Sputum Cytology – An Underutilized Diagnostic Tool: A Single Institute Experience

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Abstract: Objective: Sputum cytology is a valuable diagnostic tool which under underutilized in our clinical practice. The aim of this study is to report our experience utilizing this tool to diagnose various respiratory disorders and to report the utility and accuracy of this procedure in our institute. **Design:** A retrospective analysis of all sputum smears from Jan 1995 to December 2010. **Settings:** The Department of Pathology at King Abdulaziz University hospital Jeddah, Western region of Saudi Arabia. **Subjects and Methods:** All sputum cytology samples received at the Department of Pathology were reviewed. **Interventions:** Cytology smears, clinical history and surgical follow-ups were reviewed. **Main Outcome measures:** The data was analyzed to calculate sensitivity, specificity, and predictive values. **Results:** A total of 191 cases of sputum cytology were examined during this period and only 38 (20%) patients had a subsequent follow up biopsies. Cytology diagnosis was categorized (reporting system of our laboratory) as atypical in 4 cases, malignant in 5 cases, inflammatory in 17 cases, insufficient in 21 cases, and negative in 144 patients. The subsequent histological follow-up in 38 cases was categorized as malignant in 21cases, inflammatory /benign in 12 cases and negative in 5 cases. Cross-tabulating the cytology with surgical follow-up revealed 3 true-positive, one false-positive, 16 true-negative, and 15 false-negative cases. **Conclusion:** Sputum cytology showed high specificity (94%) and positive-predictive value (75%) and low sensitivity (16.7%) and a negative-predictive value (52%). The low sensitivity limited the sputum-cytology as a screening tool. But in patients suspected of having malignant lesions the high specificity of this tool can be utilized to get diagnosis before proceeding to invasive procedures.

1. Introduction

Lung cancer outcome has improved a lot by early screening and detection by multiple modern diagnostic techniques. The current the methodologies available that can be utilized in reaching a diagnosis of lung cancer are: sputum cytology; flexible bronchoscopy [FB]; and transthoracic needle aspiration (TTNA). Recently positron emission tomography (PET) scanning has emerged to help in achieving the diagnosis and staging of lung cancer as well [1].

In order to decide which specific diagnostic modality to be used effectively, it should fulfill two main criterions: the first criterion is that it should have maximum yield with regards to diagnosis and staging of the disease. Secondly it should be minimally invasive. The diagnostic modality should also take into account the patient clinical condition and the treatment plan which will be offered to them after the specific diagnosis [1].

Sputum cytology examination was widely used at the end of the 20th century for discovering lung cancer in high-risk patient at an early stage and it was viewed by clinicians as a simple, non-invasive, cheap investigation. Early reports on sputum cytology suggested that positive identification of lung cancer could be achieved in 57% to 66% of patients with a clinically obvious tumor [2].

Literature of Sputum cytology established that this non-invasive method is an acceptable method of establishing the diagnosis of cancer in suspected patients. Several studies identified that sensitivity of sputum cytology in diagnosing suspected lung lesion ranged from 0.42 to 0.97, while the specificity ranged from 0.68 to 1.0. These studies also showed that the pooled sensitivity of sputum cytology was 0.66, and the pooled specificity was 0.99 [1,3]. **Sing et al.** and **Rivera et al.** declared in their studies that sputum specimens are most valuable in the detection of early and peripheral carcinomas and that the diagnostic yield in lung carcinoma depends on the location of the tumor, the histological type and the stage [4,1].

Studies from National Cancer Institute (NCI) has reviewed the role of sputum cytology as a screening tool and has shown 85 to 90% 5-year survival rate in small number of patients with negative radiological examination for lung cancer and positive by sputum cytology alone. The most common histological type of carcinoma encountered in these studies was squamous cell carcinoma [5].

The diagnostic accuracy of sputum cytology also depends on the number of samples obtained, the preservation technique of the sample, the location of the tumor (central vs peripheral) and the size of the tumor. Patients yielding positive sputum cytology often

have: bloody sputum; low FEV1 values; large tumor volume (> 2.4 cm); centrally located tumors; and squamous cell histology [1].

2. Material and Methods

All consecutive sputum samples received at King Abdulaziz University Hospital, Department of Histopathology were reviewed over the period of fifteen years (from January 1st, 1995 to December 31st, 2010).

All the sputum cytology specimens in this study where collected and prepared in adherence (as much as possible) to the international guide lines for sputum cytology specimen collection and preparation.

A series of three (3) sputum specimens, one each day for three days, were collected as recommended by the university laboratory policy and procedure. Deep cough specimens were required if malignancy was suspected. Specimens are immediately processed to avoid cell degeneration and growth of contaminating micro-organisms. The gross/ physical specimen characteristics (volume in mL, gross appearance) were described and recorded in the final sputum cytology report (macroscopic section).

