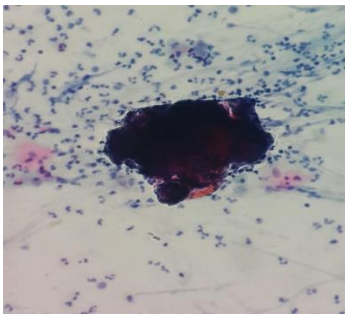

Figure 1. Necrotic calcified deposit in a tuberculosis patient, Pap stain X100

Figure 2. Curschman spiral in an asthmatic patient, Pap stain X100

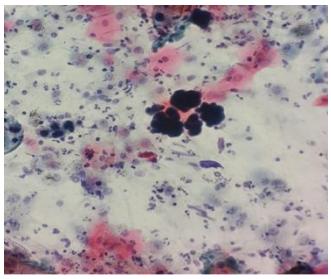

Figure 3. Cluster of malignant cells in a case of poorly differentiated squamous cell carcinoma, Pap stain X100

Discussion

Carcinoma of the lung is the leading cause of mortality in both sexes, so early diagnosis and treatment are very important. Fiberoptic bronchoscopy has been in regular use for investigating patients with suspected lung cancer for many years.

Nevertheless, there are few studies that have pointed on the diagnostic yield of bronchial cytology for evaluating the patients with non-neoplastic lung diseases. Shroff (11) followed 200 patients with chronic respiratory symptoms in 1985 in India and divided the bronchial brushing cytologic findings into 5 categories:

1. Positive smears (41%).
2. Smears with predominant chronic inflammatory features (10%).
3. Smears with acute inflammatory changes (15.5%).
4. Smears with normal cytologic features (30%).
5. Unsatisfactory specimens (24%).

He reported also the incidence of some findings like reserve-cell hyperplasia and squamous metaplasia in every group.

Similar observations were made by Choudhury *et al*., (2012), with a study on 35 cases in the department of pathology LMC, New Delhi (12).

Laucirica *et al*., (2007), focused on cytological features of several non-neoplastic occupational and environmental diseases and grouped them into 2 categories: reactive cellular changes and noncellular elements in a review article on 2007. They stated that squamous metaplasia and reserve cell hyperplasia are spectrum of reparative processes of respiratory epithelium that are commonly from chronic irritation by toxic effects of cigarette smoking and inflammatory processes such as sarcoidosis, tuberculosis, chronic bronchitis, organizing pneumonia or bronchiectasis. (13).

Idowu, and Powers (2010), on a review article on 2010 focuses on the cytological characteristics of main types of primary lung carcinoma and the challenging potential pitfalls in the evaluation of respiratory cytology specimens (3).

As with many other previous studies, Reddy *et al*., (2014), showed the high efficacy of bronchial wash and brush cytology in the diagnosis of lung cancers, and noted that these techniques could be used concurrently with bronchial biopsy whenever required (7).

Sarma *et al.,* (2013), reported the bronchial cytology with sensitivity of (89.96%) specificity (90.9%), positive predictive rate (96.3%), accuracy (90%), false negative rate (10.34%) and false positive rate (9.1) in the diagnosis lung cancers (6).

At first, the purpose of this study was to consider the bronchial cytologic findings in patients with benign diseases. So, we have just reviewed the negative reported smears, and surprisingly we found 31 cases of lung cancer that previously were reported negative.

Causes of false negative reports in this study can be classified as the followings:

Pulmonologist sampling and fixation

There was no cytological sign of malignancy in 8 cases out of 31 false negative patients (25%), and this may be due to peripheral lesions that couldn't be sampled. Low cellularity (16.1% of total false negatives) and unsatisfactory specimens (12.9%) are also included in this category. The cause of false negative result in 3 cases (9.67%) was poor fixation, especially in bronchial brushing specimens. So, most causes of errors contributed to sampling and fixation.

Cytotechnician and pathologist screening

We found 8 cases that overt malignant cells and clusters were missed because of improper screening and the paucity of malignant cells. Another reason may be due to the use of conventional methods of sample processing in spite of the fact that many studies have shown that thin prep is superior to cytospin for microscopic evaluation of non-gynecologic non-FNA specimens. Thin-prep demonstrated more uniform distribution of cells, with superior nuclear chromatin morphology, less cellular overlapping and background debris (14). The use of thin-prep method may also solve the problem of poor fixation because the amount of cell loss and cellular fixation may be dependent on the experience of preparation staff but the uniformity and simplicity of thin prep method reduce this dependence on operator skill.

Similar observations regarding the causes of false negatives were done by Nodit *et al*., (2005), (15) who had a detailed analysis to determine the causes of pulmonary cytology false negatives in 2005. They found 32 cases of false negatives composed of 13 cases with crush artifacts (cellular crushing and air drying), 11 cases with not recognized few malignant cells and no accessible tumor in 8 cases. So sampling issues had the major role of misdiagnosis in their study (97%). They recommended immediate interpretation and use of transmucosal FNA to reduce some causes of errors.

Feeley *et al*., (2006), (16) also searched for the causes of 57 false negative reported samples of bronchial washings and brushings. They noted that the majority were due to peripheral tumor location and specimen inadequacy, but malignant cells were missed in 5 cases that in most of them paucity of malignant cells was an explanation of failure. Recommendations for reducing the false negative rates in this study were improved communication with clinician regarding the cases in relation to specimen adequacy and FNA in cases with peripherally located the tumor in radiology.

The most frequent non-neoplastic cases in this study were tuberculosis, pneumonia, asthma, sarcoidosis, and RA. The most frequent findings in tuberculosis patients were secondary inflammation, reserve cell hyperplasia, and multinucleated giant cells. A surprising cytologic finding in tuberculosis cases was a necrotic calcified deposit that may be due to caseation, but we found similar deposits in the few cases of pneumonia, RA, SLE and pulmonary emboli. Increased mucus and curschmann's spiral were prevalent features of asthma patients.

Bhatia *et al*., (2008), noted in a review article that three types of reaction patterns seen in lung infections act as clues to the diagnosis :1- necrosis, 2-various types of inflammatory reactions, including suppurative and granulomatous inflammations, 3-epithelial cell changes including ciliocytophthoria, regenerative atypia, and nuclear inclusions or changes suggestive of viral infections. They noted also that when we see epithelioid cell granuloma with polymorphous exudates tuberculosis and fungal infections must be considered in the differential diagnosis and when the caseous necrosis is accompanied by epithelioid cell granulomas tuberculosis is a top differential diagnosis (17). In a new study by Tamura *et al*., (2014), they found that the existence of epithelioid cell granuloma in sputum cytology is rare and limited to pulmonary mycobacteriosis particularly tuberculosis (18). Das (2000) worked on FNA cytology in the diagnosis of tuberculous lesions and noted that epithelioid granuloma with necrosis is the most common findings in pulmonary tuberculosis (19), but other differential diagnoses should be considered in the presence of epithelioid cells ,multinucleated giant cells or necrotic material in the cytologic specimens, as these components can be seen in other lesions like sarcoidosis, leprosy, mycosis, silicon granulomatosis, These lesions can be distinguished from TB by clinic and ancillary techniques (19).

Cytological findings in patients with benign lung diseases are nonspecific, so the role of cytology for diagnosis of these lesions is limited. However, in the appropriate clinical and radiologic setting, the cytology can render valuable diagnostic information.

The important point of view is satisfactory technical preparation and staining, careful screening of all smears and use of new preparatory techniques, for decreasing the rate of errors.

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