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Extrapulmonary Tumors and Sarcoidosis: An Incidental or Real Association?☆

Tumores extrapulmonares y sarcoidosis. ¿Relación casual o real?

To the Editor:

Sarcoidosis is a systemic granulomatous disease of unknown etiology that usually affects young patients, with an estimated incidence in Spain of 1.36/100 000 inhabitants.[1] The pathogenesis of sarcoidosis is thought to be related with exposure to certain environmental factors in genetically predisposed individuals.[2,3] Whether or not patients with sarcoidosis have a greater risk of developing cancer is debatable,[4,5] but reports in the literature of the tumor appearing before the diagnosis of sarcoidosis are rare and limited to case series. We report a series of 14 patients who were diagnosed with sarcoidosis during oncological follow-up of extrathoracic cancers.

We performed a retrospective, descriptive, observational follow-up (January 2012–June 2017) of patients with extrathoracic tumors referred to the bronchoscopy unit for the exploration of new mediastinal lymphadenopathies on a chest computed tomography (CT).

A total of 2420 patients were evaluated, of which 437 candidates met the study criteria; 404 were finally included. Reasons for exclusion were contraindication for endobronchial ultrasound for various reasons (12 cases), mediastinal lymphadenopathies already present at the time of cancer diagnosis (15 cases), or patient's refusal to perform more diagnostic tests (6 cases). All patients underwent linear endobronchial ultrasound for lymphadenopathy aspiration (Olympus BF-UC180F; Olympus ViziShot needle NA-201SX-4022, 21G) under sedation with midazolam. Fourteen patients (7 men and 7 women; mean age at diagnosis of the tumor 54.2 ± 13.9 years) were diagnosed with sarcoidosis on the basis of clinical and radiological criteria with histological confirmation[6] (mean age at sarcoidosis diagnosis: 56.6 ± 13.7 years). Mean time between both diagnoses was 2.4 ± 2.3 years. The most common tumors were gastrointestinal (three cases), breast, gynecological, and oropharyngeal (two each) (Table 1). Two patients had two tumors (cervical-ovarian and epiglottal-tonsillar; interval between diagnoses 36 and 4 months, respectively). Most tumors were diagnosed in early stages [stages I–II; 12/16 (75%); stage III: 3/16 (18.8%); stage IV: 1/16 (6.2%)]. The stations most often aspirated were the subcarinal (7; 100%) and lower right paratracheal [4R; 9/14 (64.3%)]. Eight patients (57.1%) had sarcoidosis at radiological stage II and six patients presented stage I (42.9%). Eight of the 14 patients (57.1%) were asymptomatic, 4 (28.6%) had arthralgia, 2 (14.3%) had asthenia, 1 (7.1%) had polyneuropathy, and another (7.1%) had skin involvement. In all cases, cultures to identify *Mycobacterium tuberculosis* in lymphadenopathy samples were negative. In addition to bilateral enlargement of the mediastinal lymph node chains, seven patients (50%) had diffuse bilateral millimetric pulmonary nodules. Increased mediastinal uptake on positron emission tomography was observed in 7 of the 14 patients (SUVmax 16.2 ± 12.9; range 4.2–24.9). Only 10 of the 14 patients received chemotherapy (four cisplatin and two docetaxel) (Table 1). Two patients were treated with corticosteroids (those with polyneuropathy and skin involvement) for 3 and 24 months (maximum doses of 50 and 30 mg prednisone, respectively). Response was favorable in both cases. Mean patient follow-up was 57.8 ± 24.1 months after diagnosis of the tumor (with only one tumor relapse and no deaths), and 28.1 ± 15.8 months after the sarcoidosis diagnosis.

