Lung cancer – diagnostic problems

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Introduction

Diagnosis of any disease rests on three fundamental steps. Listening to a patient’s problems (symptoms – experience(s) that, according to the individual is not normal), clinical examination, and appropriate investigations. Symptoms are by far the most important step in the process of diagnosis. These are the first clues that guide the physician about the possible system of the body that is affected, and at times, also the specific diagnosis (e.g., bronchial asthma). Even if the diagnosis is not obvious, history and physical examination are often good pointers towards the line of investigations that need to be pursued.

Diagnosis of lung cancer is an exception to this general plan of action in medical practice, for more than one reason. Firstly, it does not produce symptoms early enough in the natural history of the disease on most occasions and hence they are not suitable to be useful diagnostic pointers. To add to our difficulties, symptoms when present are often non-specific and those due to paraneoplastic syndromes may be completely misleading. Secondly, when more specific symptoms are present, it is often too late in the natural history of the disease (e.g., puffy face or hoarseness of voice), to be considered “useful” for diagnosis. In a disease like lung cancer, getting the diagnosis right is not enough; it has to be done early enough to be meaningful for the patient. Nevertheless, features like sudden changes in the character of cough, stridor (sometimes in patients who are already wheezing) and rarely bronchorrheoa when present, should alert the physician regarding the need for additional investigations to exclude lung cancer.

Physical signs again, most of the times appear too late. A localised monophonic wheeze or a lobar collapse is not easy to detect and may be easily missed if the physician is not specifically looking for these. A hard lymph gland in the supraclavicular fossa or a ptosis and small pupil on one side are again evidences of far too advanced disease to expect a satisfactory result of treatment. All non-resolving pneumonias too need to be investigated.

Diagnostic problems of lung cancer include an inability to get a cytological or histopathological proof of the diagnosis, even when the clinical picture is highly suggestive. This scenario is particularly disturbing to both the treating physician and the patients and their relatives. Hence, even when everybody strongly suspects the likely diagnosis, no treatment can be offered in the absence of any documented proof.

The diagnosis of lung cancer remains incomplete without the cell type of the cancer which is currently necessary for the optimum line of treatment. Sometimes the presentation may indicate the cell type. Small-cell type1,2 is rapidly growing usually in the central airways, commonly has direct mediastinal invasion and massive lymphadenopathy, produce paraneoplastic3 syndromes and symptoms at presentation and are often related to both thoracic and distant metastasis. On the contrary, adenocarcinomas are peripherally situated, intra-thoracic symptoms are delayed, and presentation may be with pleural effusion or with one or more metastatic lesions. Squamous cell cancers tend to be confined to the thorax for a longer period of time, so that symptoms related to lungs and intra-thoracic spread are more common.

Lung cancer is usually suspected on the basis of an abnormal chest radiograph4; the early diagnosis almost all the time rests on the physician’s assessment of the abnormality seen on the chest X-ray. Unfortunately, abnormal shadows on routine chest X-rays are fairly common in our country, mostly attributable to pulmonary tuberculosis – either active or healed. Therefore, faced with such an abnormal X-ray, a physician’s responsibility is to decide firstly, whether the abnormality needs to be investigated at all (old radiology plates available may show the same abnormality for many years) and secondly if

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further studies are done, what sequence of studies to follow, so as to maximise the sensitivity and to avoid performing multiple, unnecessary procedures. This is even more relevant in our practice, as a vast majority of our population do not have any financial support for their medical expenses.

**Modalities for lung cancer diagnosis**

**Sputum cytology**

This is the least invasive and cheapest means of obtaining a diagnosis of lung cancer. The diagnostic accuracy of course depends on the local expertise available, on rigorous specimen sampling (at least three specimens), preservation techniques and location and size of the tumour. Unfortunately, many of our laboratories and institutions do not pay adequate attention to sputum collection and processing and therefore this test has a much lower sensitivity, compared to what is reported in the literature. Sputum cytology is more likely to be useful in centrally located tumors (i.e., small-cell lung cancer or squamous cell carcinoma) and in those presenting with haemoptysis. A recent review has suggested the average sensitivity and specificity rate of sputum cytology to be 0.66 and 0.99 respectively. The sensitivity of sputum cytology for central lesions is 0.71 and decreases to 0.49 for peripheral lesions.

