Case Report

Non-resolving pneumonia in a young patient with fungal granulomatous infection: an unusual presentation of lung malignancy.

Yathukulan S[1*], Gunapala A[1], Charles JC[2]

[1]National Hospital Colombo, Sri Lanka.
[2]Teaching Hospital, Jaffna, Sri Lanka.

Abstract

We present a case of unusual presentation of non-small cell lung cancer as non-resolving pneumonia in a nonsmoker young female patient without preexisting lung disease. Various infective and non-infective etiologies are associated with non resolving pneumonia. Super added bacterial and fungal infections may mask the definite diagnosis of tuberculosis, lung malignancy or vasuclitis. When our patient did not respond to long course of broad spectrum of antibiotic treatment, lung malignancy was considered as differential diagnosis. We emphasize to have high suspicion of lung malignancy in young patients with non-resolving pneumonia with opportunistic fungal infection.

Keywords: Non-resolving pneumonia, lung cancer, granulomatous infection, mediastinal mass, non-small cell lung cancer

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*✉**Correspondence:** yathukulan1990@gmail.com https://orcid.org/0009-0003-0157-8162

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Introduction

Lung cancers are the second most common cancers in men and women [1]. Though Smoking is a well-established risk factor for small cell lung cancer, non small cell lung cancer commonly occurs in non-smokers [1]. Environmental pollution, occupational hazards and certain genetic mutations are identified risk factors for non small cell lung cancer [2]. Adenocarcinoma constitutes the predominant histology in the majority of non small cell lung cancer patients [2]. More than one histological subtype can be present in non small cell lung cancer and the prognosis is based on the proportion of each histological subtype [2]. The presence of metastasis also influences the prognosis [3]. Unusually, lung cancers can mimic pneumonia, and radiological features of consolidation and air bronchogram can occur [4]. We present a case of young woman with non-resolving pneumonia who failed to respond to a combination of a broad spectrum of antibiotic and antifungal treatment, found to have lung malignancy.

Case Report

A 37year old previously healthy female patient presented the history of fever with cough,worsening dyspnea with left shoulder pain for two weeks. The fever was intermittent and low-grade in nature with chills and had not responded to paracetamol or antibiotics. She had a productive cough with yellow sputum and developed two episodes of small amount of hemoptysis. She did not have any contact history of

tuberculosis (TB), travel history abroad, past blood transfusion or history of drug abuse. She was initially treated in the private sector for two weeks with IV antibiotics. She became oxygen-dependent within a few days of admission to the private sector. Then she was transferred to the National Hospital of Sri Lanka as she deteriorated while on treatment. Her investigations are summarized in Table 1. She was found to have a superior mediastinal mass lesion in the ultrasound scan (USS) chest.

Due to non-resolving pneumonia and the presence of granulomatous inflammation in biopsy, she was given antituberculosis treatment (ATT) in addition to antibiotic treatment in the private sector. ATT was stopped in our hospital after discussing with the chest medicine and microbiology team. She was given intravenous antibiotics and antifungal drugs after liaising with a microbiologist and mycologist. She became ill, and her quality of life was severely affected due to worsening dyspnea. She had lung crepitations with reduced air entry involving all three zones bilaterally throughout the illness, suggesting consolidation with effusion with increased work of breathing. Widening of the mediastinum and diffuse shadows of consolidation was seen in the chest x-ray CXR. Examination of the rest of the systems was unremarkable.

She underwent biochemical and radiological evaluation as directed by a multidisciplinary team decision involving a general physician, chest physician, microbiologist, histopathologist, and radiologist regarding extensive evaluation of non resolving pneumonia and she was found to have a superior mediastinal mass lesion. Video-assisted thoracoscopic surgery-guided biopsy of the lesion revealed granulomatous inflammation and was positive for fungal spores and hyphae. We could not wean her off her oxygen. Receptor studies and immunohistochemistry confirmed primary lung malignancy. Then, she was transferred to Apeksha Hospital, Maharagama (a specialised cancer treatment hospital) for chemotherapy, and we lost follow-up afterwards.

Discussion

This is a case of a young female patient who was treated for poorly resolving pneumonia, and found to have lung malignancy. This case emphasizes the importance of a high index of suspicion of malignancy in a young patient with non-resolving pneumonia. Even though the initial histology for malignancy is negative for this patient, lung malignancy can be found through subsequent immunohistochemistry. Poorly resolving pneumonia is defined as radiological and clinical evidence of pneumonia which is not improved after adequate treatment [5]. It warrants aggressive evaluation from revisiting the history and looking for alternative etiologies. Various investigations are needed, from simple blood investigations to advanced radiological investigations in a pragmatic way. If adequate clinical clues are present in physical examination guiding for definite aetiology, an extensive evaluation is not needed. In young patients with non-resolving pneumonia, aetiology must be actively sought to exclude malignancy [6]. Delay in the diagnosis of lung cancer may progress to advanced stages and affects prognosis.

Most of the non-resolving pneumonia (NRP) is due to bacterial infections [6]. But connective tissue diseases, malignancies and granulomatous diseases, including sarcoidosis and fungal infections, are the other causes of NRP[7]. Granulomatous disease due to fungal and bacterial infections may hinder the diagnosis of malignancy and delay the treatment[8]. In our case, she was earlier treated for NRP secondary to TB and fungal infection. The presence of air bronchogram and consolidation suggested pneumonia but widened mediastinum in the CXR was the only finding that led to the identification of superior mediastinal mass.

