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# A case of Adenocarcinoma of the Lung Associated with Sarcoidosis

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Sarcoidosis, a systemic granulomatous disease of undetermined etiology, is characterized by variable clinical presentation and course. Although sarcoidosis and lung cancer are both frequently encountered pulmonary diseases, their simultaneous occurrence in the same patient is unusual. The causal relationship between the two diseases remains unclear, and the concurrence can cause a diagnostic dilemma and make preoperative staging difficult. We report a case of concurrent sarcoidosis with lung cancer who was initially diagnosed with pulmonary sarcoidosis.

Key words: lung adenocarcinoma, malignancy, sarcoidosis

## CASE REPORT

A 68-year-old nonsmoking woman presented to the chest outpatient service with a 7-day history of productive cough tinged with blood and 4-months of hoarseness in April 2010. She denied other systemic diseases, except sarcoidosis proved by mediastinoscopy with a biopsy of superior mediastinal lymph nodes (Fig.1) at a local hospital in December 2009. She received treatment with prednisolone 20mg daily after diagnosis and the dosage was tapered to 5mg daily on her feedback due to poor medical response. The clinical symptoms of sarcoidosis persisted with no resolution of the lung lesions in the follow-up chest radiograph and she came to our hospital to seek a second opinion.

On admission, her presenting vital signs were: temperature, 36.1°C; pulse rate, 65 beats/min; respiration rate, 20 breaths/min; blood pressure, 120/81 mmHg. There were no signs of jugular venous distention, enlarged thyroid gland or lymphadenopathy. Her lungs were clear and the heart sounds were distinct. Her abdomen was soft without masses or organomegaly. She had no rashes or peripheral edema. The neurological examination revealed a normal mental status without focal neurological deficits. No cutaneous or ocular lesion was seen. The electrocardiography revealed no arrhythmias or conduction abnormalities.

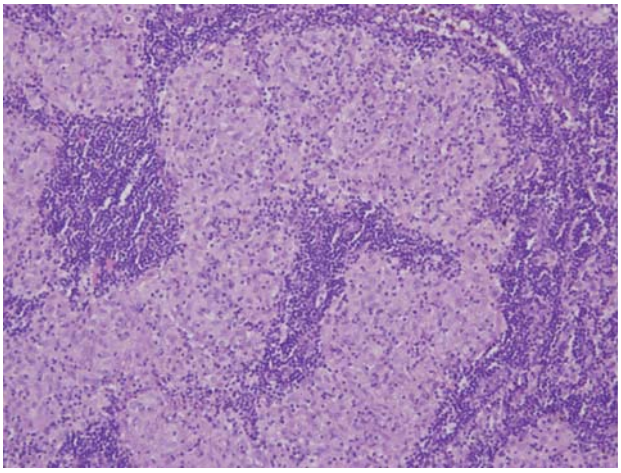

Fig. 1 Mediastinal lymph node biopsy specimen showing non-necrotizing well-demarcated granulomas (hematoxzylin and eosin stain, ×200)

Laboratory studies showed an elevated carcinoembryonic antigen level (74.6 ng/ml, normal 0.0-5.0 ng/ml), carbohydrate antigen 19-9 level (298.2 unit/ml, normal 1.0-35.0 unit/ml) and carbohydrate antigen 125 level (102.5 U/ml, normal 0.0-35.0 U/ml). The complete blood count was disclosed as follows: total white blood cell count $5.3\times10^3/\mu l$ (normal $4\times10^3$ to $11\times10^3/\mu l$), hemoglobin 12.6g/dl (13.5–17.0g/dl), and platelet count $201\times10^3/\mu l$ ($150–400\times10^3/\mu l$). The serial negative results included a blood culture, sputum culture, sputum