**Flexible fibreoptic bronchoscopy (FOB)**

In a patient with a central lesion, FOB is the most sensitive way to confirm a diagnosis of cancer. In case the result of bronchoscopy is nonspecific, these central lesions suspicious of lung cancer must be followed-up with further investigations. Central lesions can be seen as an endobronchial mass, submucosal spread, or a peribronchial tumour causing external compression. The addition of transbronchial needle aspiration (TBNA) to obtain cytology or histology when there is a submucosal tumour spread or peribronchial tumour, increases the sensitivity of bronchoscopy. In patients with a small (<2 cm) peripheral lesion, the sensitivity of bronchoscopy is however low.

**The recent problem of cell type accuracy**

Differentiating between NSCLC and SCLC is absolutely necessary for therapeutic planning, as these are treated in a radically different manner. Generally speaking, the distinction is quite reliable on sputum cytology, TBNA cytology, bronchoscopic washings, and broncho-alveolar lavage (BAL) cytology. Bronchoscopic biopsy and CT-guided trucut biopsy provide accurate typing of lung cancer by even further classifying non-small-cell lung cancers into squamous cell, adenocarcinoma, and large-cell types.

**The common dilemmas**

There are two situations that need special mention as a diagnostic problem, namely, patients presenting with pleural effusion and the problem of a solitary pulmonary nodule.

**Pleural effusion**

Pleural effusions are common in our country, and overwhelming majority of lymphocytic exudates that we see are of tubercular origin. The crux of the matter is to correctly identify the ones where malignancy is a strong possibility and adequately investigate them. Clinical features that indicate a possible malignant disease are a relatively short history of progressive breathlessness that is rapidly relieved after thoracentesis. Cough too, usually improves after thoracentesis. Chest pain is more common with mesothelioma, which usually presents with early pain, even before the effusion develops. Pain in mesothelioma is usually diffuse on the affected hemi-thorax and has no clear pleuritic characteristics. Pain should also raise the possibility of chest wall involvement by the tumour. Malignant effusions are commonly haemorrhagic, but not always so. Radiographically, malignant effusions are less likely to get loculated. If a patient has a large effusion where the mediastinum is in midline or shifted ipsilaterally, one needs to pursue investigations more diligently to look for an underlying malignancy causing lung collapse.

It is also important to differentiate between a malignant effusion (i.e., one due to malignant involvement of pleura) and a paramalignant effusion (i.e., one due to other factors such as lymphatic blockade, atelectasis, or hypoproteinaemia). Differentiating these two is important because finding of malignant cells in the pleural...
fluid alters the stage and treatment of the particular patient. Almost all malignant effusions are exudates but a few can be transudates. Malignant transudate effusions can occur in lung cancer with obstruction of the mainstem bronchus and sometimes in lymphoma and other malignancies.

Typically, the cell count shows a lymphocytic predominance, but presence of neutrophils or eosinophils does not exclude malignant effusion. Adenosine deaminase (ADA) determination is routinely recommended in countries like ours with high prevalence of tuberculosis. It can however yield false-positive results in some cases of mesothelioma and lymphoma.

Approximately one-third of malignant effusions will show a pH of less than 7.3 at presentation. This low pH correlates with glucose values of less than 60 mg/dl. The cause of this low pH and low glucose seems to be a high tumour burden. Malignant effusions with these characteristics have been shown to have a higher diagnostic yield of cytology and poorer results of pleurodysis. Pleural fluid cytology is the simplest definitive method available for diagnosis of a malignant pleural effusion. Pleural metastases are more common in the visceral pleura and tend to be focal; and pleural fluid cytology is a more sensitive diagnostic test than percutaneous pleural biopsy, the latter being a blind sampling procedure. Particularly in patients with a negative cytology, closed pleural biopsy is highly unlikely to give a definitive diagnosis. With recent advances in imaging techniques, especially in patients with a significant pleural thickening, a CT-guided trucut biopsy has much more yield compared to blind needle biopsy. Otherwise, a thorascopic biopsy happens to be the most likely investigation to produce definitive diagnosis with a high degree of accuracy. Video-assisted thorascopic biopsy is an even less invasive diagnostic method.

