Communication

Tumor associated granulomas preceding the diagnosis of systemic thoracic sarcoidosis. A retrospective study

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Abstract: There is a relationship between systemic sarcoidosis (SS) and malignancy. Sarcoidosis results from an exaggerated immune response in genetically susceptible individuals. In oncologic patients with sarcoidosis, tumoral antigens and antineoplastic treatment are considered potential triggering factors. The observation of a patient with granulomas in a parotid carcinoma that later developed SS led us to review previous tumors of patients with SS. The aim of the study is to see if granulomas were already present in the tumors that preceded sarcoidosis. We identified 196 sarcoidosis patients, 47 of which had a previous tumor. We were able to review 29 cases 12 of which showed tumor associated granulomas (TAGs)(41.4%). This ratio is much higher than that of the normal population. We analyzed five control patients without sarcoidosis for each tumor. In conclusion, we have observed TAGs in patients who later develop SS. In our series, the ratio of TAGs in patients with SS was significantly greater than in the normal population which reinforces a pathogenic relation of SS with neoplasia. To prove our findings, we suggest reviewing the history of patients with SS in search of previous tumors. The histology of such tumors should be reviewed in an attempt to identify granulomas.

Keywords: granulomas, neoantigens, neoplasia, sarcoidosis, sarcoid-like reaction, tumoral antigens.

1. Introduction

The diagnosis of systemic sarcoidosis (SS) is based on three major criteria: a compatible clinical presentation, the finding of non-necrotizing granulomatous inflammation, and the exclusion of alternative causes of granulomatous disease [1]. Obtaining tissue material for the detection of granulomas has been historically a limiting condition for the diagnosis of SS. However, the introduction of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has facilitated enormously the access to mediastinal nodes and has proved a reliable method for detecting non-necrotizing granulomas, simplifying the diagnosis [2,3]. Several studies have demonstrated a relation between SS and malignant tumors [4-8]. Sarcoidosis can occur before, during or after cancer diagnosis [4,6]. While SS is a relatively well-known condition, sarcoid-like reaction (SLR) is defined as a non-necrotizing granulomatous reaction occurring under conditions, which do not meet the diagnostic criteria for SS [1,4]. Cases of sarcoidosis following malignancy are clinically similar to idiopathic sarcoidosis [7]. Regarding malignancy, patients with sarcoidosis must be distinguished from those in which a SLR is histologically seen in the primary tumor or draining lymph nodes since the latter do not fulfill the criteria for SS.

Sarcoidosis is considered a disorder resulting from an exaggerated immune response to an unknown antigen occurring in genetically susceptible patients [9]. In oncologic patients that develop SS, tumoral antigens are considered the most likely triggering factor [4-8]. In addition, antineoplastic treatment can also play a causative role [4-8]. Although the possibility of an immune reaction against tumoral antigens is likely, we must consider that individuals who develop SS may simply be prone to a granuloma-forming response to a variety of antigens. Therefore, the subsequent development of thoracic sarcoidosis observed in these patients is not necessarily related to tumoral antigens. Routine imaging studies in the follow-up of oncologic patients results in detection of sarcoidosis in early stages [7]. Since the possibility of metastatic disease cannot be ruled out, most of these patients undergo pathologic analysis of mediastinal lymph nodes.

The clinical observation of a patient with an extensive non-necrotizing granulomatous reaction in a parotid acinic cell carcinoma that 15 months later developed SS led us to study other patients with sarcoidosis and preexistent tumors. In these patients we have reviewed the histology of the preceding tumors, and in several cases, we found tumor associated non-necrotizing granulomas (TAGs) suggesting that a local immune reaction was already present. In addition, we observed that some of these tumors are benign or occur in patients who had received no antineoplastic treatment, which reinforces the hypothesis of an exaggerated immune response to antigen related tumors. The presence of a SLR in neoplasms or draining nodes is a well-known pathologic phenomenon but has not been directly related to the subsequent development of sarcoidosis [10,11]. In the normal population without SS, SLRs occur in 4.4% of carcinomas, in 13.8% of patients with Hodgkin's disease, and in 7.3% of cases of non-Hodgkin lymphomas [10]. They are extremely rare in sarcomas [10]. In this study, we reveal that some patients with TAGs can later develop SS and we show for the first time that the relation between SS and neoplasms extends to benign ones. To our knowledge, this association has not been previously reported. Some studies describe sarcoid-like mediastinal lymphadenopathy or cardiac sarcoidosis in association to previous or concurrent cancer [12-17]. However, such studies do not include a histologic evaluation of previously diagnosed tumors in search of TAGs.

2. Materials and Methods

Based on the above mentioned criteria for SS [1] we performed a retrospective study of patients seen at the University Hospital La Princesa in which a diagnosis of mediastinal or pulmonary sarcoidosis with pathologic evidence of granulomas was present. The study protocol was approved by the Ethics Committee of Hospital Universitario de la Princesa, Madrid, Spain (code: 4238). Lung and mediastinal lymph nodes are among the major organs affected by sarcoidosis, so we reviewed the pathology files using a search tool for cross-queries with words such as “mediastinal”, “lymph node”, “pulmonary”, “granuloma”, “sarcoidosis” or “sarcoid”. The search was made from January 2000 to December 2020. We then reviewed the cases in collaboration with the Pneumology Department and selected those patients that fulfilled a diagnosis of thoracic sarcoidosis. From all the patients diagnosed with mediastinal or pulmonary sarcoidosis, we searched for those who had had a previous neoplasm. From the Pathology department files, we retrieved the pathologic material. An important aspect of the study was to locate, in those selected patients with sarcoidosis and a previous tumor, chest imaging studies at the moment of tumor resection to demonstrate no mediastinal or pulmonary abnormalities. This was performed to exclude cases of asymptomatic preexisting sarcoidosis.

