Respiratory Medicine Case Reports 20 (2017) 125–128

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

An aggressive non-small cell lung cancer in nonsmokers: A case report of an unusual presentation of micropapillary lung adenocarcinoma

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ARTICLE INFO

Article history:
Received 14 January 2017
Received in revised form
28 January 2017
Accepted 30 January 2017

ABSTRACT

We describe a case of an unusual fast growing lung micropapillary-predominant adenocarcinoma in a nonsmoker male patient without pre-existing lung disease. Adenocarcinomas have been described to be slow growing tumors, however our patient presented a fast-growing rate over a period of 21 days. When the patient failed broad spectrum antibiotic coverage, malignancy became part of the differential diagnosis. Once malignancy was detected, prompt identification and treatment was started in order to improve prognosis of the patients.

1. Introduction

Lung cancer is the second most common cause of malignancy worldwide among both females and males. Although tobacco exposure continues to be the most important risk factor for lung cancer, especially for squamous cell carcinoma, there has been an increasing number of non-small cell lung cancer among nonsmokers [1]. Histologically, lung adenocarcinoma (AC) accounts for most of non-small cancer and is the most common one among nonsmokers [2]. Novel studies have shown that lung cancer in nonsmokers appears to be caused by different risk factors such as environmental pollution and occupational exposure among others. Gene mutations have also been implied as a strong risk factor for lung cancer among nonsmokers, as seen with EGFR gene mutation, which have been identified to be different from those with a smoking history [3]. In 2011 a new classification was published by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society [4]. Invasive lung AC, which is the most common cause of cancer, is divided into five groups based on growth pattern and/or shape of the tumor. These are: lepidic, acinar, papillary, micropapillary and solid. Of these, micropapillary-predominant adenocarcinoma (MPA) was added as a new histological subtype and has been reported as an aggressive variant of adenocarcinoma with a poor prognosis [5]. In more than 90% of lung AC cases, two or more components exist, for which reason the prognosis of lung AC varies based on the proportion of each histopathologic component [6]. In addition to histological pattern, staging also drives the prognosis of lung cancer with the presence of metastasis inflicting the most negative factor. For this reason, it is imperative to confirm or exclude the presence of metastasis immediately after a diagnosis is known.

Although not the usual presentation, adenocarcinomas can present with radiological findings such as infiltration, consolidation with air bronchograms mimicking pneumonia. It has been reported that malignant pulmonary lesions can present with up to 500 days of volume doubling time, being adenocarcinomas one of the slowest growing tumor [7]. Our case presents a fast-growing tumor with unusual presentation and spread via lymphatic mechanism. It has been recognized that slow-growing tumors usually have a better prognosis than rapidly growing tumors.

2. Case presentation

A 60-year-old Hispanic nonsmoker male without past medical history presented himself to an outpatient clinic evaluation with gradually worsening productive cough of white sputum and

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http://dx.doi.org/10.1016/j.rmcr.2017.01.012

shortness of breath for one month period. He denied having fever, chills, hemoptysis, weight changes, and contact with sick people or travel within that time. Significant physical findings included chronically ill looking patient, tachypneic, with peripheral oxygen saturation of 93% at room air, no evidence of lymphadenopathy, lung auscultation relevant for bilateral rhonchi and diminished breath sounds that were more prominent on the left side. Due to physical findings and symptoms the patient was transferred to emergency room (ER) for further evaluation and was hospitalized. Significant laboratory results included a white blood cell count of 16.33 × 10ˆ3/μL, microcytic anemia, arterial blood gases with respiratory alkalosis and hypoxemia, creatinine value of 1.4 mg/dL and normal procalcitonin level. Microbiology samples including sputum culture, blood culture and urine culture, were all negative. Initial chest radiograph revealed a left lower lobe consolidation suggestive of pneumonia (see Fig. 1). Further characterization with a chest CT scan described the consolidation with air bronchograms, adjacent tree-in-bud nodules, no pleural effusions, and a patent airway (see Fig. 2A and B). Additionally, tree-in-bud nodules and opacities were present in the contralateral lung and in the left upper lobe. In a period of 3 weeks a broad spectrum antibiotic therapy with fluoroquinolones and cephalosporins did not achieve improvement in the patient's condition. A second chest CT was done later, showing that the opacities were more extensive and involved more sub segments of the lungs (see Fig. 3A and B). A bronchoscopy with bronchial washing revealed atypical cells. To further investigate this unexpected finding, a wedge lung biopsy via video assisted by thoracoscopic surgery (VATS) of the left lower lobe consolidation finally confirmed the presence of lung adenocarcinoma. The histological pattern was micropapillary (50%), lepidic (40%), and acinar (10%) patterns. The specimen was positive for the epidermal growth factor receptor (EGFR) mutation with a single deletion in exon 1. FISH analysis was negative for ROS 1 rearrangement and ALK rearrangement. For staging purposes the patient underwent a fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET CT) which demonstrated an FDG-avid hypermetabolic process within the left lower lobe consolidation of a maximum standardized uptake value (SUV_{max}) of 12.2. Additionally within the other involved areas in the upper lobe and in the contralateral lung with some extension of this process into the inferior aspect of the left upper lobe with SUV_{max} of 4.8. Also of interest, a moderate high tracer uptake is also seen in a band like diffuse pattern on the right lung middle lobe along the major fissure and medial aspect of the right lower lobe with an