Pick-and-smear preparations were made from 'suspicious' areas of the specimen, which may appear as gray/white or blood-tinged mucus strands. Different areas of the specimen were sampled. Specimen was placed onto appropriately labeled frosted-end glass slides for direct smearing; the material was spread and manipulated between two opposing slides to produce a thin, mirror image, even layer of specimen on each slide

Four smears are prepared. Three smears are fixed immediately in 95% alcohol (or equivalent) and one smear is air-dried; three smears are stained with the Papanicolaou stain and one is stained with Diff-Quik. Mucoid specimens are treated with Mucolex solution (Shandon), equal volume of Mucolex solution is added to the specimen, mix then centrifuge.

Sputum specimens are regarding as being unsatisfactory when no pulmonary macrophages are identified. All stained slides are screened for abnormal findings. No radiological or demographic data was collected since it was beyond the scope of this study. A summary of the findings is prepared using current acceptable terminology based on established cytomorphologic criteria and adopted as protocol reporting system in our laboratory, and released on a standard report format.

A total of 191 sputum cytology cases were collected and categorized as: Atypical, Malignant, Inflammatory, Insufficient and Negative (Table 1). The records and the histopathological slides of 38 patients that had subsequent surgical follow up biopsies were retrieved and examined. The surgical histopathological categories were as follow: Malignant, Inflammatory and Negative (Table 2). Correlation of the sputum cytology and surgical biopsy was performed (Table 3), sensitivity, specificity, positive and negative predictive values were calculated.

3. Results

A total of 191 Sputum smear /cytology diagnosis were collected and categorized as atypical, malignant, inflammatory, insufficient and negative (Table 1). The detailed cytological diagnosis were: 4 cases atypical cells, 5 malignant cases of which 3 were adenocarcinoma, 1case non-small cell carcinoma and 1 case squamous cell carcinoma.. Inflammatory cases were 17 of which 8 cases were fungal infection (5 Candida, 2 aspergillus, 1 fungal hyphae unclassified), 4 cases of tuberculosis infection and 5 cases were only abundant inflammation. Insufficient or inadequate for diagnosis were 21 cases and negative for malignancy 144 cases.

The subsequent histological follow-up in 38 cases was categorized as malignant in 21 cases, inflammatory /benign in 12 cases and negative in 5 cases (Table 2). Of the 21 malignant cases in surgical follow-up, we identified 3cases of adenocarcinoma that were diagnosed on both surgical follow-up and cytology as adenocarcinom (true-positive), 3 cases were diagnosed as inflammatory/ benign on cytology while on surgical follow-up were malignant (false negative). 3 cases were insufficient for diagnosis, and 12 cases were diagnosed as negative for malignancy on cytology while were malignant on surgical follow-up biopsies (false negative) (Table 3). 16 cases were diagnosed as negative on both cytology and surgical follow-up (true negative). One case was diagnosed as positive on cytology but was negative on surgical follow-up (false positive). Excluding the 3 non-diagnostic cases(insufficient for diagnosis), there were 3 true-positive cases, 16 true-negative cases, one false-positive case and 15 false-negative cases. The sensitivity was 16.7%, specificity of 94%, positive predictive value of 75% and negative predictive value of 52%.

Table 1: Summary of sputum cytology diagnosis categories

Cytology Dx Categories	Count
Atypical	4
Malignant	5
Inflammatory	17
Insufficient	21
Negative	144
Grand Total	**191**

Table 2: Summary of surgical diagnosis categories

Surgical Dx Categories	Count
Malignant	21
Inflammatory	12
Negative	5
Grand Total	**38**

Table 3: Cytohistological correlation of sputum cytology and surgical biopsy follow-up.

Cytology Dx Category	Surgical Dx Categories			
	Inflammatory	Malignant	Negative	Total
Atypical		1		1
Malignant		2	1	3
Inflammatory		3	1	4
Insufficient		3		3
Negative	12	12	3	27
Grand Total	**12**	**21**	**5**	**38**

4. Discussion

An adequate sputum sample is composed of mucus and various types of respiratory cells that are cleared by the mucociliary apparatus and includes bronchial epithelial cells, few squamous cells and abundant alveolar macrophages. Before the development of fibreoptic bronchoscopy (FB), sputum cytology was the only alternative to thoracotomy for tissue diagnosis of many pulmonary neoplasms. At that time sputum was the most common respiratory tract specimen examined because it is relatively easy to collect and causes minimal discomfort to the patient. Unfortunately, utilization of sputum cytology as the mainstay in respiratory cytology has declined significantly probably due to the advent of bronchoscopy, tans thoracic imaging guided fine needle aspiration (FNA), trans-bronchial needle aspiration, EUS-guided FNA and due to the low-sensitivity of sputum cytology. **Kennedy et al.** underlined the valuable role of sputum cytology in early detection of lung cancer in selected patients and suggested reevaluation of the role of sputum cytology [5]. Furthermore, many studies have reported that sputum cytology has resulted in detection of lung cancer at an early stage and improved 5-years survival rate [5].