We reviewed all histologic and cytologic slides corresponding to the diagnosis of sarcoidosis and a previous tumor. Three pathologists examined the pathologic samples together, and only considered those cases unanimously agreed upon. We used a semiquantitative scale to evaluate the quantity of granulomas: rare, when only isolated granulomas were seen; moderate, when easy to identify; and abundant, when there was a remarkable finding. We also classified the distribution of granulomas as intratumoral, peritumoral or both. For each tumor preceding a sarcoidosis diagnosis we selected five controls from the

same entity in patients without sarcoidosis. Meanwhile, since no other cases were available regarding sebaceous lymphadenoma, we used five Warthin tumors and five pleomorphic adenomas as controls. In these cases, the same three pathologists performed a detailed search for granulomas.

3. Results

From the first search, 433 patients were identified with 196 fulfilling the criteria for SS [1]. The medical records of 47 (23.9%) patients revealed the existence of a previous tumor. The pathologic files of our department contained histologic material from 29 of these 47 patients. The tumors of the remaining 18 patients were treated in different medical centers and the histologic slides were unavailable for review. We reviewed the complete pathologic material of these 29 patients, including the mediastinal or pulmonary samples, where non-necrotizing granulomas were observed, and the previous tumor. We found TAGs in 16 of the 29 tumors. Four cases had to be excluded as the time interval between the diagnosis of SS and the previous tumor was too short (less than 8 weeks) and the possibility of simultaneous presentation could not be excluded. The remaining 12 constitute the basis of this study, with Table 1 summarizing their main clinicopathologic features.

Table 1. Main clinicopathological features of patients with systemic sarcoidosis and preceding TAGs

No	Age[1]/gender	Preexisting neoplasm with granulomas	Sarcoidosis location and clinical stage	Time elapse (months)	Granulomas quantity	Granulomas distribution
1	55/M	Parotid gland acinic cell carcinoma	Mediastinal and lung, II	15	Abundant	Intratumoral
2	59/F	Parotid gland oncocytoma	Mediastinal, I	30	Moderate	Peritumoral
3	60/M	Bone marrow with lymphoma	Mediastinal, I	92	Abundant	Peritumoral
4	72/M	Mediastinal lymphoma	Mediastinal and lung, II	40	Rare	Intratumoral
5	81/M	Parotid gland sebaceous lymphadenoma	Mediastinal, I	28	Moderate	Intratumoral
6	37/M	Squamous cell carcinoma of tongue	Mediastinal and lung, II	12	Rare	Peritumoral
7	77/F	Rectal adenocarcinoma and liver metastases	Mediastinal and lung, II	7	Moderate	Peritumoral
8	55/F	Cutaneous neurofibroma	Mediastinal and lung, II	22	Rare	Peritumoral
9	53/F	Rectal adenocarcinoma	Mediastinal, I	28	Moderate	Intratumoral and peritumoral
10	81/M	Small bowel GIST	Mediastinal, I	16	Focal	Intratumoral
11	70/F	Cutaneous intraepidermal carcinoma	Mediastinal, I	6	Moderate	Peritumoral
12	87/F	Diffuse large B cell lymphoma	Mediastinal, I	107	Moderate	Intratumoral

Abbreviations: TAGs-tumor associated granulomas, M-male, F-female, GIST-gastrointestinal stromal tumor. 1 Age at the time of sarcoidosis diagnosis.

The time interval between the diagnosis of sarcoidosis and the preceding neoplasia varied from six to 107 months with a mean period of 34 months. In nine patients chest imaging studies (four X-rays and five CT scans) were performed at the moment of neoplasm excision and showed no evidence of mediastinal lymphadenopathies or pulmonary involvement. The two patients with cutaneous tumors (neurofibroma and intraepidermal carcinoma) had no thoracic image study since excision was done using local anesthesia. At the time of tumor excision, none of the 12 patients had symptomatology related to thoracic SS. In case 12, lymphoma with TAGs involved the mediastinum so there was no possibility of a previously normal imaging study. Nine of the 12 tumors were malignant neoplasms and three were benign (Figures 1-4). It is remarkable that three of them were parotid gland tumors (Figures 1, 2a, 2b, 2e, 2f).