Although tumour markers in pleural fluid cannot be considered as definitive for diagnosis, they can be of help in selecting patients for further investigations, with more invasive techniques. It has been found that using a panel of several tumour markers in pleural fluid (CEA, CA-125, CA 15-3 and CYFRA 21-1), more than one-third of cytology negative malignant pleural effusions could be identified by at least one marker. Flow cytometry may play a role in the study of possible malignant effusions and can complement cytology by identifying malignant cell blocks.

**Solitary Pulmonary Nodule (SPN)**

A solitary pulmonary nodule is radiologically defined as an intra-parenchymal lung lesion that is ≤ 3 cm in diameter and is not associated with atelectasis or adenopathy. When > 3 cm in diameter, these are called masses. Most of these are incidental findings on routine diagnostic work ups. Incidence of SPN in India is not known, but in USA more than 150,000 patients present with this diagnostic dilemma to their physicians every year. With the greater availability and increasing frequency of chest CT scans, incidence is likely to increase further, globally as well as in India. The differential diagnosis of SPN includes neoplastic, granulomatous, vascular, and congenital lesions. Primary malignancy, according to publications from western countries, is found in approximately 35% of SPNs and solitary metastasis can account for another 23%. Indicators of a possible malignant disease are older age, cigarette smoking, and a previous history of cancer. In our country, the percentage of a malignant SPN is likely to be lower with an increased prevalence of tuberculous granulomas, but exact figures are not available. This makes the identification of malignant SPNs even more difficult. As a principle, all SPNs should be considered malignant, until proved otherwise, as a diagnosis of cancer at this stage might result in a curative surgery.

It is quite difficult to recognise underlying cancer in a SPN. The rate of failure to diagnose lung cancer from chest X-ray varied from (25 - 90%) in a number of different studies with differing study designs. Queckel et al looked at chest X-ray retrospectively in 259 patients with proven NSCLC and found a 19% incidence of missed diagnoses. Traditionally, the presence of “benign” calcification (central, diffuse, laminar, popcorn) or absence of growth over a 2-year time period are believed to be reliable indicators of benign disease. Smooth margin of a spherical nodule is generally associated with a benign disease. However 20 - 34% of SPNs with this appearance are also malignant, most notably those nodules that represent metastatic disease.
Spinal CT with IV contrast is the imaging modality of choice and should be done in all newly diagnosed SPNs. At times, CT scans will show metastatic disease elsewhere. Lesions like hamartomas (fat density), arteriovenous malformations, fungal balls, will all have very characteristic findings on a CT scan. Around 84 - 90% of nodules with a spiculated margin, nodules > 2 cm in diameter and cavitating nodules with thick wall (> 15 mm) are more likely to be malignant.

Positron emission tomography (PET) fused with computed tomography scanning is a relatively new imaging modality (PET-CT). The recognition that combined metabolic and morphological information yielded by PET/CT can have a significant impact on staging and re-staging or detection of recurrent disease has led to greater utilisation of PET/CT in oncological practice. However, it is also true that 2-[18F] fluoro - 2 deoxcy-D-glucose (FDG) uptake is not specific for malignancy as many different physiological variants and benign pathological conditions can also exhibit increased glucose metabolism. This is particularly important in clinical practice in India – because of widespread prevalence of tuberculous granulomas, making its use somewhat circumspect in a diagnostic work-up. Obviously, we need more data on use of PET/CT from TB endemic countries for the diagnosis and staging of lung cancer.

In conclusion, it should be apparent to the readers that despite considerable technical advances of imaging techniques, the diagnostic work-up for lung cancer still relies heavily on clinical perspectives and that no single clinically based algorithm can be applied to all the cases.

References