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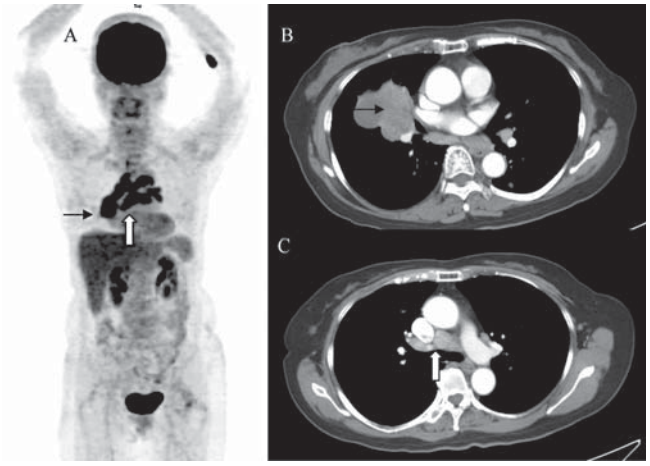


Fig. 2 Whole body $^{18}$F-FDG PET scan showing: An ill-defined lobulated spiculated soft-tissue mass, measuring about 6.2 cm in size, showing intense FDG uptake (initial SUVmax. of 6.1/7.7) over the RML of the lung (black arrow, compatible with chest CT findings, B). Multiple varying-sized FDG-avid nodules, showing soft-tissue density and increased FDG uptake, over the bilateral hilar regions, aortopulmonary window, pretracheal retrocaval space, subcarinal and precarinal spaces with "Lambda" appearance. The largest one measuring about 2.0 cm with initial/delayed SUVmax of 5.7/7.5 in the PTRC space (white arrow, compatible with chest CT findings, C).

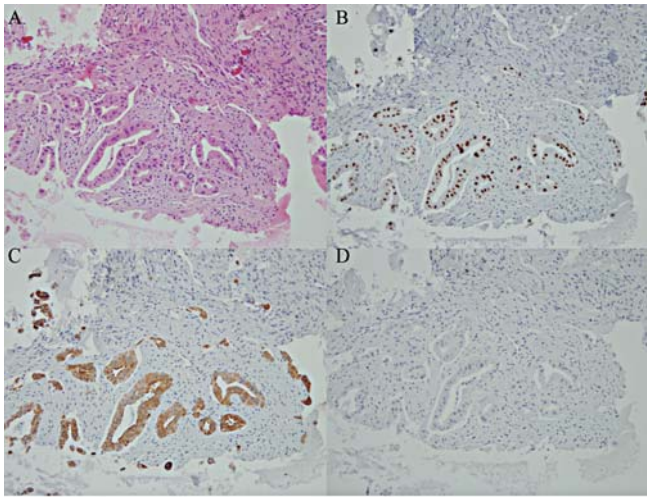


Fig. 3 CT-guiding core needle biopsy of the pulmonary mass specimen showing
A: Hyperchromatic glandular tumor cells infiltrating the fibrotic stroma (Hematoxzylin-Eosin stain ×200).
B: Nuclear staining to thyroid transcription factor-1, indicative of pulmonary origin (×200).
C: Glandular tumor cells are positive cytoplasmic staining for cytokeratin 7 (×200).
D: Glandular tumor cells are all negative for cytokeratin 20 (×200).

specimens for chlamydia pneumoniae antigen, as well as mycoplasma antibody in serum and mycobacterium tuberculosis culture in sputum.

The repeat chest radiograph taken on this admission showed a lobulated soft tissue lesion over the right hilar region. In April 2011, the computed tomography (CT) scan of the chest revealed the lesion had grown from 5.0 cm to 6.4 cm in diameter as compared with that taken in July 2010. Newly developed multiple small nodules of varying sizes (from 0.5 mm to 5.5 mm) were distributed in the posterior segment of both the upper lobes and lower lungs. Multiple enlarged nodes (maximal size: more than 2 cm) at the bilateral mediastinum and hilar regions were also found (Fig. 2).

