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Case report

Systemic sarcoidosis mimicking metastatic renal cell carcinoma with subsequent cardiac involvement

Michael Frohlich^a, Najwa Buhlaiga^b, Hangjun Wang^c, Francois Patenaude^b, Christian Sirois^d, Lama Sakr^{a,*}^a Department of Medicine, Division of Pulmonary Disease, Jewish General Hospital, Pavilion G Room 203, 3755 Côte-Sainte-Catherine Road, Montreal, Quebec, H3T 1E2, Canada^b Department of Medicine, Hematology Service and Department of Oncology, Jewish General Hospital, Pavilion E7, 3755 Côte-Sainte-Catherine Road, Montreal, Quebec, H3T 1E2, Canada^c Divisions of Pathology and Molecular Genetics, Jewish General Hospital, Pavilion G Room 108, 3755 Côte-Sainte-Catherine Road, Montreal, Quebec, H3T 1E2, Canada^d Department of Surgery, Division Thoracic and Upper Gastrointestinal Surgery, Montreal General Hospital, Pavilion L Room 8-505, 1650 Cedar Avenue, Montreal, Quebec, H3G 1A4, Canada

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ABSTRACT

There exists a well-established association between sarcoidosis and many solid and hematologic malignancies however it is a less frequently described phenomenon in patients with renal cell carcinoma. Moreover the majority of described cases presented with local sarcoid-like reactions in close proximity to the tumor with comparatively few reports of more distant disease. Given the relatively low number of cases there remains a great deal of uncertainty surrounding the clinical behaviour of sarcoidosis in the setting of renal cell carcinoma.

We report the case of a patient with surgically resected renal cell carcinoma who, several years later, developed bilateral pulmonary nodules, intra-thoracic lymphadenopathy as well as splenic, hepatic and osseous lesions. After extensive investigation, culminating in video-assisted thoracoscopic surgical resection, he was found to have sarcoidosis. He remained asymptomatic for many years before being diagnosed with cardiac sarcoidosis, which was found to be inactive and did not require any treatment. Both his sarcoidosis and underlying renal cell carcinoma have remained in remission to date.

This case highlights the variable behaviour of sarcoidosis in these patients and underscores the importance of obtaining an accurate tissue diagnosis in the setting of suspected metastatic disease. Additionally, it underscores the importance of close monitoring and long-term follow up as these patients may develop significant organ involvement, even many years after diagnosis. Interestingly the patient's renal cell carcinoma remained in remission, raising questions about whether the development of sarcoidosis portends a better prognosis in patients with an underlying solid malignancy.

1. Background

Sarcoidosis is a multi-system disorder that is characterized histologically by the presence of non-caseating granulomas in multiple organs throughout the body, most commonly the lungs, intra-thoracic lymph nodes, skin or eyes [1]. While most cases of sarcoidosis are felt to

be idiopathic a certain proportion have been associated with malignancies, anti-neoplastic therapies or more recently, immune checkpoint inhibitors [2,3].

A confounding factor in many patients is that many malignancies may also produce so-called sarcoid-like reactions, defined by the presence of non-necrotizing granulomas in the tissue without systemic

Abbreviations: CT, computed tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; IFN- γ , interferon γ ; IL, interleukin; RCC, renal cell carcinoma; MRI, magnetic resonance imaging; PET, positron emission tomography; Th1, T-helper cell type 1; Th17, T-helper cell type 17; TTNA, transthoracic-needle aspiration.

* Corresponding author. Division of Pulmonary Diseases, Department of medicine, Jewish General Hospital, Pavilion G Room 203, 3755 Côte-Sainte-Catherine Road, Montreal, Qc, H3T 1E2, Canada.

E-mail address: lama.sakr@mcgill.ca (L. Sakr).

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symptoms [4]. There remains a great deal of uncertainty in the literature regarding whether these represent two different diseases or different presentations of a single disease entity, and whether patients with sarcoid-like reactions may eventually develop more widespread systemic manifestations [5].