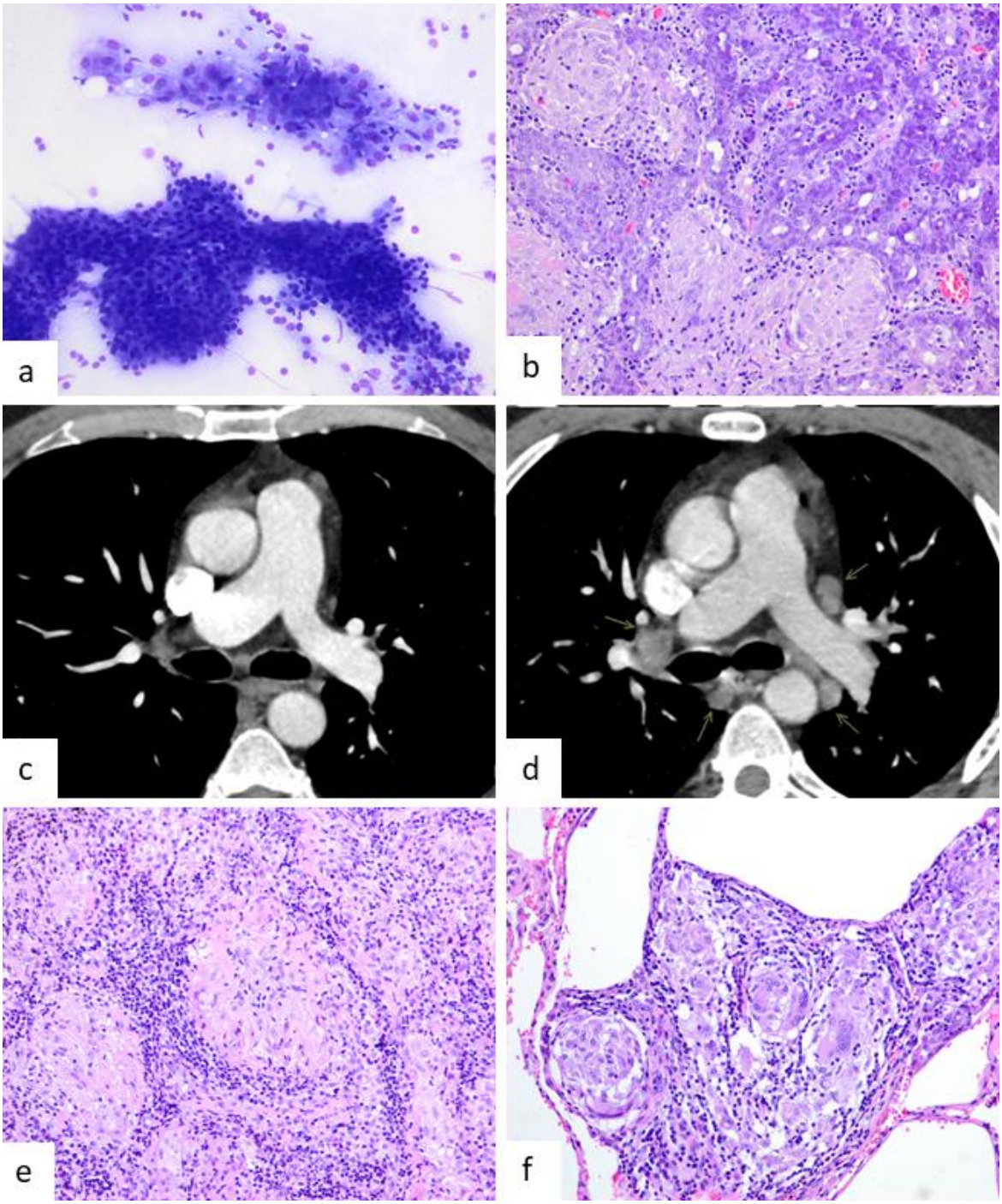

Figure 1. Images from patient 1 that motivated the study. (a,b) Parotid acinic cell carcinoma showing granulomas in a fine needle aspiration sample and subsequent surgical specimen (Diff-Quik, x400, HEx400, respectively). (c,d) The first CT scan (c) was performed 6 months after surgery and shows no abnormalities. A second CT scan (d) performed 15 months after surgery shows evident mediastinal lymphadenopathies (gray arrows) that were absent in the previous one. (e,f) Mediastinal lymph node and lung biopsy showing numerous non-necrotizing granulomas (HE, x400).

