CASE REPORT

Case of invasive mucinous adenocarcinoma mimicking chronic eosinophilic pneumonia

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Keywords

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Abstract

Invasive mucinous carcinoma is difficult to distinguish from other lung diseases; therefore, confirmation of the diagnosis may be delayed. A 64-year-old woman was admitted with a six-month history of cough, febrile sensation, and shortness of breath, with worsening symptoms. A computed tomography scan of the chest revealed bilateral homogenous ground-glass opacities and consolidation with sub-pleural predominance. The percentage of eosinophils in the serum and induced sputum was elevated and a diagnosis of chronic eosinophilic pneumonia was established. Despite administration of a systemic steroid, she did not rapidly respond. We performed a percutaneous needle biopsy and finally confirmed invasive mucinous adenocarcinoma.

Introduction

Chronic eosinophilic pneumonia (CEP) is characterized by multiple and dense areas of homogeneous peripheral air-space consolidation on chest radiographs and computed tomography (CT) scans, persistent symptoms, a required response to steroid therapy, and possible relapses.¹ An increased number of eosinophils in bronchoalveolar (BAL) fluid assist in the diagnosis of patients presenting with CEP symptoms.¹ A biopsy is usually not required if the clinical findings are characteristic, and the response to a trial of corticosteroids is rapid and complete.¹ Therefore, in patients with clinically diagnosed CEP, the absence of a dramatic response to systemic steroid indicates that other diseases must be considered.

In 2011, multicentric bronchioloalveolar carcinoma (BAC) was redefined as an invasive mucinous adenocarcinoma.² For these tumors, the most common features on a chest high-resolution computed tomography (HRCT) scan are predominant ground-glass opacities, consolidations, or multiple nodules.³ But, because these radiological findings are usually indistinguishable from other lung diseases, such as atypical pneumonia, tuberculosis, or metastatic lung cancer, establishing a diagnosis can often be delayed. Herein, we

describe a case of invasive mucinous adenocarcinoma that mimicked chronic eosinophilic pneumonia.

Case report

A 64-year-old woman was admitted to our hospital with a progressive cough, a febrile sensation, and dyspnea lasting six months. She had no other underlying chronic diseases and had not taken any medications that might influence her immune status. She had no history of smoking or alcohol abuse.

Her vital signs were: blood pressure, 112/88 mmHg; heart rate, 80 beats/minute; respiratory rate, 24/minute; and body temperature, 36.5°C. Auscultation revealed coarse crackles in both lung fields. A systemic review of the occupational, travel, and home environments did not reveal the reason for the pulmonary infiltration. Her family history included a father with lung cancer.

Chest radiography showed multiple nodular infiltrations at the whole lung level with bilateral costophrenic angle blunting (Fig 1). The white blood cell count was 3700/mm³ with 55.5% segmented neutrophils, 26.3% lymphocytes, and 13% eosinophils. C-reactive protein and procalcitonin were 0.49 mg/dL and 0.02 mg/dL, respectively. Routine

Figure 1 Chest radiography shows multiple nodular infiltration of the entire lung with bilateral costophrenic angle blunting.

blood chemistry tests were normal. Rheumatoid factor, myeloperoxidase antineutrophil cytoplasmic autoantibody, proteinase 3-ANCA, and antinuclear antibody were all negative. An enzyme-linked immunosorbent assay (ELISA) for the human immunodeficiency virus antibody was negative. The results of ELISA for parasites, such as *Toxocariasis canis*, *Paragonimiasis westermani*, *Cysticercus cellulosae*, and *Sparganium*, were all negative.

Arterial blood gas analysis while breathing room air showed hypoxemia and an increased alveolar-arterial oxygen gradient of 81.3 mmHg with pH, 7.432; PCO₂, 36.5 mmHg; PO₂, 60.7 mmHg; mHCO₃, 23.9 mmol/L; and SaO₂, 91.6%. After administration of 40% oxygen, the hypoxia was corrected and a ventilation/perfusion (V/Q) mismatch was revealed.

A spirometry test showed a forced expiratory volume in 1 second (FEV1) of 1.41 L (63% predicted), forced vital capacity (FVC) of 2.01 L (61.0% predicted), and FEV1/FVC ratio of 69%. The flow-volume loop demonstrated obstructive airway disease, but no significant response was observed following the administration of salbutamol.