While sarcoidosis and sarcoid-like reactions are well-described phenomena in a variety of solid and hematologic malignancies [6], they are more rarely reported in patients with renal cell carcinoma (RCC). Moreover in patients with RCC, the non-necrotizing granulomas have predominantly been found to occur within, or adjacent to, the primary tumor. Involvement of distant organs such as the pulmonary parenchyma, thoracic lymph nodes and bone marrow is less common [7] and presents a significant clinical challenge as it may mimic metastatic disease and result in unnecessarily aggressive investigations and treatment.

We report a case of a patient with surgically resected RCC presenting with progressively enlarging pulmonary nodules, thoracic lymphadenopathy, splenic hepatic and osseous lesions who was initially thought to have metastatic disease but on further investigation was diagnosed with sarcoidosis. Several years later the patient was found to have infiltrative cardiac disease suggestive of cardiac sarcoidosis. This case provides new insights into the clinical spectrum of malignancy associated sarcoidosis and underscores the need for close monitoring and follow up, even if there is no evidence of widespread systemic sarcoidosis initially.

2. Case report

A 48-year-old Caucasian male underwent a right radical nephrectomy in June 2007 after he was found to have a 14 × 10 cm right renal mass. Pathologic analysis of the surgical specimen revealed RCC with clear cell and papillary features, Fuhrman grade III/IV, with invasion into the perirenal sinus fat but not the renal vein, inferior vena cava or adrenal gland. There was no evidence of distant metastatic disease and he was therefore deemed to have pT3aN0M0 RCC, or stage III disease.

He underwent a follow up CT scan of the chest, abdomen and pelvis in August 2007 and was found to have several small (<4mm) pulmonary nodules with small (<1cm) subcarinal and right hilar lymph nodes. On subsequent imaging over the next several years there was some interval growth of the nodules and in April 2012 a dominant part-solid nodule in the right upper lobe had reached 1.4 × 1.1 cm in size (Fig. 1). There were also slowly growing hypodensities in the liver and spleen. Given the above findings there was suspicion for recurrence of the patient's RCC and he was sent by his oncologist for a transthoracic needle aspiration (TTNA) of the right-upper lobe nodule in July 2012, which was non-diagnostic and showed only a single multinucleated giant cell. A PET scan was subsequently done in September 2012 (Fig. 2), which demonstrated widespread FDG-uptake in the lungs (SUV-6.9), hila (SUV-5.7) and supraclavicular regions bilaterally (SUV-5.6), the mediastinum (SUV-5.7), the spleen (SUV-4.8) and the porta hepatis (SUV-8.5).

Given the suspicion for metastatic disease he underwent an endobronchial ultrasound guided transbronchial needle-aspiration (EBUS-TBNA) of the subcarinal and right hilar lymph nodes in October 2012, which showed benign lymphocytes with no evidence of malignancy, mycobacterial and fungal infection. A repeat PET scan in January 2013 was unchanged so in February 2013 a fine-needle aspiration of the right supraclavicular lymph node was performed, which again showed only benign cells. Ultimately, he underwent right upper, and lower, lobe wedge resections in April 2013 and the pathology revealed non-necrotizing granulomas on both specimens (Fig. 3), with no evidence of fungal or mycobacterial infection on smear (potassium-hydroxide and auramine-rhodamine respectively), culture or polymerase chain reaction, suggesting a diagnosis of systemic sarcoidosis.