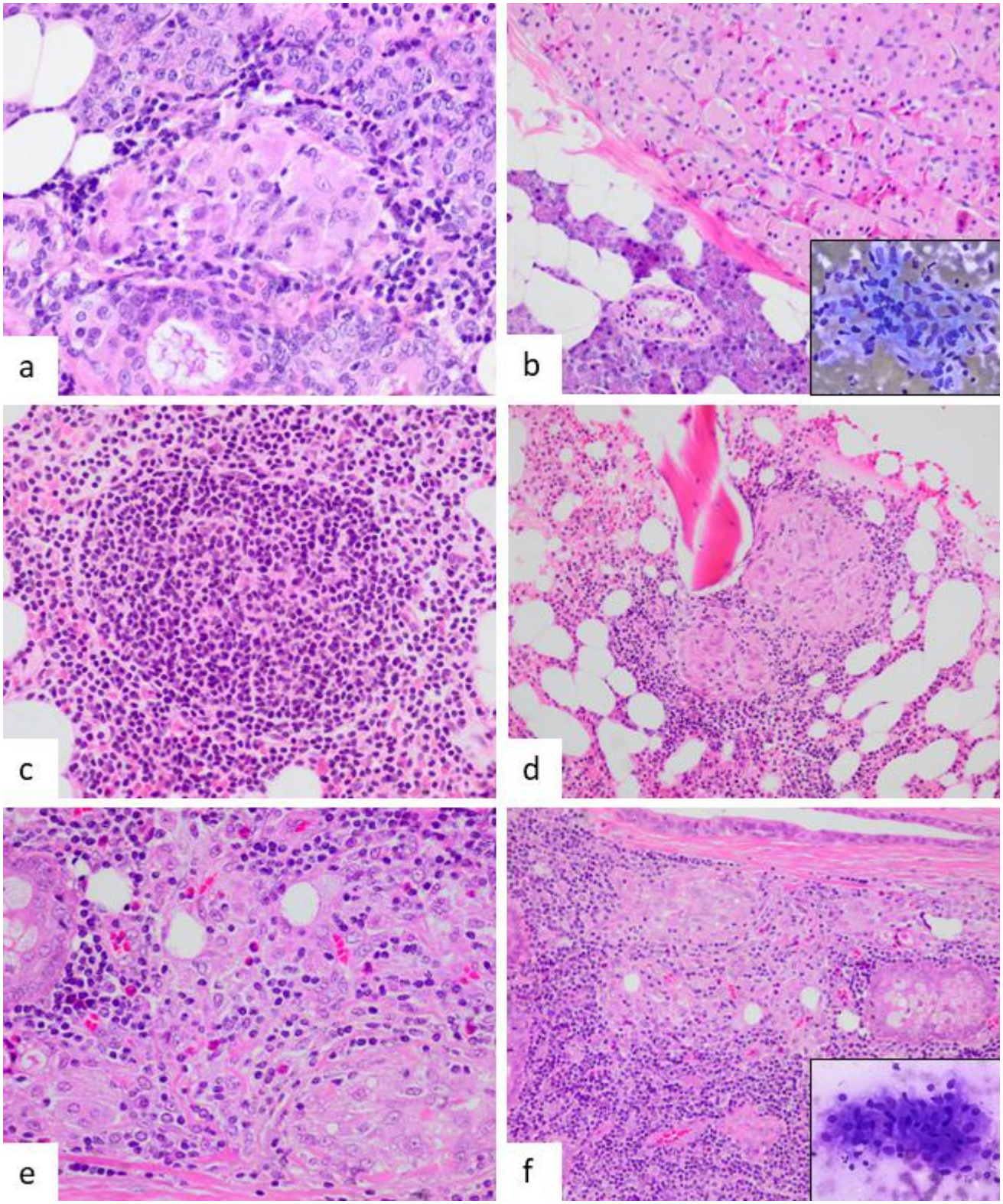

Figure 2. (a,b) Peritumoral granulomas in the case of parotid oncocytoma (case 2) (HE, x600 and x200, respectively). The inset reveals a granuloma in a fine needle aspiration sample of an enlarged mediastinal lymph node performed 30 months later (Diff-Quik, x400). (c,d) Bone marrow showing follicular lymphoma involvement and numerous non-necrotizing granulomas (case 3) (HE, x400 and x200, respectively). (e,f) Two images of sebaceous lymphadenoma showing intratumoral granulomas (case 5) (HE, x200 and x400).

In one case TAGs were present in the primary tumor (rectal adenocarcinoma) and liver metastases (Figures 3c, 3d). Regarding the abundance of TAGs, in four cases, they were a rare finding, in six, moderate, and in two, abundant; in only one case did

intratumoral and peritumoral TAGs coexist. In five cases the granulomas were exclusively intratumoral (Figures 1, 2e, 2f, 4a, 4b, 4c) and in the remaining six only peritumoral (Figures 2a, 2d, 3, 4d). The squamous cell carcinoma of the tongue was well-differentiated and keratinizing but the granulomas we considered were peritumoral, located distally from the main tumor and showing no foreign-body morphology or relation with keratin (Figure 3a). A diagnosis of mediastinal or pulmonary non-necrotizing granulomatous involvement was achieved by biopsy in five cases and by EBUS-TBNA cytology in the remaining seven (Figures 1-4). All histologic granulomas, tumor-associated, mediastinal and pulmonary were non-necrotizing and showed variable amounts of multinucleated giant cells, some of which contained asteroid and Schaumann bodies (Figure 3d).