This study shows that the development of new mediastinal lymphadenopathies in a cancer patient does not necessarily mean tumor extension, even if hyperenhancement is observed, and the possibility of sarcoidosis (or other diseases) must be considered.[7] Histological confirmation is always needed.[8] Another important finding is that the diagnosis of sarcoidosis was always subsequent to the tumor diagnosis. The inverse order has been described more often, and very few published series report a diagnostic chronology of tumor followed by sarcoidosis.[9,10]

It is sometimes difficult to differentiate between sarcoidosis, tuberculosis or a sarcoid-like reaction. The diagnosis of tuberculosis, a real possibility in our region which has an incidence of 21.3 cases/100 000 inhabitants/year,[11] was ruled out in all cases by a negative culture for *M. tuberculosis* in a sample of mediastinal lymphadenopathy obtained by endobronchial ultrasound. A sarcoid-like reaction (development of non-caseifying epithelioid cell granulomas in patients who do not fully meet the criteria for sarcoidosis) can occur in cancer patients in the first regional lymph node chain to which a particular tumor might metastasize, taking into account the strategic position occupied by each nodal group.[12,13] This phenomenon is more common in testicular cancers and lymphomas. As mediastinal lymphadenopathies would be the first chains to which lung and pleural cancers would metastasize, these tumors were excluded from the study. Moreover, the fact that our patients were in remission, yet presented systemic symptoms or mediastinal lymphadenopathies with uptake on PET[7] (six and seven of our patients, respectively), was suggestive of a diagnosis of sarcoidosis. However, even with these differentiating factors, it may be difficult to distinguish between these two entities.

Although the association between cancer and sarcoidosis was formerly believed to be incidental, the current thinking is that certain etiopathogenic mechanisms may be involved in genetically predisposed individuals, such as immune hyperresponsiveness of the host to the cancer itself (or antigens produced by the tumor),[9] or the treatment of the tumor itself,[12] as in the case of nivolumab in metastatic melanoma.[13]

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Table 1
Characteristics of the 14 patients.

Case	Sex	Age at diagnosis of cancer/sarcoidosis (years)	History of cancer					History of sarcoidosis					
		Interval between diagnoses (years)	Origin of cancer/stage	Treatment		Cancer relapse[a]	Follow-up (months[b])	Clinical characteristics	CT	Treatment/months	SUVmax	Follow-up (months[c])	LFT
				Regimen	Chemotherapy agent								
1	F	50.6 59.3 8.7	Colon T1N1M0	Surg + ACT	FOLFOX	No	115	Arthralgia	HMLNCE Pulmonary nodules (2)	10.7	No	14	Obstruction
2	F	49.9 53.8 3.9	Ovarian T1N0M0	Surg + ACT	Carbotaxol	No	54	Polyneuropathy	HMLNCE BPMN	24.9	CS/3	7	Normal
3	F	43.4 44.5 1.1	Rectum T3bN1bM0	Surg + ACT + RT	Capecitabine	No	40	Arthralgia Asthenia	HMLNCE BPMN	Negative	No	27	Normal
4	M	62.3 66.7 4.4	Stomach T2N2Mx	Surg + ACT	5-fluorouracil	No	67	Asymptomatic	HMLNCE	10.1	No	18	Normal
5	F	62.5 63.9 1.4	Breast T1N2M0	Surg + ACT	Docetaxel	No	56	Skin involvement Arthralgia	HMLNCE BPMN RP lymph nodes	Negative	CS/24	37	Normal
6	M	53.6 53.9 0.3	Tonsil T2NxMx	Surg + ACT + RT	Docetaxel Cisplatin Xeloda	No	45	Arthralgia	HMLNCE BPMN	11.2	No	43	Obstruction
7	F	26.6 28.3 1.7	Ovarian Stage IIIc and Cervix T1N1M0	CT + RT CT + conization	Cisplatin Etoposide	No	62	Asymptomatic	HMLNCE	Negative	No	37	Normal
8	M	73.3 74.4 1.1	Parotid gland T4cN2M0	CT + RT	Cisplatin	No	75	Asymptomatic	HMLNCE	4.2	No	65	Normal
9	M	35.4 37.4 2	Testicle T1N3M0	CT	Bleomycin	No	60	Asymptomatic	HMLNCE	Negative	No	35	Normal
10	M	60.6 65.5 4.9	Bladder T4N2M0	CT	Cisplatin Gemcitabine	No	79	Asthenia	HMLNCE Inguinal LNE	Negative	No	22	Obstruction DLCO 64%
11	M	71.7 72.1 0.4	Melanoma T1N0M0	Surg	–	No	10	Asymptomatic	HMLNCE BPMN	Negative	No	5	Normal
12	F	41.1 44.4 3.3	Breast T1cN0M0	Surg + RT + tamoxifen		Yes	63	Asymptomatic	HMLNCE BPMN	6.5	No	23	Normal
13	M	68.1 68.6 0.5	Kidney T1aN0M0	Surg	–	No	47	Asymptomatic	HMLNCE	Negative	No	37	Obstruction
14	F	59.8 60.8 1	Tonsil T1-2N0M0 and Epiglottis T1N0M0	Surg	–	No	36	Asymptomatic	HMLNCE BPMN	8	No	24	Normal

