

6. Voldby N, Folkersen BH, Rasmussen TR. Mediastinitis: a serious complication of endobronchial ultrasound-guided transbronchial needle aspiration. *J Bronchology Interv Pulmonol*. 2017;24:75–9.
7. Steinfort DP, Johnson DF, Irving LG. Infective complications from endobronchial ultrasound-transbronchial needle aspiration. *Eur Respir J*. 2009;34:524–5.

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Mediastinal sarcoid-like reaction in cancer patients



Sarcoidosis is a multisystem disease of unknown origin characterized by the presence of noncaseating epithelioid cell granulomas.

When these granulomas develop in the lymph nodes, and the patient does not meet criteria for the diagnosis of systemic sarcoidosis we refer to this as a sarcoid-like reaction.¹

Because of the clinical implications of the diagnosis of lymph node metastasis, mediastinoscopy plays a key role in the differential diagnosis in these patients.

We conducted a retrospective chart review of all patients who had undergone mediastinoscopy in our hospital from 2010 to 2015 with a diagnostic of sarcoidosis or sarcoid-like reaction and history of solid organ malignancy.

Seventy-four mediastinoscopies were performed by three different surgeons. There were 9 cases of biopsy-proven presence of noncaseating epithelioid cell granulomas and the stain and the culture for acid-fast Bacilli and fungi were negative.

5 patients met criteria for the diagnosis of systemic sarcoidosis. 3 of the 4 patients who did not have a diagnosis of systemic sarcoidosis had a history of malignancy organ solid. We present these 3 cases in order to focus on sarcoid-like reaction in cancer patients.

Cases reports

Case 1

A 39 year-old man with a previous history of testicular seminoma, in 2012 was treated with cisplatin, bleomycin, and etoposide, after the appearance of retroperitoneal lymph node metastasis. A year later in a computed tomography (CT) control intrathoracic lymph node was revealed. It showed a 15 mm premediastinal and 20 mm right paratracheal lymph nodes.

In positron emission tomography combined with a computed tomography scan (PET-CT) showed premediastinal and right paratracheal lymph nodes with a maximum "standardized uptake value" (SUV) of 4.8 (Fig. 1).

There was no elevation of the tumour markers beta-human chorionic gonadotropin (beta-hCG). In view of the clinical history, we suspected a recurrence of tumour lymph nodes, and a mediastinoscopy was performed. Histopathological examination of the resected lymph nodes showed a noncaseating epithelioid cell granuloma in which no tumour cells were observed. No retroperitoneal or intrathoracic lymph nodes recurrence has been observed during follow-up.

Case 2

A 47 year-old man with a previous history of rectum cancer, received chemo and radiotherapy neoadjuvant, cisplatin and capecitabine. After that, low anterior rectal resection and liver metastasectomy was performed. And the treatment was completed with 12 cycles of FOLFOX and bevacizumab.

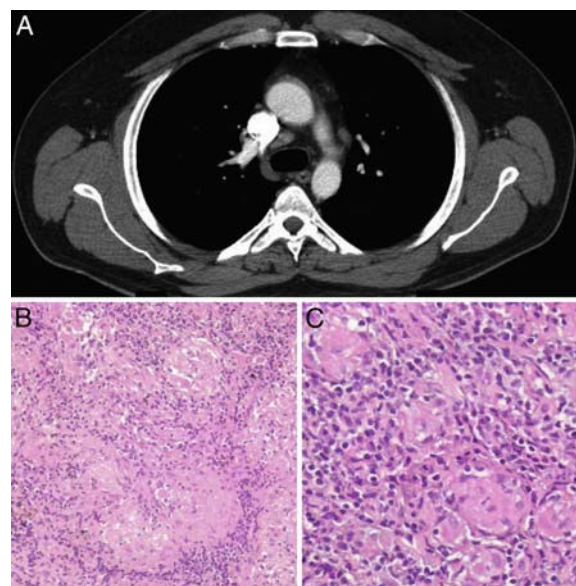


Figure 1 (A) Axial CT in which mediastinal lymph nodes are observed. (B and C) Non-caseating granulomas associated with lymphocytic infiltrate. H&E (10× and 20×).

After 2 years of follow up, mediastinal lymph nodes were observed during a computed CT control. The maximum size of the lymph nodes was 17 mm. Physical examination, laboratory tests, including carcinoembryonic antigen were unremarkable. In PET-CT, we observed mediastinal lymph nodes with a maxim SUV of 6.2. Endobronchial ultrasound with fine-needle aspiration (FNA) was performed but not a significant amount of histological tissue was obtained.

Mediastinoscopy and biopsy were performed, and the diagnosis was sarcoid-like reaction. No recurrence of cancer has been observed during follow-up.