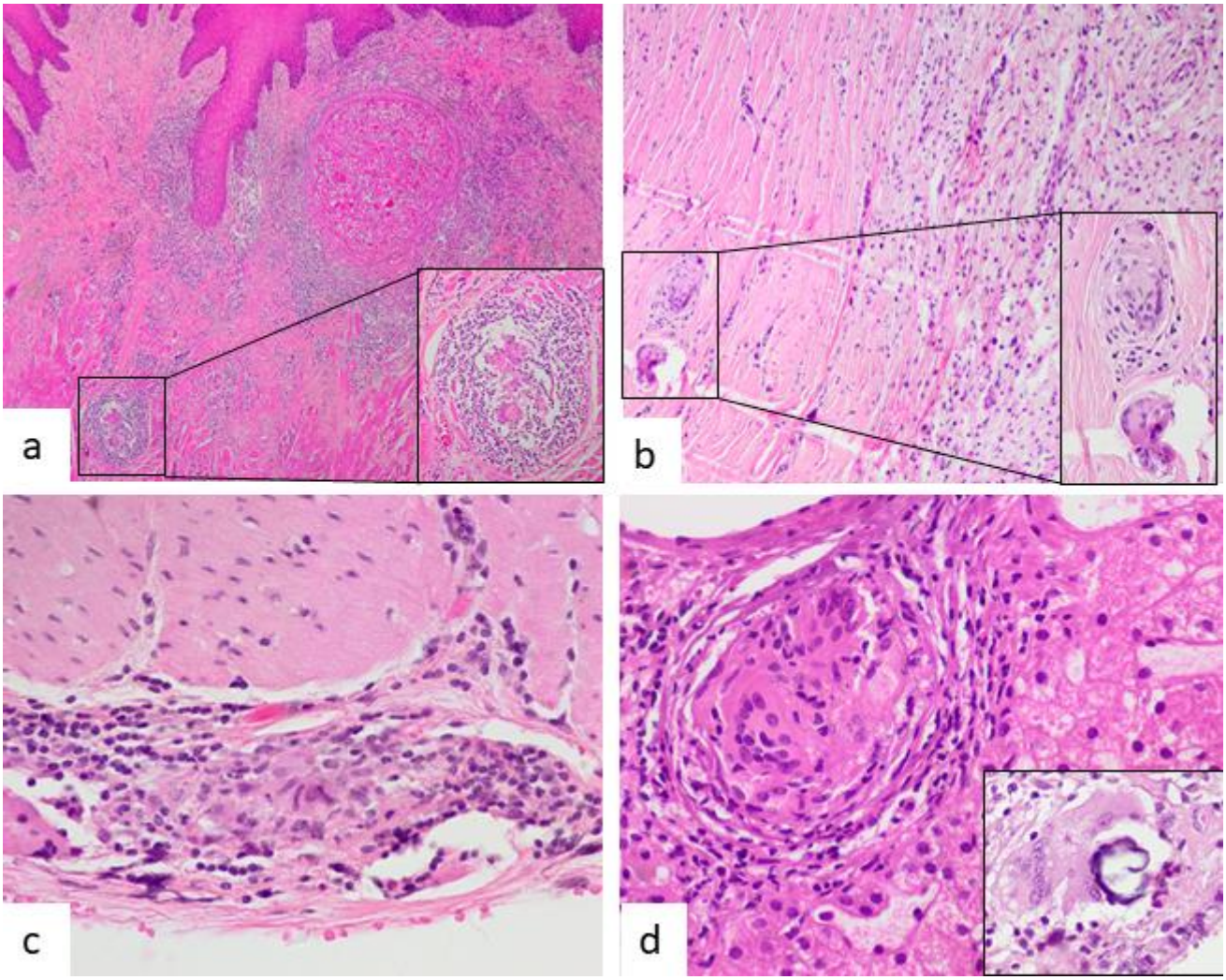

Figure 3. (a) Peritumoral granulomas in a squamous cell carcinoma of the tongue. Granulomas are peritumoral and have no relation with keratin material (case 6) (HE,x 40). The inset highlights the absence of foreign body component and non-necrotizing morphology. (b) Peritumoral granulomas in a case of cutaneous neurofibroma (case 8) (HE, x100, inset x400). (c,d) Peritumoral granulomas in a case of rectal adenocarcinoma (subserosal) and its hepatic metastases (case 7) (HE, x600 and x400). The inset in image d reveals a pulmonary giant cell with an asteroid and calcified Schaumann bodies biopsied 7 months later (HE, x600).