The patient remained fairly asymptomatic apart from an occasional dry cough and follow-up imaging revealed spontaneous regression of the pulmonary, splenic and hepatic lesions. However, several years later he began to complain of exertional dyspnea and was noted to have a new right-bundle branch block. He underwent a transthoracic echocardiogram that demonstrated new patchy wall motion abnormalities in a non-

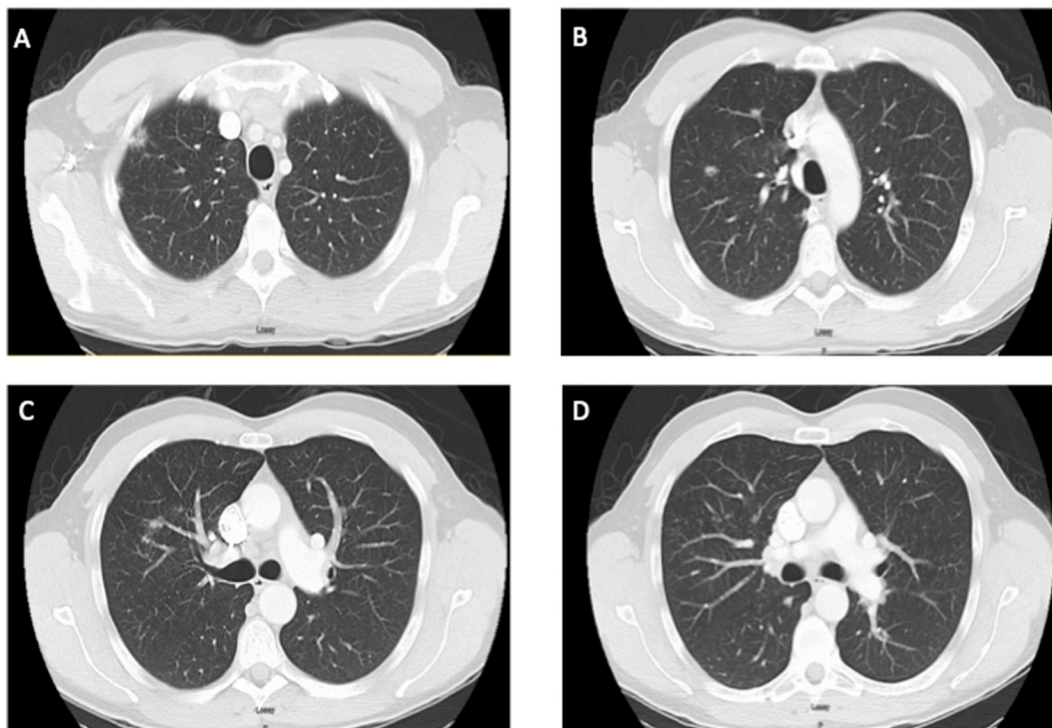


Fig. 1. Computed tomography (CT) scans of the chest demonstrating ill-defined subpleural and peribronchovascular nodularities, predominantly distributed in the mid- and upper-lung zones.