Granulomatous lung diseases are a group of infective and noninfective disease that forms granulomas in various regions of the lungs during the cause of illness [9]. Granuloma is a type of chronic inflammation that has a collection of inflammatory cells in different layers to contain a focus [9]. Our patient had non-caseating granuloma, which was against the diagnosis of TB. Despite having a histology-proven fungal infection as a diagnosis, strong clinical suspicion for malignancy needs immunohistochemistry study for specific receptors or molecules such as EGFR, and Napsin[10].

The diagnosis of this patient was masked by the presence of a fungal infection. When fungal infections are unusually present in immunocompetent patients, alternative diagnoses of malignancy always need to be excluded. Fungal infections remain asymptomatic in immunocompetent patients [5]. But, invasive disease occurs in immunocompromised individuals as widespread involvement with ill-defined granulomas[9]. Diagnosis of fungal infections isusually serological than histological [5]. Serological investigations were negative for *Aspergillus*, *Histoplasma* and Coccidiomycosis in our patient. But fungal spores and hyphae was identified histology in two different biopsy samples.

Lung malignancies are commonly present as a superior mediastinal mass lesion [11]. Either it can be primary lung malignancies or lymphomas. Bronchoalveolar lavage (BAL), transbronchial lung biopsy and Computed tomography-guided biopsy help in making histological confirmation [11]. Smoking is a well-established risk factor for lung cancer [12]. Our patient didn't have a history of passive or active smoking. Patients with non small cell lung cancer are usually

asymptomatic and become symptomatic once the cancer is well advanced[1]. Approximately 70% of patients will have dissemination at the time of diagnosis [10]. Treatment of non small cell lung cancer in the early stage is surgery, and combined chemoradiotherapy is given for advanced disease [10]. Palliative chemotherapy is considered in a patient with metastasis. The 5-year survival rate of non small cell lung cancer remains at 15% despite advancements in treatment [10].

Table 1: Summary of investigations

Investigation	Result
Blood, Sputum and Bronchioalveolar lavage culture and Antibiotic sensitivity tests	No growth
TB GeneXpert and Acid fast bacilli Culture Antibiotic sensitivity test in Sputum, Pleural fluid, Pleural biopsy	Negative
Mantoux test	Negative
Blood picture	Normochromic normocytic anemiaandRouleaux formation, No evidence of abnormal lymphocytes or blast cells
Lung function test	Very severe restrictive pattern
2D Echocardiogram	Ejection fraction60 %, no vegetation, normal left ventricular function
HIV type 1, type 2 antibody, Hepatitis antigen b, Mycoplasma antibody, Histoplasmosis urinary antigen and serum antibody, Aspergillosis Galactomanan antigen, Cociddomycocisis antigen and antibody, Brucellosis antigen and antibody	Negative
Antinuclear antibody	1/80 DS DNA negative
D Dimer	2.1 mg d/L
Serum protein electrophorosis	normal
Lactate dehydrogenase	340
Serum calcium	7.7 (9.3 corrected)
Urinary calcium creatinine ratio	0.03 mg/mg
Angiotensin converting enzyme levelslevels	Normal
USS - chest	Ultrasonically visible soft tissue area towards the left side of superior mediastinum. Bilateral pleural effusion with basal atelectasisis.
Chest X-ray	Widening mediastinum bilateral pleural effusion with bilateral lower zone airspace shadow with airbronchogram features of consolidation.
Contrast enhanced computed tomography of neck and Chest	There are multiple enhancing small cervical lymph nodes in the bilateral 1B, 11, 111, V cervical level and supraclavicular region. Large node in is left side level 1B. Multiple regions of consolidation involving bilateral lower lobes, Apico posterior segment of the left side upper lobe and lateral segment of right side middle lobe. These are mainly sub pleural in location. Some of them have air bronchogram in it. No lung nodules or cavitatory lesions. There are multiple sub centimeter size mediastinal lymph nodes involving bilateral upper and lower para tracheal groups. No hilar lymphadenopathy. Bilateral pleural effusion is present. Fluid seen in the left side oblique fissure. No paraaortic lymphadenopathy in visualized abdomen
Video assisted thorocoscopicsurgeryguided mediastinal and pleural biopsy	Suppurative granulomatous inflammation in a background of inflamed granulation tissue response favoring granulomatous empyema. Underlying lung tissue with acute organizing pneumonia definite atypical cells, well-formed granuloma or malignancy,

	definite lymphoid tissue are not present
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Acid Fast Bacilli stain in biopsy	Negative for acid fast bacilli
Grocott stain in biopsy	Few septated short hyphae and small rounded spores are identified
Computed tomography guided mediastinal core biopsy	Malignant tumor composed of irregular cords and nests of cells infiltrating heavily inflamed, desmoplastic stroma. Immunohistochemical (IHC) stain shows AE1/AE3- Diffuse and strong cytoplasmic positivity of in tumor cells. CK7- Diffuse and cytoplasmic positivity in tumor cells, showing a glandular pattern focally.TTF-1-Diffuse and strong nuclear positivity in tumor cells. Napsin-A- Diffuse and strong cytoplasmic positivity in tumorcells. WT1- Focal and strong nuclear positivity in tumor cells. Suppurative granuloma with superadded fungal infection.

Conclusion

In patients with poorly resolving pneumonia, the common aetiology is a bacterial infection. But, inadequate response to antibiotics for a long duration should raise suspicion of an alternative diagnosis of pulmonary tuberculosis, malignancy and fungal infections. Especially in young patients malignancy must be excluded in mediastinal mass lesions despite having histological evidence of granuloma.

Conflict of interest

None

Consent

Written informed consent was obtained from the patient.

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