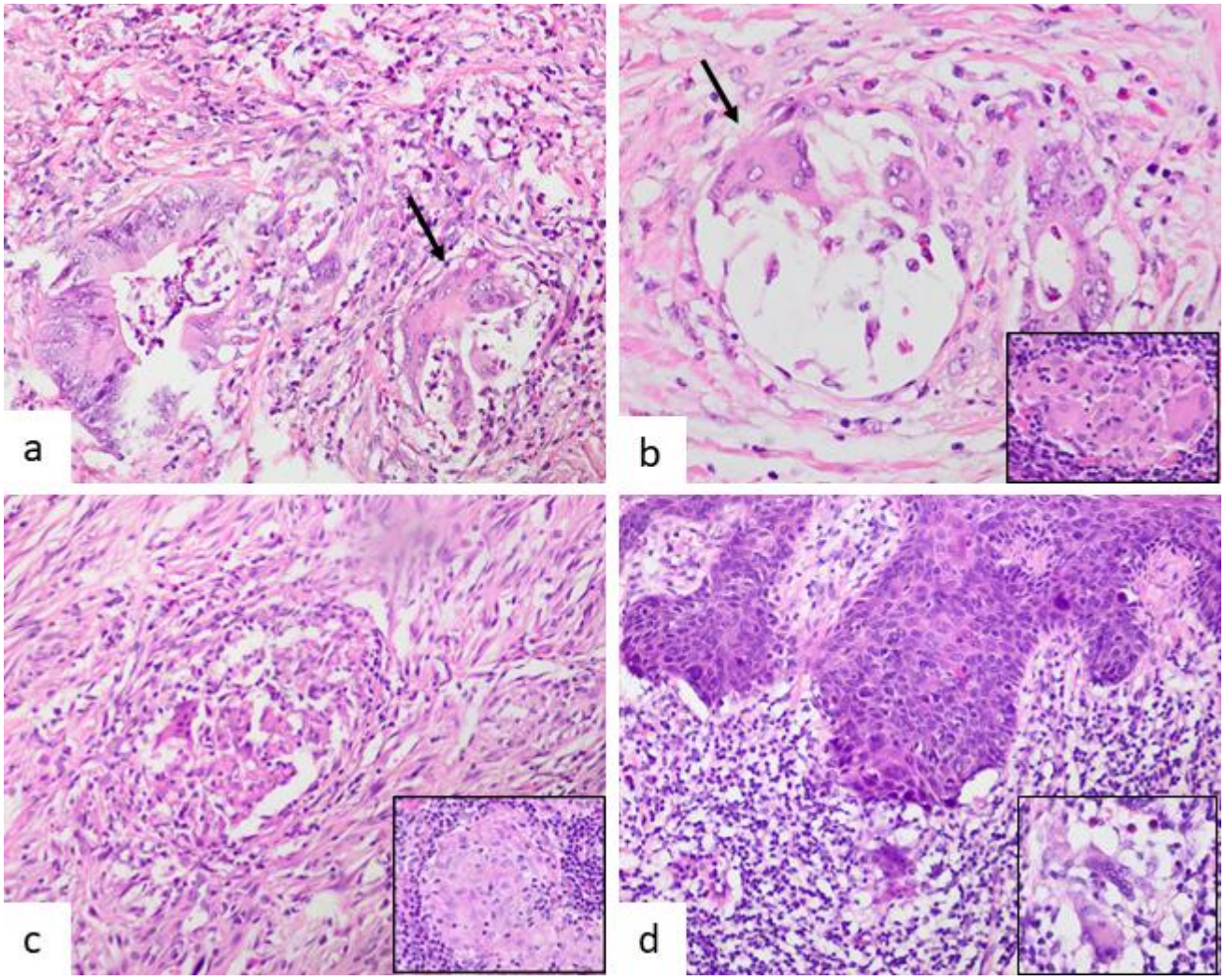

Figure 4. (a,b) Intratumoral granulomas in a case of rectal adenocarcinoma. In both images granulomas (black arrows) are in close relation with malignant glands (case 9) (HE, x400 and x600 respectively). The inset in image b shows a mediastinal non-necrotizing granuloma from a biopsy performed 28 months later (HE, x400). (c) Intratumoral granuloma in a case of gastrointestinal stromal tumor. The lower right inset reveals a mediastinal granuloma biopsied 16 months later (case 10) (HE x400 and x400). (d) Peritumoral granulomas in a case of cutaneous intraepidermal carcinoma (case 11) (HE, x200). Granulomas and giant cells are admixed with numerous lymphocytes. The inset reveals an ill-defined granuloma (HE, x600).

Granulomas were accompanied by lymphocytes and occasionally eosinophils but not neutrophils. In all cases, histochemical staining with Ziehl-Nielsen stain gave negative results.

In the 65 controls, we found a granulomatous reaction in four cases. Two cases were present in squamous cell carcinomas of the tongue and were of the foreign body type. One was clearly related to the suture material of a previous biopsy, the second one was intratumoral, and had a close relation to keratin produced by tumoral cells. A third case corresponded to liver metastasis of a mucinous intestinal adenocarcinoma and the granulomatous reaction was of the foreign body type and related to mucoid material. Only one case of intestinal liver metastases showed focal peritumoral TAGs similar to the ones observed in case 7. We consider it a true SLR, and in this case, not associated to systemic sarcoidosis.

4. Discussion

In this study, we have reported the presence of TAGs in a series of patients who months or years later developed SS. The ratio of TAGs in this study (12/29, 41,4%) is clearly higher than the general SLR ratio (between 4.4-13.8%) [10]. In our opinion this is not a coincidental fact and two possible explanations may justify this association. Firstly, it may represent an initial phase of immune triggering against tumoral antigens that later

expand in intensity and extension. Neoplasms accumulate genetic alterations, some of which produce mutated peptides that are presented by human leukocyte antigen molecules and elicit T-cell responses [18]. These immunogenic mutated peptides, known as neoantigens, are foreign in nature and have tumor specificity. They are being used as promising targets to develop personalized clinical interventions [19]. Secondly, it can reflect the hyperreactive immune status of these patients to a variety of antigens, and the development of subsequent SS is not necessarily due to tumoral antigens. Whatever the cause, the fact is that tumors in patients with SS have a higher ratio of non-necrotizing granulomas and these can precede its diagnosis.