ACT, adjuvant chemotherapy; BPMN, bilateral pulmonary micronodules; CS, corticosteroids; CT, chemotherapy; F, female; HMLNCE, hilar-mediastinal lymph node change enlargement; LFT, lung function tests; LNE, lymph node enlargement; M, male; RP, retroperitoneal; RT, radiation therapy; Surg, surgery; SUVmax, standardized maximum uptake value on positron emission tomography.

[a] Before or after sarcoidosis diagnosis.

[b] Follow-up after cancer diagnosis (months).

[c] Follow-up after sarcoidosis diagnosis (months).

The main limitation of this study is that we may have generated some bias by limiting inclusion to patients referred to a bronchoscopy unit, as this procedure might not be requested in all patients, metastasis of the underlying tumor perhaps being assumed in many cases.

In conclusion, the appearance of mediastinal lymphadenopathies in patients with extrapulmonary tumors should not be assumed to be tumor recurrence, and other causes, including sarcoidosis, must be considered. Histological diagnosis is the technique of choice in these cases. Although the relationship between cancer and sarcoidosis and the pathogenic mechanisms that might link them have not been clearly established, either the tumor itself or else the anticancer treatment may possibly promote the development of sarcoidosis in genetically predisposed individuals. More studies are needed to clarify this association and its clinical value and prognosis.

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Risk Stratification in Chronic Obstructive Pulmonary Disease: Can the Spanish Guidelines be Improved?☆

Estratificación de riesgo de la enfermedad pulmonar obstructiva crónica. ¿Se puede mejorar la propuesta de la guía española?

To the Editor:

The risk stratification of patients in the 2017 edition of the Spanish COPD guidelines (GesEPOC)[1] is simpler than that in the first edition.[2] Although the multidimensional indices, BODE and BODEx, have shown good ability to predict mortality, they are rarely used in clinical practice. For this reason, the new GesEPOC guidelines propose a dichotomous stratification of high and low risk, according to the presence or absence of three risk factors: FEV_1<50%, mMRC functional dyspnea grade >2 (or = 2 in patients already receiving bronchodilators), and a history of exacerbations. It occurred to us that a quantitative classification that took into account the number of risk factors present in each patient could offer advantages with respect to the dichotomous classification, allowing patients to be classified into escalating risk categories, in a similar manner to the BODE/BODEx indices, while being easier to apply in clinical practice than stratification based on multidimensional indices.

In order to verify this hypothesis, we performed a retrospective study of all patients seen in the dedicated COPD clinic of a university hospital. The study population comprised all consecutive patients with a diagnosis of COPD according to the GOLD initiative criteria[3] and a history of smoking (cumulative exposure >10 pack-years), seen between January 2008 and April 2017 (726 subjects). The patients were selected from a healthcare database in which body mass index, lung function, mMRC functional grade (with and without treatment), history of exacerbations in the year prior to the index date (date of the first clinic visit), and moderate (requiring treatment with antibiotics or steroids) or severe exacerbations (requiring attention in the emergency room or admission) were systematically recorded. Patients were classified according to: (1) a quantitative scale using BODEx index quartiles;[2] (2) the high–low risk dichotomous scale recommended by GesEPOC 2017;[1] and (3) a 4-level quantitative scale, on the basis of the number of risk factors present in each patient (0, 1, 2 or 3). We performed a survival analysis for the three scales according to the Kaplan–Meier method, using the log-rank test for the comparison of survival curves. A Cox's proportional hazards analysis was performed, using age and comorbidity measured by the Charlson index as covariates. We compared the ability of the two quantitative scales to predict overall mortality using receiver operator curves (ROC), comparing the areas with the DeLong method.[4]

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