A CT scan of the chest revealed multifocal lobular consolidation and ground-glass attenuation with crazy-paving appearance, subpleural dominance in both lung fields, and dense peribronchial consolidation in the left lower lobe (Fig 2).

Flexible bronchoscopy was performed and no endobronchial lesions were detected. Although the BAL from the lateral basal segment of the left lower lobe was sent for analysis, cell lysis was unfortunately observed. We performed an additional study using induced sputum, and the percentage of

eosinophils in the induced sputum was 18%. Sputum and BAL fluid cultures did not reveal any causative pathogens, and cytology provided no evidence of malignant cells. Based on observations of eosinophilia in both serum and sputum, the diagnosis of idiopathic CEP was suggested, and oral prednisolone (55 mg, 1 mg/kg) was commenced. After treatment with a systemic steroid for two weeks, the patient's respiratory symptoms showed mild improvement, but the multifocal pulmonary infiltrations remained unchanged.

We performed a fluoroscopic percutaneous needle biopsy for the dense consolidation in the left lower lobe. Microscopic examination at a magnification of $\times 400$ showed mucinous tumor cells consisting of tall columnar cells with abundant apical mucin, which had lepidic growth along the alveolar walls with fibrous scarring in some areas (Fig 3). We finally diagnosed invasive mucinous adenocarcinoma. The human epidermal growth factor receptor (EGFR) mutation was additionally analyzed in the lung biopsy specimen by performing DNA sequencing of exons 18–21 in the EGFR tyrosine kinase domain, but no mutations were observed.

Two-[Fluorine-18] fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) imaging and whole-body CT scans, with the exception of the brain, revealed multiple consolidative lesions in both lungs with no FDG uptake (Fig 4). No abnormal hypermetabolic lesions were observed that would suggest malignancy.

After four cycles of first-line chemotherapy with pemetrexed and cisplatin and four cycles of second-line chemotherapy with paclitaxel and carboplatin, the extent of the multiple lung lesions increased; thus, this was considered a progressive disease. Seven months after diagnosis, the patient experienced headaches. Magnetic resonance imaging (MRI) of the brain revealed a new $6.3 \times 5.6 \times 5.4$ mm, thin rim enhanced, small cystic nodule in the right side cerebellum and we considered this a cystic metastatic lesion. The patient refused additional palliative chemotherapy and we are conducting regular follow-ups.

The Ethical Review Committee approved this report. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Discussion

The typical chest radiographic findings in CEP are non-segmental infiltration with peripheral predominance (so called "photographic negative of pulmonary edema").¹ In one review of the findings in 40 patients with CEP, chest HRCT scans showed bilateral areas of consolidation in 100% of the patients and ground-glass opacities in 88%.⁴ Integrating these characteristic clinical and radiological findings could preclude the need for a pathological examination in most cases of CEP, and indicates the need for systemic administration of corticosteroids.¹

Figure 2 Chest tomography reveals lobular consolidation and ground-glass attenuation with crazy-paving appearance and subpleural dominance in both lung fields (a–d). (d) Dense peribronchovascular consolidation in the left lower lobe.

Figure 3 Microscopic examination at a magnification of $\times 400$ shows mucinous tumor cells consisting of tall columnar cells with abundant apical mucin, which had lepidic growth.

We initially suggested that our patient had idiopathic CEP because of the typical radiological findings, progressive respiratory symptoms, and increased percentage of eosinophil in the serum and sputum at initial presentations. But, because our patient did not show a rapid response to the systemic steroid, we performed a histological confirmation through percutaneous needle biopsy, instead of follow-up BAL for a more definite evaluation. We finally diagnosed multicentric BAC. According to the new international histopathological classification of adenocarcinoma of the lung, multicentric BAC has been redefined as invasive mucinous adenocarcinoma.⁵ For the evaluation of eosinophilia in the sputum, we ruled out various conditions, such as drugs, parasite infection, idiopathic pulmonary fibrosis, interstitial lung disease, and asthma. After the diagnosis of invasive mucinous adenocarcinoma, we suggested that eosinophilia in the sputum might relate to the malignancy.