Cases of TAGs in patients with a previous diagnosis of SS have been reported [20-22] but we have found no descriptions of the inverse phenomenon: TAGs preceding the diagnosis of sarcoidosis. This last observation is interesting for several reasons. First, it reinforces the relation of sarcoidosis with neoplasia and not only with malignant tumors but also with benign ones. The medical literature regarding sarcoidosis and neoplasms is restricted to malignant tumors. If, as hypothesized, tumoral antigens are responsible for triggering the immune system of genetically predisposed individuals, it makes no difference if those antigens belong to a malignant or benign tumor. In this sense, the lack of references is probably due to the relatively low clinical interest raised by benign tumors, an antecedent that is most probably overlooked by clinicians. We have observed TAGs in patients with cutaneous neurofibroma, parotid oncocytoma and sebaceous lymphadenoma that later developed SS. Further studies will help us establish whether benign neoplasms are also associated with sarcoidosis. A second interesting point concerns the pathogenic mechanism underlying the association of cancer and subsequent sarcoidosis. In addition to tumoral antigens or neoantigens, it has been hypothesized that chemotherapy can predispose sarcoidosis development [23,24]. The most common drugs associated with granulomatous reactions are antiretroviral therapy, interferons, tumor necrosis factor-alpha antagonists and immune checkpoint inhibitors [23,24]. However, in several studies, including ours, a relatively large percentage of patients received none of those drugs or chemotherapy. Rituximab is among the list of drugs that can induce a granulomatous reaction [23] and was given to three of our patients. In these patients, rituximab could be related to thoracic sarcoidosis but not with TAGs since these were present before treatment. From this, we could conclude that tumoral antigens could play an important role in the initiation of the immune activation even if there is a relatively large interval between the appearance of the tumor and the development of SS. In our study, the list of tumors with TAGs preceding sarcoidosis is highly variable, so no specific antigens can be identified. We have observed them in benign and malignant epithelial and mesenchymal tumors as well as lymphomas. Another interesting feature is the distribution of granulomas. In six cases, they were exclusively peritumoral, located in the normal tissue surrounding the tumor. This peritumoral location has been observed in TAGs related or not to SS [17,22]. We therefore recommend performing a close examination of peritumoral tissue when trying to detect the presence of TAGs.

As the title of the study reflects, we must emphasize that in our series TAGs preceded the "diagnosis" of SS since we cannot rule out the possibility of minimal mediastinal involvement at the time of tumor diagnosis. In this sense the impossibility of having pathological proof of non-mediastinal granulomatous involvement at the time of tumor diagnosis may be considered an intrinsic limitation of the study. Although thoracic X-rays may have a low sensitivity for the recognition of initial phases of SS, the five CT studies performed were normal and patients had no related symptomatology. However, even if there was minimal subclinical involvement of mediastinal nodes at the time of tumor diagnosis the main message of the study remains the same: patients with SS and previous tumors have a high incidence of TAGs.

A relevant observation of this study concerns mentioning the presence of TAGs in the final diagnosis of the pathologic report. Pathologists often describe them but mostly they are not specifically mentioned in the final diagnosis. This is important because clinicians focus on the final pathologic diagnosis and many descriptions are not read. Adding

"tumor associated non-necrotizing granulomas are present" to the main diagnosis text may help the clinician consider SS if the patient subsequently develops mediastinal lymphadenopathies or pulmonary lesions. In conclusion, we have observed TAGs in patients who months or years later develop SS. In our series, the ratio of TAGs in patients with SS was significantly greater than in the normal population which reinforces a pathogenic relation of SS with neoplasia. Since the introduction of EBUS-TBNA in clinical practice, the number of patients with a definite diagnosis of SS has increased. To further prove our findings, we suggest reviewing the clinical history of patients diagnosed with SS in search of a previous tumor, and when one is identified, the histologic slides should be reviewed in an attempt to identify TAGs.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Crouser, E.D.; Maier, L.A.; Wilson, K.C.; Bonham, C.A.; Morgenthau, A.S.; Patterson, K.C.; Abston, E.; Bernstein, R.C.; Blankstein, R.; Chen, E.S.; et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* **2020**, *201*, e26–e51, doi:10.1164/rccm.202002-0251ST.
2. Chee, A.; Khalil, M.; Stather, D.R.; MacEachern, P.; Field, S.K.; Tremblay, A. Cytologic Assessment of Endobronchial Ultrasound-Guided Transbronchial Needle Aspirates in Sarcoidosis. *Journal of Bronchology & Interventional Pulmonology* **2012**, *19*, 24–28, doi:10.1097/LBR.0b013e3182442925.
3. Trisolini, R.; Baughman, R.P.; Spagnolo, P.; Culver, D.A. Endobronchial Ultrasound-guided Transbronchial Needle Aspiration in Sarcoidosis: Beyond the Diagnostic Yield. *Respirology* **2019**, *24*, 531–542, doi:10.1111/resp.13537.
4. El Jammal, T.; Pavic, M.; Gerfaud-Valentin, M.; Jamilloux, Y.; Sève, P. Sarcoidosis and Cancer: A Complex Relationship. Front. Med. **2020**, 7, 594118, doi:10.3389/fmed.2020.594118.
5. Brincker, H.; Wilbek, E. The Incidence of Malignant Tumours in Patients with Respiratory Sarcoidosis. Br J Cancer **1974**, 29, 247–251, doi:10.1038/bjc.1974.64.
6. Cohen, P.R.; Kurzrock, R. Sarcoidosis and Malignancy. *Clinics in Dermatology* **2007**, *25*, 326–333, doi:10.1016/j.clindermatol.2007.03.010.
7. Arish, N.; Kuint, R.; Sapir, E.; Levy, L.; Abutbul, A.; Fridlender, Z.; Laxer, U.; Berkman, N. Characteristics of Sarcoidosis in Patients with Previous Malignancy: Causality or Coincidence? *Respiration* **2017**, *93*, 247–252, doi:10.1159/000455877.
8. Grados, A.; Ebbo, M.; Bernit, E.; Veit, V.; Mazodier, K.; Jean, R.; Coso, D.; Aurran-Schleinitz, T.; Broussais, F.; Bouabdallah, R.; et al. Sarcoidosis Occurring After Solid Cancer: A Non fortuitous Association Report of 12 Cases and Review of the Literature. *Medicine* **2015**, *94*, e928, doi:10.1097/MD.0000000000000928.
9. Baughman, R.P.; Culver, D.A.; Judson, M.A. A Concise Review of Pulmonary Sarcoidosis. *Am J Respir Crit Care Med* **2011**, *183*, 573–581, doi:10.1164/rccm.201006-0865CI.
10. Brincker, H. Sarcoid Reactions in Malignant Tumours. *Cancer Treatment Reviews* **1986**, *13*, 147–156, doi:10.1016/0305-7372(86)90002-2.
11. Pavic, M.; Debourdeau, P.; Vacelet, V.; Rousset, H. Place de la pathologie granulomateuse au cours des cancers. *La Revue de Médecine Interne* **2008**, *29*, 39–45, doi:10.1016/j.revmed.2007.09.041.
12. Kennedy, M.P.; Jimenez, C.A.; Mhatre, A.D.; Morice, R.C.; Eapen, G.A. 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, doi:10.1186/1749-8090-3-8.
13. DePew, Z.S.; Gonsalves, W.I.; Roden, A.C.; Bungum, A.O.; Mullon, J.J.; Maldonado, F. Granulomatous Inflammation Detected by Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in Patients With a Concurrent Diagnosis of Cancer: A Clinical Conundrum. *Journal of Bronchology & Interventional Pulmonology* **2012**, *19*, 176–181, doi:10.1097/LBR.0b013e31825f8eda.