The patient received a gallium-67 whole body tumor scan in May 2011, which revealed markedly increased gallium uptake at the superior mediastinum, bilateral pulmonary hilar, and parahilar regions. The following whole body positron emission tomography (PET) scan displayed an ill-defined lobulated spiculated soft-tissue mass, measuring about 6.2 cm in size, showing intense $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) uptake over the right middle lobe (RML) of the lung. Multiple varying-sized $^{18}$F-FDG -avid nodules showed soft-tissue density and increased uptake, over the bilateral hilar regions, aortopulmonary window, pretracheal retrocaval space, subcarinal and precarinal spaces (Fig. 2).

The patient underwent a CT-guided biopsy of the right lung lesion and the pathology report indicated a moderately differentiated adenocarcinoma characterized by hyperchromatic small glandular tumor cells infiltrating the desmoplastic stroma with immunohistochemical stains: positive thyroid transcription factor-1, positive cytokeratin 7, negative cytokeratin 20 and positive epidermal growth factor receptor (EGFR: intensity 1+, percentage 20%) (Fig. 3). Under a diagnosis of adenocarcinoma of the lung in RML, $cT_{2b}N_3M_0$, at least, stage IIIb by the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7$^{th}$ edition[1] and gene mutation of EGFR exon 21, the patient chose targeted therapy with gefitinib rather than concurrent chemoradiation. Marked regression of tumor (sized from 6.4 cm to 3.5 cm) and multiple lymph nodes at the bilateral mediastinum and hilar regions were found by the chest radiograph and the chest CT taken three months later (Fig. 4).

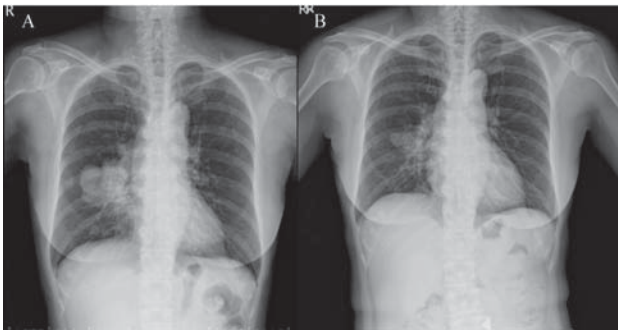


Fig. 4 (A) Chest radiograph showing a lobulated soft tissue lesion about 6.4 cm in size over the right hilar region and the prominence of bilateral hilar shadows. (B) Decreased lung mass size of about 3.5 cm over the right hilar region following treatment with gefitinib for three months.

## DISCUSSION

Sarcoidosis is a systemic granulomatous disorder of unknown cause frequently presenting hilar and mediastinal lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The incidence of sarcoidosis is 15 to 40 per 100,000 of the population per year, and concomitant malignancy is found in 1.2 to 2.5% of patients with sarcoidosis.[2] The main types of concomitant malignancy are lung cancer, lymphoma, testicular, and uterine cancer. The disease is a diagnosis of exclusion best supported by the following three elements: (1) compatible with clinical and radiologic findings; (2) tissue biopsy specimen revealing noncaseating epithelioid granulomas; and (3) the absence of known granulomagenic agents.[3]

Among the methods of biopsy, endobronchial ultrasound-transbronchial needle aspir ation (EBUS-TBNA) of mediastinal lymph nodes has facilitated diagnosis, and often eliminates the need for more invasive procedures, such as mediastinoscopy. It may be superior to standard TBNA for sampling of the mediastinal lymph nodes.[2] However, the false negative rate of TBNA and EBUS-TBNA in the mediastinal staging of non-small cell lung cancer (NSCLC) should be considered, even in those cases in which the cytologic analysis shows negative results due to the possibility of a sampling error.