BAC presents diverse radiographic features, ranging from unifocal to multifocal disease. The radiographic spectrum of BAC has been classified into three patterns: (i) solitary nodules or masses; (ii) localized consolidation; and (iii) multicentric or diffuse disease.^{6,7} Of these patterns, multicentric

Figure 4 Two-[fluorine-18] Fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) imaging reveals multiple consolidative lesions in both lungs without FDG uptake.

disease, which consists of multiple nodules or consolidations, occurs in about 30% of patients with BAC and maintains a poorer prognosis than that of localized disease.⁶ In 1999, Akira *et al.* reported HRCT findings of diffuse BAC in 38 patients.³ Although major HRCT findings of diffuse BAC were classified into three patterns of predominantly ground-glass ($n = 4$), consolidation ($n = 22$), or multiple nodules ($n = 12$), most patients had a mixture of these features.³

Attempts have been made to distinguish BAC from other pulmonary diseases. Aquino *et al.* analyzed radiological features for 20 patients to distinguish consolidative BAC from pneumonia, and the BAC group commonly showed coexisting nodules and a peripheral distribution of consolidation.⁸ The other study conducted to distinguish consolidative BAC from pneumonia reported that the BAC group had air bronchograms with a stretched, sweeping, narrowed appearance, widening of the branch angle at bifurcations, and bulging of the fissure.⁹

When compared to HRCT findings of bronchogenic tuberculosis, the frequency of CT findings was not different between the diffuse BAC and bronchogenic tuberculosis groups.³ The diffuse BAC group showed characteristic ground-glass opacity remote from the consolidation and lower lung predominance.³ However, because the radiographic features are often nonspecific, they may play a limited role in the differential diagnosis.³

Although data for BAC are limited to small series, many studies have reported a high FDG-PET false-negative rate for localized BAC.⁶ But reports on diffuse BAC using FDG-PET are limited.¹⁰ One study using FDG-PET in 15 patients with BAC (eight with solitary disease and seven with multifocal disease) reported that six (86%) patients with multifocal disease had a positive scan, and only one had a negative scan.¹⁰ Distinctively, our patient showed a negative PET scan, despite multifocal disease.

In conclusion, invasive mucinous adenocarcinoma could manifest as bilateral areas of consolidation and ground-glass opacities with peripheral predominance on HRCT scans of the chest, like CEP. Invasive mucinous adenocarcinoma may need to be distinguished from CEP through histological confirmation in a patient who does not respond to systemic steroids.

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Disclosure

No authors report any conflict of interest.

References

- 1 Allen JN, Davis WB. Eosinophilic lung diseases. *Am J Respir Crit Care Med* 1994; **150**: 1423–38.
- 2 Austin JH, Garg K, Aberle D *et al.* Radiologic Implications of the 2011 classification of adenocarcinoma of the lung. *Radiology* 2013; **266**: 62–71.
- 3 Akira M, Atagi S, Kawahara M, Iuchi K, Johkoh T. High-resolution CT findings of diffuse bronchioloalveolar carcinoma in 38 patients. *AJR Am J Roentgenol* 1999; **173**: 1623–9.
- 4 Johkoh T, Müller NL, Akira M *et al.* Eosinophilic lung diseases: diagnostic accuracy of thin-section CT in 111 patients. *Radiology* 2000; **216**: 773–80.
- 5 Travis WD, Brambilla E, Noguchi M *et al.* International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011; **6**: 244–85.

- 6 Gandara DR, Aberle D, Lau D *et al.* Radiographic imaging of bronchioloalveolar carcinoma: screening, patterns of presentation and response assessment. *J Thorac Oncol* 2006; **1** (9 Suppl.): S20–6.
- 7 Bonomo L, Storto ML, Ciccotosto C *et al.* Bronchioloalveolar carcinoma of the lung. *Eur Radiol* 1998; **8**: 996–1001.
- 8 Aquino SL, Chiles C, Halford P. Distinction of consolidative bronchioloalveolar carcinoma from pneumonia: do CT criteria work? *AJR Am J Roentgenol* 1998; **171**: 359–63.
- 9 Jung JI, Kim H, Park SH *et al.* CT differentiation of pneumonic-type bronchioloalveolar cell carcinoma and infectious pneumonia. *Br J Radiol* 2001; **74**: 490–4.
- 10 Heyneman LE, Patz EF. PET imaging in patients with bronchioloalveolar cell carcinoma. *Lung Cancer* 2002; **38**: 261–6.