



Case report

Sarcoidosis or cancer? That is the question

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ABSTRACT

Sarcoidosis is a granulomatous inflammatory disease of unknown etiology. Sarcoid like granuloma may develop concurrently or following cancer. Detection of granuloma in mediastinal lymph nodes biopsy in patient with pulmonary nodules may be a concern for undiagnosed lung cancer. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a diagnostic modality of choice for the lung lesions.

We discussed A 71-year-old man with history of chronic obstructive lung disease (COPD), who presented with a lung nodule and mediastinal lymphadenopathies. The nodule was 9.9 mm when detected and his endobronchial ultrasound-guided transbronchial fine needle aspiration (EBUS-TBNA) of lymph nodes in station 7 & 4R showed normal lymph node structure. Two years later, his surveillance chest CT scan indicated an increase in the size of the nodule to 15 mm, and PET/CT showed Fluorodeoxyglucose (FDG) avid nodule & mediastinal Lymph nodes. He complained of Shortness of breath after 2–3 climbs of stairs, without any history of cough or fever. He quit cigarette smoking recently and smoked 50 pack years before. He underwent another set of EBUS and was referred for sarcoidosis treatment due to finding non-necrotizing granuloma in 4L and 11L lymph nodes. The patient also underwent another biopsy of the nodule concerning the possibility of cancer sarcoid syndrome. A poorly differentiated lung adenocarcinoma positive for GATA3, positive for P63 and CK7, TTF-1 was reported.

Concurrent lung cancer and granulomatous reaction in mediastinal lymph nodes are being reported more often. Recent studies have shown a better survival of patients with diagnosis of cancer and granulomatous findings of sarcoidosis. Performing lung biopsy from any nodular lesion in a patient with sarcoidosis is essential for the differential diagnosis and early therapeutic measures.

1. Introduction

Sarcoidosis is a granulomatous inflammatory disease of unknown etiology and a diagnosis of exclusion. It requires both compatible clinical features and pathologic findings for differential diagnosis. The role of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has been discussed in recent studies as a more accurate diagnostic modality for findings related to the lung lesions [1]. Sarcoid like granuloma may develop concurrently or following cancer.

Our and others reported an improved survival among cancer patients who developed granulomatous reactions of sarcoidosis. Presence of the granuloma was associated with a lower incidence of stage 4 disease (metastasis). (OR = 0.195, 95% CI 0.073–0.521, $p = 0.001$) with a significant survival improvement at 2, 4, 6 and 10 years following the cancer diagnosis [2]. Steinfert et al. showed that among patients with

non-small cell lung carcinoma, sarcoid reaction of lymph nodes is only present in stage I of the lung cancer. A better outcome has been reported in patients with cancer which could be related to a strong cell-mediated antitumor response [3]. The presence of granulomatous sarcoidosis reaction among the patients with non-small cell lung carcinoma has predicted a lower rate of disease recurrence after definitive surgical resection [4]. Concurrent diseases and the association between cancer and sarcoidosis require further evaluation of any lesion in these patients. The similarity between signs and symptoms of lung sarcoidosis and lung cancer may result in a delay in cancer diagnosis when the cancerous lung lesion could be treated surgically in an early stage.

We discuss a case with confirmed sarcoidosis and a lung nodule in CT scan that pathology results of the nodule showed a concurrent diagnosis of lung cancer and sarcoidosis.

Abbreviations: COPD, chronic obstructive lung disease; EBUS-TBNA, Endobronchial ultrasound-guided transbronchial fine needle aspiration; CT, Computed tomography; RLL, Right lower lobe; FDG, Fluorodeoxyglucose.