In our case, the patient was treated with prednisolone under a diagnosis of sarcoidosis in stage II of the chest radiograph findings of bilateral hilar lymphadenopathy, increased bilateral lung marking with mild peribronchial wall thickening, and chronic granulomatous inflammation according to the pathology report of the mediastinal node biopsy.[4] Poor response to medical treatment was noted and she received a gallium-67 whole body tumor scan which could not differentiate metastatic lymphadenopathy from sarcoidosis. The PET scan showed $^{18}$F-FDG uptake over the RML of lung, which was compatible with lung malignancy. The multiple $^{18}$F-FDG-avid nodules in both the hila and mediastinum were consistent with the diagnosis of sarcoidosis, but the condition of superimposed nodal metastases could not be ruled out. She received a lung mass tissue biopsy and moderately differentiated adenocarcinoma was confirmed.

With regard to non-invasive imaging findings, there are many false-positive results with $^{18}$F-FDG PET studies because increased activity is present not only in the malignant tumors, but also in the granulomatous lesions such as sarcoidosis. Therefore, $^{18}$F-FDG PET is not a useful method to differentiate sarcoidosis from malignant tumors.[5]

L-3-[$^{18}$F]-fluoro-$\alpha$-methyltyrosine ($^{18}$F-FMT) as an amino-acid tracer for PET imaging has been developed and its potential use for detecting neoplasms has been confirmed. A preliminary evaluation revealed $^{18}$F-FDG showed high uptake in sarcoidosis and lung cancer, whereas $^{18}$F-FMT demonstrated significant uptake only in lung cancer.[5] $^{18}$F-FMT PET in combination with $^{18}$F-FDG PET is potentially useful for diagnosing sarcoidosis in patients whose lesions could not be excluded from the possibility of coexistent malignancy.

As for the pathology results, the presence of granulomas on tissue biopsy alone is inadequate for diagnosing sarcoidosis. When the radiographic findings of bilateral hilar lymphadenopathy are seen in cancer patients, it is tough to differentiate sarcoidosis from metastatic lymphadenopathy, which have different clinical importance and require varying treatment plans. In addition, possible sarcoid reactions in malignant tumors rather than systemic sarcoidosis should be suspected when localized groups of epithelioid cell tubercles of the sarcoid type are observed in various tissues as a response to the infiltrative processes, such as malignant diseases, and the reactions may lead to the onset of sarcoidosis.[6]

In our case, the left mediastinal lymph node biopsy is suggested to be differentiated from the $N_2$ and $N_3$ lesion, which could affect the pathological stage from stage IIIa to IIIb, but the patient refused for personal reasons.[1] An improvement in the bilateral hilar and mediastinal lesion was found following gefitinib use, which correlated with mediastinal downstaging. Therefore, the initial stage IIIb seems to be more reasonable for the diagnosis.

Concerning steroid use, in a Cochrane review of cor-

ticosteroids for pulmonary sarcoidosis in stage II and III, treatment with oral steroids for 6 to 24 months improved chest radiograph findings compared with placebo.[7] The initial dose of prednisolone was suggested to be 20-40 mg daily for 4-6 weeks, followed by slow tapering over 2-3 months. In this case, the patient was initially treated with prednisolone 20mg daily, which may be titrated to 40mg daily gradually rather than be tapered to 5mg daily personally if clinical symptoms persist. In view of the standard treatment for advanced NSCLC, platinum-based chemotherapy is the mainstay of treatment and corticosteroids are not indicated in any combination therapy.[8] Prednisone or methylprednisolone may reduce the inflammation caused by lung cancer or radiation therapy, but have no effect in treating lung cancer.

## CONCLUSION

Clinicians should be aware of the potential risk of malignancy in sarcoid patients. When sarcoid patients develop new lesions or adenopathy, the histologic biopsy should be considered to rule out coexisting neoplasms. Additionally, the method of $^{18}$F-FMT PET with $^{18}$F-FDG PET may play a role in the initial evaluation. Further, the treatment response to prednisolone may help differentiate the clinical dilemma, especially in advanced sarcoidosis. If the symptoms, radiographic abnormalities, and pulmonary function tests do not improve, more intervention for lung malignancy should be initiated to avoid possible misdiagnosis.

## DISCLOSURE

The authors declare this study has no conflict of interest.

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