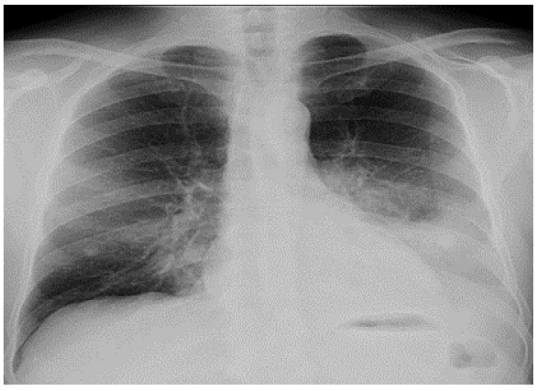

Fig. 1. Initial chest radiograph revealed a left lower lobe consolidation suggestive of pneumonia.

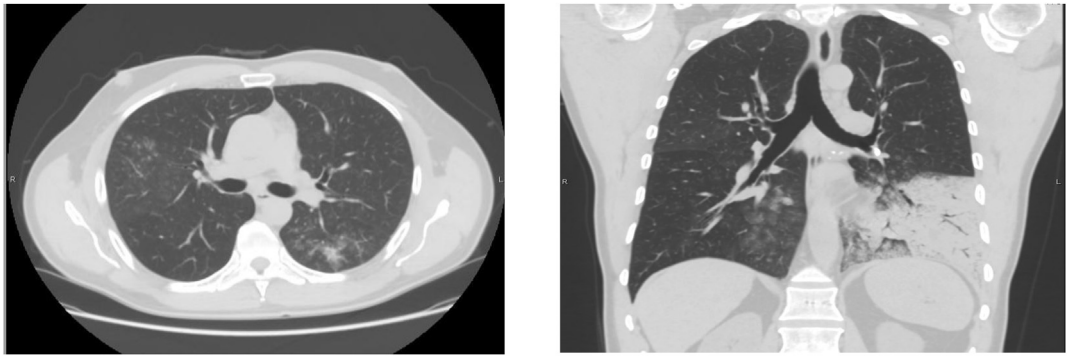

Fig. 2. A, B: Axial and coronal views respectively. Initial chest CT scan showed a consolidation with air bronchograms, adjacent tree-in-bud nodules, no pleural effusions, and a patent airway.

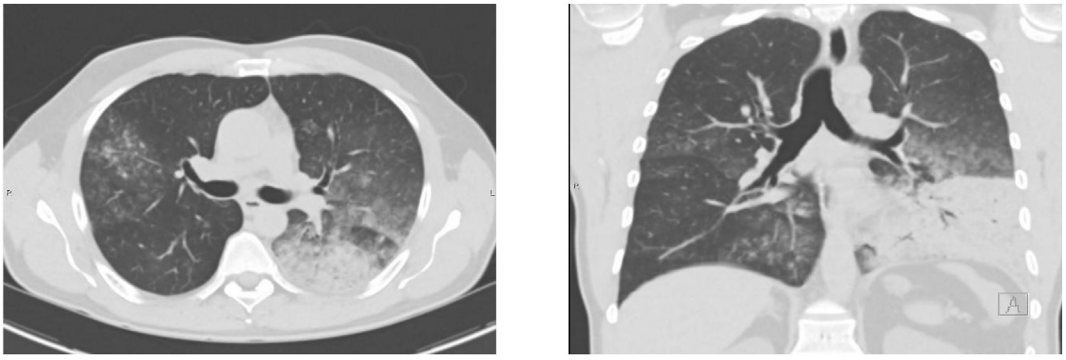

Fig. 3. A,B: Axial and coronal views respectively. Second CT scan showing the opacities were more extensive and involved more sub segments of the lungs.