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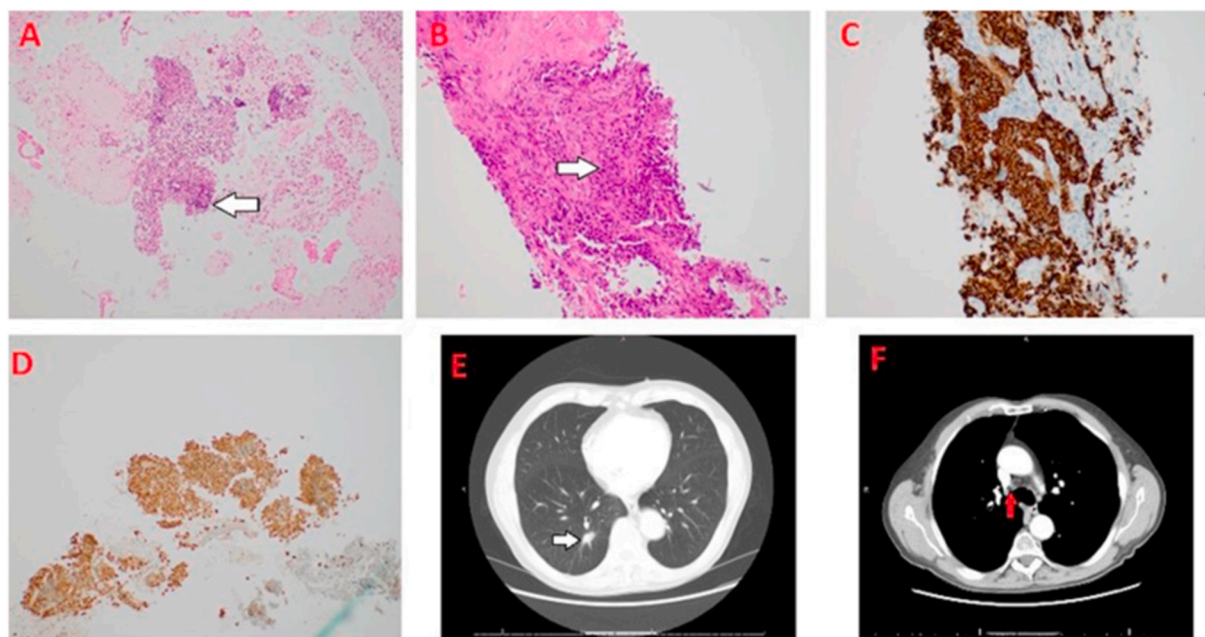
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A. Granuloma in lymph node cytology **B.** Granuloma with power of 20 **C.** Immunostaining with positive CD-68 highlights histiocytes in granulomas **D.** Core biopsy immunostaining positive CK7 with Poorly differentiated adenocarcinoma **E.** Arrow shows Pulmonary Nodule in Right lower lobe **F.** Arrow shows mediastinal lymphadenopathy

Fig. 1. A. Granuloma in lymph node cytology B. Granuloma with power of 20 C. Immunostaining with Positive CD-68 highlights histiocytes in granulomas D. Core biopsy immunostaining positive CK7 with Poorly differentiated adenocarcinoma E. Arrow shows Pulmonary Nodule in Right lower lobe F. Arrow shows mediastinal lymphadenopathy.

1.1. Case history

A 71-year-old man known case of chronic obstructive lung disease (COPD) with a past medical history of 50 pack years cigarette smoking, presented with a lung nodule and mediastinal lymphadenopathies. The nodule was 9.9 mm in right Lower Lobe (RLL) when detected. He underwent Endobronchial ultrasound-guided transbronchial fine needle aspiration (EBUS-TBNA) of lymph nodes in station 7 & 4R which were reported normal lymph node structure. Two years later, his surveillance chest CT scan showed that the size of nodule increased to 15 mm, and PET/CT showed Fluorodeoxyglucose (FDG) avid nodule & mediastinal Lymph nodes. He complained of Shortness of breath after 2–3 climbs of stairs, without any history of cough or fever. He quit cigarette smoking recently and smoked 50 pack years before. His pulmonary function test was consistent with mild flow obstruction. He underwent another set of EBUS and was referred for sarcoidosis treatment due to finding non-necrotizing granuloma in 4L and 11L lymph nodes (Fig. 1). Concerning to cancer sarcoid syndrome the patient underwent another biopsy for pulmonary nodule prior sarcoidosis treatment. A poorly differentiated adenocarcinoma consistent with lung origin was reported. Immunohistochemistry staining of the nodule showed focally positive for GATA3, positive for P63 and CK7, TTF-1. The lung tissue was negative for Thyroglobulin, CK20, NAPSIN A, P40, CD56, and Synaptophysin. Patient was referred to thoracic surgery for surgical intervention. The patient did not have any signs or symptoms of systemic sarcoidosis.

2. Discussion

Concurrent lung cancer and granulomatous reaction in mediastinal

lymph nodes are being reported more often. We reported a case with poorly differentiated adenocarcinoma of lung with concurrent non-necrotizing granuloma. Performing lung biopsy from the single nodular lesion was the diagnostic key for this patient.

EBUS-TBNA is an excellent modality for evaluation of pulmonary lung lesions. The possibility of reaching to the lesions for sampling through EBUS has narrowed down the differential diagnosis by providing more accurate pathologic findings from the lung lesions. This modality is specifically providing high accuracy in stage one sarcoidosis [1,5].

The possible association between sarcoidosis and malignancies has been debated throughout the years. The first epidemiologic study that found a higher than expected incidence of malignancy through a nationwide sarcoidosis registry was done by Brincker and Wilbek in Denmark dated as 1974 [6]. Chopra et al. indicated an increased relative risk of cancer in patients with sarcoidosis compared to general population although there was a low absolute risk among them [7].

A systematic review and meta-analysis showed a significant, although moderate, relationship between the two diseases. Significant relative risks of cancer was found respectively in the following types of cancer in association with Sarcoidosis: skin (RR, 2.00; 95% CI, 1.69–2.36), hematopoietic (RR, 1.92; 95% CI, 1.41–2.62), upper digestive tract (RR, 1.73; 95% CI, 1.07–2.79), kidney (RR, 1.55; 95% CI, 1.21–1.99), liver (RR, 1.79; 95% CI, 1.03–3.11), and colorectal cancers (RR, 1.33; 95% CI, 1.07–1.67) [8].