14. Chee, A.; Tremblay, A. EBUS, Granulomas, and Cancer: What Does This Represent? *Journal of Bronchology & Interventional Pulmonology* **2012**, *19*, 171–173, doi:10.1097/LBR.0b013e31825f5c05.
15. Grosu, H.B.; Ost, D.E.; Morice, R.C.; Eapen, G.A.; Li, L.; Song, J.; Lei, X.; Lazarus, D.R.; Casal, R.F.; Jimenez, C.A. Mediastinal Granulomatous Inflammation and Overall Survival in Patients with a History of Malignancy. *Annals ATS* **2015**, *12*, 1534–1541, doi:10.1513/AnnalsATS.201506-318OC.
16. Lashari, B.H.; Asai, M.; Randleman, G.; Sack, M.; Patel, R. Sarcoid-Like Mediastinal Lymphadenopathy in Gynecologic Malignancy. *Pulmonary Medicine* **2018**, *2018*, 1–4, doi:10.1155/2018/5141575.
17. Arora, K.; Divatia, M.K.; Truong, L.; Shen, S.S.; Ayala, A.G.; Ro, J.Y. Sarcoid-like Granulomas in Renal Cell Carcinoma: The Houston Methodist Hospital Experience. *Annals of Diagnostic Pathology* **2017**, *31*, 62–65, doi:10.1016/j.anndiagpath.2017.07.003.
18. Garcia-Garijo, A.; Fajardo, C.A.; Gros, A. Determinants for Neoantigen Identification. *Front. Immunol.* **2019**, *10*, 1392, doi:10.3389/fimmu.2019.01392.
19. Chen, F.; Zou, Z.; Du, J.; Su, S.; Shao, J.; Meng, F.; Yang, J.; Xu, Q.; Ding, N.; Yang, Y.; et al. Neoantigen Identification Strategies Enable Personalized Immunotherapy in Refractory Solid Tumors. *Journal of Clinical Investigation* **2019**, *129*, 2056–2070, doi:10.1172/JCI99538.
20. Moder, K.G.; Litin, S.C.; Gaffey, T.A. Renal Cell Carcinoma Associated With Sarcoidlike Tissue Reaction. *Mayo Clinic Proceedings* **1990**, *65*, 1498–1501, doi:10.1016/S0025-6196(12)62171-5.
21. Bhatti, P.; Waight, M.; Bromage, D.; Sado, D. Cardiac Sarcoidosis in a Patient with Testicular Seminoma. *BMJ Case Rep* **2019**, *12*, e229912, doi:10.1136/bcr-2019-229912.
22. Ouellet, S.; Albadine, R.; Sabbagh, R. Renal Cell Carcinoma Associated with Peritumoral Sarcoid-like Reaction without Intratumoral Granulomas. *Diagn Pathol* **2012**, *7*, 28, doi:10.1186/1746-1596-7-28.
23. Cohen Aubart, F.; Lhote, R.; Amoura, A.; Valeyre, D.; Haroche, J.; Amoura, Z.; Lebrun-Vignes, B. Drug-induced Sarcoidosis: An Overview of the WHO Pharmacovigilance Database. *J Intern Med* **2020**, *288*, 356–362, doi:10.1111/joim.12991.
24. Chorti, E.; Kanaki, T.; Zimmer, L.; Hadaschik, E.; Ugurel, S.; Gratsias, E.; Roesch, A.; Bonella, F.; Wessendorf, T.E.; Wälscher, J.; et al. Drug-Induced Sarcoidosis-like Reaction in Adjuvant Immunotherapy: Increased Rate and Mimicker of Metastasis. *European Journal of Cancer* **2020**, *131*, 18–26, doi:10.1016/j.ejca.2020.02.024