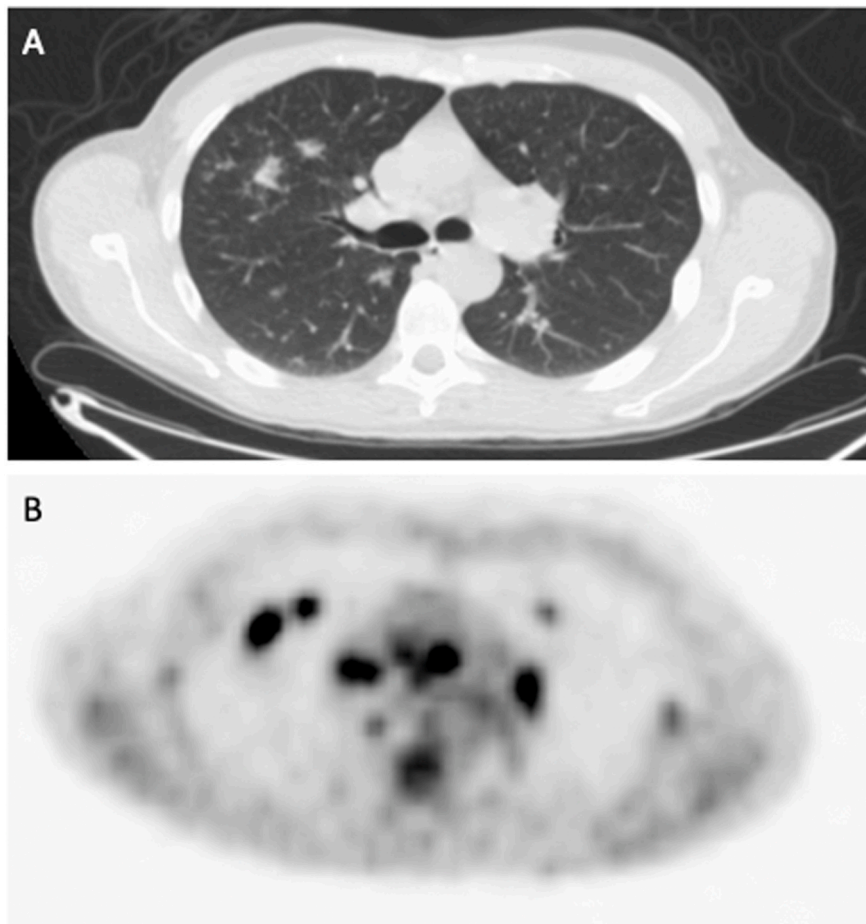


Fig. 2. (a) CT scan of the chest demonstrating ill-defined parenchymal nodularities and enlarged hilar and mediastinal lymph nodes. (b) ^{18}F FDG-PET demonstrating enhanced FDG uptake in the corresponding parenchymal nodularities and lymph nodes.

coronary distribution that had not been present two years prior. Subsequently, a cardiac MRI was performed which showed sub-pericardial late gadolinium enhancement in the basal and mid-anterior segments and transmural late gadolinium enhancement in the distal anterior segment. He also underwent a cardiac PET scan that showed patchy FDG-uptake in the left and right ventricles, specifically in the basal and anterolateral wall (SUV-6.7), septum (SUV-8.1) and apex (SUV-7.8). Taken together, especially given his diagnosis of sarcoidosis, these findings were felt to be highly sensitive and specific for cardiac sarcoidosis. Arrhythmogenic right ventricular cardiomyopathy was another diagnosis raised on the basis of the MRI findings but was felt to be less likely given the clinical context. The most recent cardiac MRI in December 2019 showed only minimal late-gadolinium enhancement and mild biventricular dysfunction consistent with inactive sarcoidosis. As of February 2020 he remains well with no evidence of active pulmonary or extra-pulmonary disease, and no recurrence of his renal cell carcinoma.

3. Discussion

Although a wide-variety of paraneoplastic syndromes have been described in RCC [8] it has a much less well-established association with sarcoidosis and sarcoid-like reactions, with only thirteen such cases reported in the literature to date in contrast to the reported rate of 4–14% in the overall pool of patients with malignancy of any type [6,7]. While malignancy-associated and idiopathic sarcoidosis appear to be histologically identical, the degree to which the behaviour of malignancy-associated sarcoidosis mirrors that of idiopathic sarcoidosis

in terms of clinical progression and end-organ involvement is less clear [9].

There remains a great deal of debate regarding the exact pathophysiologic mechanisms underlying sarcoidosis in malignancy. The precise immunopathogenesis of idiopathic sarcoidosis is poorly understood but is thought to involve activation of CD4^+ helper T-Cells by an unknown antigen with subsequent differentiation towards a Th1/Th17 phenotype, production of interferon- γ (IFN- γ) and interleukins 2, 12 and 17. IFN- γ along with the aforementioned interleukins is thought to result in macrophage activation and recruitment to tissues with subsequent release of tumor-necrosis factor- α leading to initiation and propagation of granulomatous inflammation [10,11]. One mechanism that has been suggested for malignancy-associated sarcoidosis is that either via their release, or shedding during necrosis, malignant cells release soluble tumor antigenic factors that may serve as the initial trigger in this complex immune cascade.