Regrettably, screening asymptomatic smokers with sputum cytology does not decrease mortality from lung cancer due to its low-sensitivity. However; sputum cytology has a high specificity and positive predictive value and can be clinically very useful for symptomatic individual [4, 6]. It has been shown that sputum cytology has an important role especially in patients with relative or absolute, contraindication to bronchoscopy examination. Moreover, it is reported that sputum cytology can be helpful in diagnosing peripheral lesions, inaccessible to bronchoscopy, or if bronchoscopy has failed in providing diagnostic material [2]. Furthermore, sputum cytology has a role if a tissue diagnosis is needed to direct the patient treatment, and surgery is unlikely to be performed, then sputum cytology represent the appropriate non-invasive procedure [2]. **Rivera and Mehta** recommends sputum cytology for patients who present with centrally located tumors (*i.e.*, SCLC or squamous call carcinoma) and in those who present with hemoptysis, with a central lesion with or without radiographic evidence of metastatic disease, and in whom a semi-invasive procedure such as bronchoscopy or TTNA might pose a higher risk [1].

Multiple studies have stated that the accuracy of sputum cytology and sensitivity of diagnosing lung cancer is difficult to summarize because of a range of methodological problems which are strongly related to the number of sputum samples and the specimen adequacy [1]. **Schreiber et al.** and **Rivera et al.** emphasized the importance of adequate sampling and claimed that many institutions have no established Programs for sputum collection and processing and that explain the lower sensitivity reported in many studies [3, 1]. To have a yielding sputum cytology results more attention has to be given to the optimal collection and submission of the sputum and to the method of sputum preparation [7, 11, 12]. Deep cough specimen of the lower respiratory tract containing numerous pulmonary macrophages is mandatory to obtain [9]. In fact sputum induction increases the detection of lung cancer [10]. Furthermore, it was emphasized that positive samples with higher sputum cytology yield are often submitted by specialist physicians such as chest physicians [2].

Collecting multiple sputum samples over several days optimizes sensitivity of sputum cytology. **Bocking et al.** have shown that the sensitivity of sputum cytology in detecting lung cancer is highly dependent on the number of sputum specimens

collected per patient, ranging from approximately 0.68 for a single specimen, to 0.78 for two specimens, to 0.85– 0.86 for three or more specimens [7]. In another study the sensitivity of sputum cytology for the diagnosis of malignancy increases with the number of specimens examined, from 42% with a single specimen to 91% with five specimens [8].The type of patients from whom the sputum was collected was another concern. Elderly individual with productive cough and exacerbation of chronic obstructive air way disease or congestive heart failure and with low clinical suspicion of malignance have low yield of positive sputum cytology [2].

The specificity of sputum examination is high, ranging from 96% to 99%, and the positive and negative predictive values are 100% and 15%, respectively reported by **Fraire *et al.*** [13]. The present study is comparable to other studies in the literature and it reports high specificity (94%) and positive predictive value (75%) and showed a lower sensitivity (16.7%) and negative predictive value (52%). The diagnostic yield in lung carcinoma as was stated by **Sing *et al.*** [4] and **Rivera *et al.*** [1] is dependent on the location of the tumor, the histological type and the stage of the tumor and that sputum specimen are most valuable in the detection of early and peripheral carcinomas [4]. Accuracy in tumor classification is 75% to 80% [14] and is tumor type dependent [15]. It is evident from the literature that sensitivity of sputum cytology depends on the location of the malignant tumor: 46% to 77% of central lung cancers but only 31% to 47% of peripheral cancers [4, 6,] In another study by **Schreiber *et al.*** the sputum cytology sensitivity was higher for central lesions than for peripheral lesions (0.71 vs 0.49, respectively) [3].

The lower sensitivity in our study can be explained by the uncontrolled protocol for sputum specimen collection, the time of collection, variation between physician and their confidence in the sputum cytology, the frequency and the number of specimen obtained by patient as well as some variations in the laboratory preparation techniques. This retrospective study establishes the high reliability and specifity of the sputum cytology examination and discloses the underutilization of this test at our institution. Furthermore, our study encourages the use of this simple non-invasive procedure in high risk patient with high clinical suspicion of lung cancer, especially in patient complaining of hemoptasis, or have central lesion and or when performing bronchoscopy is contraindicated or inappropriate. The study highlighted careful evaluation and the use of other investigational modalities in case of negative sputum cytology; since many studies have underlined that a single negative sputum result does not guarantee the absence of a malignancy, especially in a patient suspected of having lung cancer.

5. Conclusion

Sputum cytology is highly specific diagnostic tool in expert hands and to improve the yield of this simple non invasive examination a basic recommendation is to be followed: collection of multiple sputum specimens from the suspected patients involving specialist physicians is highly encouraged. Furthermore, attention has to be made during collection, submission and preparation of the sputum to improve the quality of the specimen and cytology results. Unified protocol or an institutional guide for collection, submission and preparation of the specimen should be generated and followed if increased sensitivity and specificity of sputum cytology is aimed.

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