Cohen et al. discussed this association in three settings including sarcoidosis-lymphoma syndrome or association with other hematologic malignancies, Development of sarcoidosis and solid organ tumors, and finally sarcoidosis as a paraneoplastic syndrome related to the

associated cancer. Typically, the sarcoid reactions involve regional lymph nodes or the visceral organ of tumor origin [9]. However, distance lymph node involvement are associated with less metastatic lesions and better survival [10].

There is also a reciprocal situation when the lung cancer may be diagnosed first and due to the multiple lymphadenopathies, resection of the tumor may not be considered if sarcoidosis remains undiagnosed. Therefore, it is significantly important to consider co-existence of these two conditions and differentiate the lymphadenopathies caused by non-caseating granulomas from metastasis.

3. Conclusion

Since sarcoidosis and lung cancer can be present concurrently, performing biopsy to obtain pathology results from any suspected lung lesion in a patient diagnosed with sarcoidosis is essential. Therefore we suggest that no lesion should be missed in these patients without biopsy by assuming lung involvement of sarcoidosis [11]. This meticulous approach to the differential diagnosis among sarcoidosis patients can improve the patient's outcome and prognosis while diagnosing the cancer at an earlier stage.

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Informed consent and patient details

This study involves patient data. HIPPA is waived by Miami VA Health care System IRB for this case report.

Declaration of competing interest

None.

References

- [1] T. Nakajima, K. Yasufuku, K. Kurosu, Y. Takiguchi, T. Fujiwara, M. Chiyo, K. Shibuya, K. Hiroshima, Y. Nakatani, I. Yoshino, The role of EBUS-TBNA for the diagnosis of sarcoidosis—comparisons with other bronchoscopic diagnostic modalities, *Respir. Med.* 103 (12) (2009) 1796–1800.
- [2] M. Murthi, K. Yoshioka, J.H. Cho, S. Arias, E. Danna, M. Zaw, G. Holt, K. Tatsumi, T. Kawasaki, M. Mirsaedi, Presence of concurrent sarcoid-like granulomas indicates better survival in cancer patients: a retrospective cohort study, *ERJ Open Research* 6 (4) (2020), 00061-02020.
- [3] M.P. Zaborowski, S. Michalak, Cell-mediated immune responses in paraneoplastic neurological syndromes, *Clin. Dev. Immunol.* 2013 (2013) 630602.
- [4] D.P. Steinfurt, A. Tsui, J. Grieve, M.L. Hibbs, G.P. Anderson, L.B. Irving, Sarcoid reactions in regional lymph nodes of patients with early stage non-small cell lung cancer predict improved disease-free survival: a pilot case-control study, *Hum. Pathol.* 43 (3) (2012) 333–338.
- [5] S. Dhooria, I.S. Sehgal, N. Gupta, A.N. Aggarwal, D. Behera, R. Agarwal, Role of radial endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of pulmonary nodules: case report and literature review, *Lung India* 34 (1) (2017) 61–64.
- [6] P. Ungprasert, N. Srivali, K. Wijarnpreecha, C. Thongprayoon, W. Cheungpasitporn, E.L. Knight, Is the incidence of malignancy increased in patients with sarcoidosis? A systematic review and meta-analysis, *Respirology* 19 (7) (2014) 993–998.
- [7] A. Chopra, M.A. Judson, How are cancer and connective tissue diseases related to sarcoidosis? *Curr. Opin. Pulm. Med.* 21 (5) (2015) 517–524.
- [8] M. Bonifazi, F. Bravi, S. Gasparini, C. La Vecchia, A. Gabrielli, A.U. Wells, E. A. Renzoni, Sarcoidosis and cancer risk: systematic review and meta-analysis of observational studies, *Chest* 147 (3) (2015) 778–791.
- [9] P.R. Cohen, R. Kurzrock, Sarcoidosis and malignancy, *Clin. Dermatol.* 25 (3) (2007) 326–333.
- [10] M. Murthi, K. Yoshioka, J.H. Cho, S. Arias, E. Danna, M. Zaw, G. Holt, K. Tatsumi, T. Kawasaki, M. Mirsaedi, Presence of concurrent sarcoid-like granulomas indicates better survival in cancer patients: a retrospective cohort study, *ERJ Open Res* 6 (4) (2020).
- [11] M. Muramatsu, M. Kuriyama, K. Takahashi, H. Miyamoto, T. Uekusa, T. Danbara, Y. Fukuchi, [A case of resected squamous cell carcinoma of the lung complicated with sarcoidosis], *Nihon Kokyuki Gakkai Zasshi* 38 (9) (2000) 720–725.