Case 3

A 47 year-old woman with a previous history of clear cell ovarian carcinoma, stage I, was treated with oophorectomy and adjuvant chemotherapy with cisplatin. At the time of diagnosis, mediastinal lymphadenopathy was not observed.

Six months later, CT control was performed. It revealed 24 mm subcarinal and 15 mm subaortic lymph nodes. A PET-CT showed subcarinal and subaortic lymph nodes with a maxim SUV of 2.53 and 3.3 respectively. Subcarinal lymph node biopsy was performed as a result of sarcoid-like reaction. She has been followed up and no recurrence of cancer has been observed.

Discussion

Sarcoid-like reaction in cancer patients has been reported in 4% and 14%.²

These reactions often occur in patients with lymphoma or testicular tumour,³ and usually appear in the local lymph nodes draining. However, in our study sarcoid-like reaction is in a distant location, the mediastinum.

Sarcoid-like reaction is histologically identical to sarcoidosis, except for the presence of a population of B cells, which is not observed in sarcoidosis.⁴ Reactions occur because of an immune response after an aggression, whether infectious, chemical, tumour or a foreign body.

The fact that sarcoid-like reactions could appear in distant locations supports the hypothesis that it could develop from an immunological response involving T cells. The host's immune response to cancer or cancer therapy may predispose to sarcoid-like reaction, perhaps by acting as a type of auto-Kveim reagent.⁵

It has been theorized that certain chemotherapies may cause predisposition to the development of sarcoid-like reaction, alpha interferon, cisplatin, bleomycin or interleukin 2.^{1,6} In our study, all patients had been previously treated with cisplatin, so we there are reasons to suspect that this agent could develop a role in the genesis of this disease. However, chemotherapy is not used in all patients with cancer who have sarcoid-like reaction.^{5,6} So, the development of these diseases in these patients cannot be explained by chemotherapy alone.

Mediastinal lymphadenopathy in a patient with a previous history of malignancy requires an exhaustive diagnosis

because of the potentially toxic effects of cancer therapeutics and the prognostic implications.⁵

PET-CT has a limited role in diagnosis. Chowdhury et al. identified a 1.1% of prevalence in sarcoid-like reaction in patients who were performing in PET-CT oncologic context.⁷ However, no SUV value has been determined that would enable us to discern between benign or malignant, so accurate diagnosis should always be made histologically.

Other techniques for diagnosis such as endobronchial ultrasound with fine-needle aspiration (EBUS-FNA)⁸ or guided biopsy CT have been reported. A study shows a sensitivity of 100%, a specificity of 93%, of EUS-FNA for the diagnosis of mediastinal sarcoidosis.⁹ Béchade et al. describe within a small number of patients the possibility of taking samples with the needle of 19 G to improve the histopathological examination.¹⁰

Nevertheless, mediastinoscopy takes a significant amount of histological tissue, even entire lymph nodes. It allows the diagnosis of micrometastases, which is essential for the correct diagnosis.

Conclusion

Sarcoid-like reaction is a disease that must be included in the differential diagnosis of patients with a history of malignancy and present with mediastinal lymph nodes.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Cohen PR, Kurzrock R. Sarcoidosis and malignancy. *Clin Dermatol.* 2007;25:326–33.
2. Brincker H. Sarcoid reactions in malignant tumours. *Cancer Treat Rev.* 1986;13:147–56.
3. Paparel P, Devonec M, Perrin P, Ruffion A, Decaussin-Petrucci M, Akin O, et al. Association between sarcoidosis and testicular carcinoma: a diagnostic pitfall. *Sarcoidosis Vasc Diffuse Lung Dis.* 2007;24:95–101.
4. Brincker H, Pedersen NT. Immunohistologic separation of B-cell-positive granulomas from B-cell-negative granulomas in paraffin-embedded tissues with special reference to tumor-related sarcoid reactions. *APMIS.* 1991;99:282–90.
5. Hunt BM, Vallières E, Buduhan G, Aye R, Louie B, et al. Sarcoidosis as a benign cause of lymphadenopathy in cancer patients. *Am J Surg.* 2009;197:629–32.
6. Grados A, Ebbo M, Bernit E, Veit V, Mazodier K, Jean R, et al. Sarcoidosis occurring after solid cancer: a nonfortuitous association: report of 12 cases and review of the literature. *Medicine.* 2015;94(28):e928.
7. Chowdhury FU, Sheerin F, Bradley KM, Gleeson FV, et al. Sarcoid-like reaction to malignancy on whole-body integrated (18)F-FDG PET/CT: prevalence and disease pattern. *Clin Radiol.* 2009;64:675–81.
8. Kennedy MP, Jimenez CA, Mhatre AD, Morice RC, Eapen GA. Clinical implications of granulomatous inflammation detected by endobronchial ultrasound transbronchial needle aspiration in patients with suspected cancer recurrence in the mediastinum. *J Cardiothorac Surg.* 2008;3:8.

