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DOI: 10.1183/09031936.00170912

Sarcoid-like lesion is a frequent benign cause of lymphadenopathy in neoplastic patients

To the Editor:

Sarcoidosis is a systemic granulomatous disease of unknown origin, characterised by the widespread development of noncaseating epithelioid cell granulomas in more than one organ system. Clinical and radiographic aspects of sarcoidosis and malignancy might mimic one another, making the distinction between the two difficult in some cases. Cancer and sarcoidosis have been associated in some case series but this association remains controversial; several studies from the literature suggest that this association is not fortuitous [1, 2]. Sarcoidosis may precede, follow or occur concurrently with cancer, both haematological malignancies and solid tumours [2].

We wanted to evaluate the incidence of morphological features of sarcoidosis in patients followed up for previous cancer who develop hilar/mediastinal lymphadenopathies with no pulmonary lesions. We performed a retrospective chart review of all patients who were referred to our pulmonology department (Morgagni Hospital, Forlì, Italy) in the period between January 2007 and December 2011 with a new onset of hilar/mediastinal lymphadenopathies (with no pulmonary lesions) during follow-up for previous malignancies. Patients underwent endobronchial ultrasound (EBUS) or transoesophageal ultrasound (EUS) trans-bronchial needle aspiration (TBNA) under deep sedation (*i.v.* propofol). Lymphadenopathies were diagnosed 49 ± 69 months after the diagnosis of previous malignancy (minimal and maximal duration between cancer diagnosis and EBUS/EUS was 3 and 334 months, respectively). All pathology specimens were reviewed at our institute. Specimens were classified as inadequate (in the absence of lymphocytes) or diagnostic (in the presence of malignant cells, granulomas and mature lymphocytes). A granuloma was defined in this study as a discrete nodular aggregate of epithelioid histiocytes. In the case of inadequate samples, patients were addressed to standard cervical mediastinoscopy or video-assisted thoracoscopy for further investigations before any surgical treatment. In case of a positive cytological result of malignancy at EBUS-TBNA, patients were treated accordingly. The study was approved by the local institutional review board and all subjects gave written informed consent.

As shown in table 1, a total of 48 patients underwent EBUS/EUS-TBNA; for all patients, the procedure was completed without problems and the feasibility of the procedure was 100%. The mean patient age was 63 yrs (range 20–81 yrs); 31 patients were male and 17 were female. Patients had been followed-up for lung cancer (n=10), lymphoma (n=9), breast cancer (n=7), urologic cancer (n=6), gastrointestinal tumours (n=6), larynx/pharynx tumours (n=4), gynaecological tumours (n=3) or other cancer (n=8) (table 1). Six patients had a history of two or more tumours in the past. None of the patients had suffered local recurrence or distant metastasis before the procedure was performed. Procedure was diagnostic in 45 (94%) patients while inadequate specimens were obtained in three (6%) patients. Among the 45 adequate samples, EBUS/EUS-TBNA showed non-necrotising granulomas with mature lymphocytes in a background suggestive of sarcoidosis in 12 (26.7%) patients, lymph node metastases in 13 (28.9%) patients and hyperplastic nonspecific lymphadenopathy in 20 (44.4%) patients (table 1). Negative samples were confirmed by surgical intervention in three cases while 17 patients were followed-up for 12 months; none of the patients suffered relapse or oncological events during the period of follow-up and all patients were alive and free of disease at the time of writing. Among the 12 patients with non-necrotising granulomas, 11 (92%) patients were asymptomatic at the time of EBUS/EUS-TBNA and during the subsequent follow-up (average time 14 months); only one patient required steroid treatment for asthenia.

When the noncaseating epithelioid cell granuloma lesion of sarcoidosis is present but without accompanying systemic symptoms, this is referred to as a ''sarcoid-like reaction'' and is not distinguishable in terms of histopathological criteria [3].

TABLE 1 Characteristics of patients

Patients n	48
Age yrs	63 (20–81)
Sex	
Male	31 (65)
Female	17 (35)
Primary cancer	
Lung cancer	10 (21)
Lymphoma	9 (19)
Hodgkin n	5
Non-Hodgkin n	4
Breast cancer	7 (15)
Urological	6 (13)
Gastrointestinal	6 (13)
Larynx/pharynx	4 (8)
Gynaecological tumours	3 (6)
Other	8 (17)
Results	
Inadequate	3 (6)
Diagnostic	45 (94)
Sarcoidosis	12 (26.7)
Metastasis	13 (28.9)
Hyperplastic nonspecific lymphadenopathies	20 (44.4)

Data are presented as n (%) or mean (range), unless otherwise stated. Six patients had a history of two or more tumours in the past.

A sarcoid-like reaction may occur in association with malignancies, either adjacent to the primary malignant site or to local drainage nodes. The proximity of sarcoid-like reactions to the primary tumour location prompted the initial hypothesis that granuloma formation is a result of a local reaction to tumour products and is probably due to the result of an immunological response to an antigenic trigger [4]. Meanwhile, sarcoid-like reactions in distant locations support the theory that there are soluble circulating tumour antigenic factors [5]. Cancer-associated sarcoid-like reactions have been observed both in patients with haematological malignancies (chronic lymphocytic leukaemia, chronic myelogenous leukaemia, Hodgkin or non-Hodgkin disease, T-cell lymphoma, *etc.*) and solid tumours. Whether the presence of sarcoid-like reactions correlates with a different prognosis of the associated neoplasms is unclear.

Differentiating sarcoid-like reactions from systemic sarcoidosis is vital, as a wrong diagnosis of sarcoidosis and the subsequent delay in properly treating the underlying malignancy can be catastrophic [6, 7]. To our knowledge, only a few studies have examined the prognostic significance of the presence of a sarcoid-reaction in malignancies. STEINFORT *et al.* [8] demonstrated that in patients undergoing definitive surgical resection of early-stage nonsmall cell lung cancer, the presence of sarcoidal reactions in regional lymph nodes may be associated with a reduced rate of disease recurrence, compared with those without this pathological finding; previous reports have noted improved prognosis in patients with sarcoidal reactions in Hodgkin lymphoma [9, 10].

The finding of hilar/mediastinal lymphadenopathies during follow-up for malignancies usually raises suspicion of cancer recurrence. This was a small retrospective study, with all the limitations inherent in such methodology, but it suggests that sarcoidosis or sarcoid-like reaction should be considered in the differential diagnosis of patients with a history of malignancy who develop hilar and/or mediastinal lymphadenopathies. Both cancer and sarcoid-like reaction are ^{18}F-fluorodeoxyglucose avid; therefore, a positron emission tomography scan may be useful in selecting possible biopsy sites, by identifying organ involvement not appreciated by routine methodology, but not in differentiating between the two entities. If uncertainty remains, tissue diagnosis is strongly recommended to avoid misdiagnosis and overtreatment. Larger series are needed to achieve significance and enable more accurate conclusions to be drawn regarding prognosis and optimum management of these patients [6].

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Statement of Interest: None declared.

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DOI: 10.1183/09031936.00141212