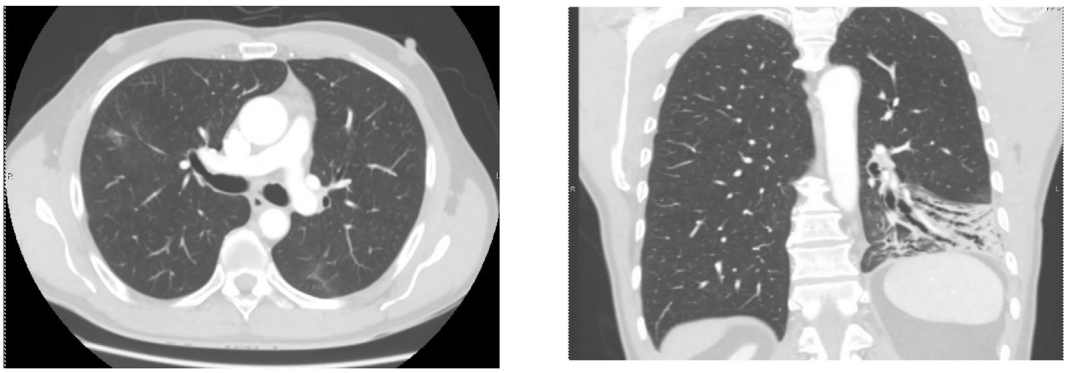

Fig. 4. A, B: Axial and coronal views respectively. Third CT scan 3 months after chemotherapy, showing significant radiological improvement of the previously described opacities.

SUV_{max} of 5.5–6.4 respectively. No hilar or mediastinal adenopathy was identified. Soon after diagnosis, the patient was started on erlotinib due to positive EGFR tumor marker with abnormal results. After 3 months of therapy a third chest CT scan was conducted showing significant radiologic improvement of the previously described opacities (see Fig. 4A and B).

3. Discussion

Our patient came to the ER with clinical symptoms and radiological findings suggestive of an infectious process. He received treatment for pneumonia, however when poor response to treatment was observed, malignancy was suspected and was confirmed. After excluding this, the result was remarkable for an unusual aggressive lung AC with rapid progression.

Adenocarcinoma of the lung is often called the “masquerader” confused with pneumonia, producing diffuse pulmonary infiltrations that can mimic an infectious process. Its presentation may be confused with pneumonia; in fact, most of the patients will fail a course of antibiotic treatment before lung adenocarcinoma is diagnosed [8]. Even though lung AC are heterogeneous when examined histologically, it is important to understand that they also exhibit mixed growth patterns such as, acinar, solid, lepidic and papillary. Those with papillary growth show 2 types of papillary architecture: true papillary structures with papillae containing a layered glandular epithelium surrounding a fibrovascular core and micropapillary growth in which the papillary tufts lack a central fibrovascular core and extensively shed within alveolar spaces [9]. Micropapillary growth patterns have been associated with an aggressive clinical course compared with adenocarcinoma in situ. MPA is associated with non-smoking history, male sex, and frequently metastasizes to the contralateral lung, mediastinal lymph nodes, bone, and adrenal glands, correlating with high mortality [9].

MPA is defined by a micropapillary pattern (MPP), the primary histological pattern observed semi-quantitively in 5% increments on resection specimens. Warth et al. demonstrated that the predominant histological pattern in lung AC has a statistical significance in terms of survival and MPA has the poorest outcome compared with other histological patterns [10]. Interestingly, another study showed that even minimal amount of MPP (<5%) is associated with poor prognosis [11]. However, it is not clear whether the higher the percentage of MPP correlates with the poorest prognosis [11]. The clinical significance of minor micropapillary components that are not micropapillary predominant in primary lung AC needs further study. When it comes to staging, PET CT SCAN it has become the choice for routine evaluation before planning treatment. It has been noticed that the higher the SUV_{max} value, the greater the risk of recurrence, and among subtypes it has been found that MPA has a higher SUV_{max} than other histological patterns [11]. The evidence for the aggressive behavior, poor prognosis and risk of recurrence in nonsmoking population of this histologic pattern should raise the interest among health professionals including pathologists dealing with prompt recognition and treatment.

We should keep in mind that once an entity such as MPA has been identified, prognosis and recurrence might be affected. Although it has been reported that the growth rate of lung AC is usually slow, our patient presented significant progression of chest imaging findings within a short 21 days. Lung AC should be part of the differential diagnosis of any infectious process that is not resolved with maximized antibiotic therapy. This reinforces that pathology does not always present itself he same way and clinical suspicion is imperative to help identify and treat the malignancy improving significantly a patients' survival with early detection.

Funding statement

This case report did not receive any specific grant form any funding agency in the public, commercial or not-profit sector.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of this case.

Patient consent

A written informed consent was obtained from the patient for publication of the case.

Acknowledgments

The authors would like to express their gratitude to Patricia González BS, MBA, for the time and effort it took to correct and edit our work. We were able to do a better work with your help and knowledge.

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