9. Fritscher-Ravens A, Ghanbari A, Topalidis T, Pelling M, Kon OM, Patel K, et al. Granulomatous mediastinal adenopathy: can endoscopic ultrasound-guided fine-needle aspiration differentiate between tuberculosis and sarcoidosis? *Endoscopy*. 2011;43:955–61.
10. Béchade D, Roubaud G, Garbay D, Soubeyran I, Hé S, Cazeau AL, et al. Mediastinal sarcoidosis in an oncologic context: role of endoscopic ultrasound-guided fineneedle aspiration. *Rev Med Int*. 2013;34:600–4.

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Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia mimicking metastatic disease



Dear Editor,

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare disorder, with about 200 cases described in the most recent review studies.¹

We present a case of a 53-year old woman, complaining of a chronic non-productive cough and dyspnea. She had previously been assigned as a COPD patient. The patient was a non-smoker with no relevant exposure context. Pulmonary function tests demonstrated a mild obstructive pattern: FEV1 1.76 L (85% of predicted); FVC 3.31 L (123% of predicted); FEV1/FVC 53%. During the work-up a CT was performed showing diffuse solid pulmonary nodules (Fig. 1A), the largest in the right middle lobe (RML) measuring 18 mm (Fig. 1B), and a diffuse mosaic attenuation pattern (MAP) (Fig. 1C). A comparative study was performed with a previous CT from 4 years earlier (in 2010), which revealed an increase in nodule number and size, particularly those located in the RML. Despite the suspicion of lung metastases, due to the insidious increase of nodules dimensions, a surveillance CT was suggested. The follow-up CT, performed 9 months later (in 2015) did not show any changes in the pulmonary findings. Considering the persistence and apparent non-specificity, after a multidisciplinary meeting, it was decided to biopsy the largest nodule. This coincided with the diagnosis of invasive ductal carcinoma of the left breast, which was treated with mastectomy and chemotherapy. Therefore, the transthoracic needle biopsy of the lung was postponed to 2016 and, as it shown to be a carcinoid tumour, the main concern was that a metastatic disease could not be excluded only by that biopsy. So, it was decided to perform a second biopsy, which also revealed the presence of a carcinoid tumour. Since the differential diagnosis between typical or atypical carcinoid tumours can only be performed by exeresis, it was decided to perform an atypical resection of largest pulmonary nodules. The pathologic exam disclosed features consistent with DIPNECH with tumourlets and two

typical carcinoid tumours (Fig. 2). The patient recovered well from the surgery, is now under surveillance and being medicated with inhaled corticosteroids and long-acting β_2 -agonist for treatment of the obstructive component of the pulmonary disease.

DIPNECH is characterized by the proliferation of pulmonary neuroendocrine cells (PNECs), usually located in bronchial wall and confined to epithelium.^{1,2} If these proliferations extend beyond the basement membrane, they are called tumourlets (PNECs aggregates <5 mm) or carcinoid tumours (nodules >5 mm).³ DIPNECH predominantly affects middle aged women. Characteristically it has an insidious onset and, by the time of the diagnosis, symptoms have often been present for several years. Persistent, chronic non-productive cough, exertional dyspnea and wheezing are the most frequently reported symptoms. Pulmonary function tests typically reveal an obstructive or mixed ventilatory defect, without a significant response to bronchodilators.^{1,2} Patients are usually misclassified as having asthma or COPD.

The CT abnormalities associated with DIPNECH are related to airway disease, including MAP, bronchial wall thickening, and in some cases bronchiectasis and mucoid impaction. MAP is a consequence of constrictive bronchiolitis.² The radiological hallmark of DIPNECH is the presence of solid or ground-glass nodules, which correspond to either tumourlets or carcinoid tumours. Characteristically, the nodules demonstrate an indolent growth during the follow-up.^{2,3}

The role of bronchoalveolar lavage is not established in DIPNECH, although some reports describe the presence of lymphocytosis.⁴

In the appropriate clinical (middle-aged woman with chronic cough) and radiological (pulmonary nodules with MAP) scenario, DIPNECH is the main diagnosis to be considered, however diagnosis is mainly histological and surgical biopsy is the gold standard diagnostic test.^{1,2}

Information regarding treatment and clinical course of DIPNECH is scarce and data concerning long term follow-up are limited.^{1,2} It has been described that patients maintain long-term stability or a slowly progressive symptomatology and functional decline.² Due to the indolent nature of DIPNECH, a conservative management is often adopted.²