To our knowledge this is only the second case of pulmonary parenchymal involvement by sarcoidosis in a patient with underlying RCC and certainly the first case with cardiac involvement, although cardiac sarcoidosis has been reported in a patient with underlying testicular cancer [12]. Additionally, the patient had no evidence of sarcoidosis on initial staging and received no chemo- or immunotherapeutic agents prior to diagnosis, suggesting that the development of sarcoidosis in this patient was probably due to his underlying malignancy. The fact that he developed systemic involvement after resection of the primary tumor suggests that a tumor-antigen may have been the initial trigger with an immune reaction developing, and continuing, even after definitive treatment.

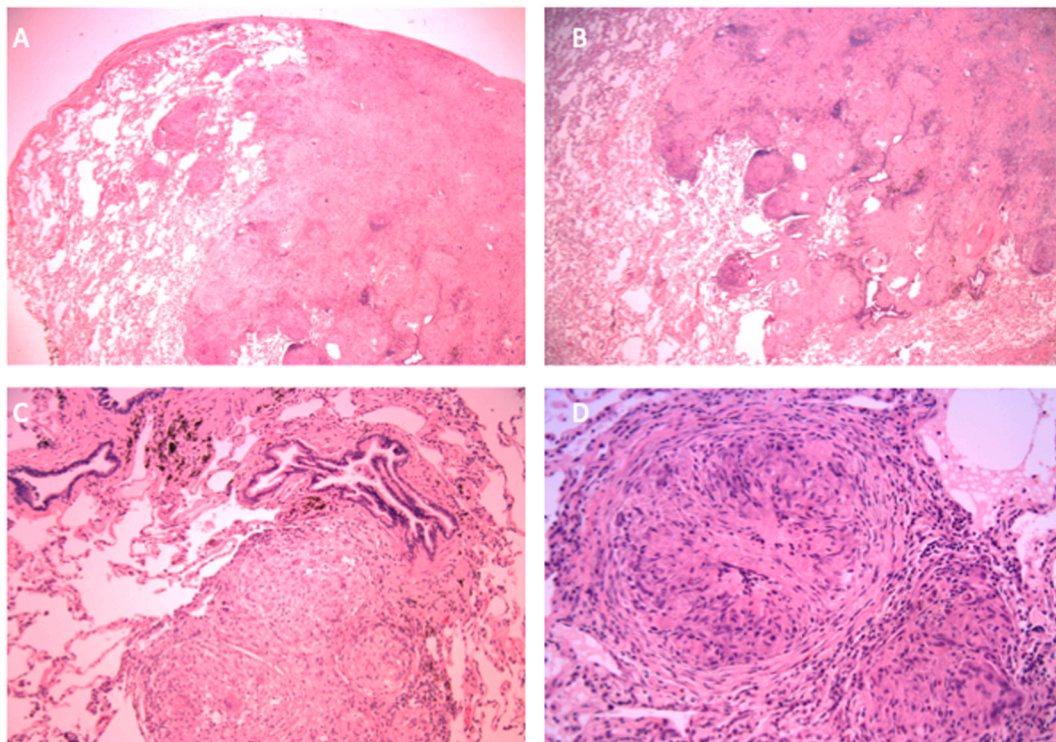


Fig. 3. Histopathological findings of the specimen obtained by video-assisted thoracoscopic surgery (VATS) wedge resection. (a) non-caseating granulomas distributed along the pleural surface. (b) non-caseating granulomas distributed around the bronchovascular bundles. (c) non-caseating granulomas adjacent to terminal bronchiole. (d) high-magnification view of a granuloma showing epithelioid histiocytes and multi-nucleated giant cells.

4. Conclusion

While sarcoidosis has been described in the setting of RCC it is a rare occurrence and the natural history and prognosis are unclear. It is nonetheless important to consider sarcoidosis in the differential of suspected metastatic RCC, even if there is evidence of hypermetabolic foci on PET scan, and to pursue definitive tissue diagnosis before commencing further treatment. Furthermore, this case highlights the clinical spectrum of RCC-associated sarcoidosis and underscores the importance of close monitoring and clinical follow-up in order to assess for reoccurrence of malignancy as well as the development of extra-pulmonary sarcoidosis.

Declaration of competing interest

None.

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