

Sarcoid-like granulomatous reaction in renal cell carcinoma: report of a case with review of the published reports

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A case of renal cell carcinoma with sarcoid-like granulomatous reaction within the tumor was reported. The granulomas were confined to the carcinoma while renal parenchyma and regional lymph nodes were completely free of involvement. Clinical workup of the patient did not reveal any evidence of sarcoidosis, tuberculosis, or any other systemic disease except for diabetes mellitus. Sarcoid-like granulomatous reaction confined to renal carcinoma is a rare finding with only a few cases reported in the published reports.

Granulomatous inflammation is one of the patterns of chronic inflammation that occurs when the cellular immunity system fails to completely clear antigenic stimuli. Granulomas are seen in a limited number of infectious and noninfectious conditions, especially sarcoidosis and tuberculosis. Sarcoidosis is an example of noncaseating granulomatous inflammation of unknown etiology that has a multisystem involvement. Noncaseating granulomas similar to those encountered in sarcoidosis may occasionally be seen in patients who do not fulfill the criteria for systemic sarcoidosis. These are termed “sarcoid-like reaction” (SLR) although the distinction between the two conditions may at times be difficult.¹⁻³

Sarcoid-like granulomas have been seen in relationship with a variety of neoplasms. Granulomas may be present within the tumor itself, in the organ of tumor involvement, in a distant organ or tissue, or most commonly in the lymph nodes draining the neoplasm.^{3,4}

We hereby report a case of renal cell carcinoma containing extensive SLR, limited to the tumor, in the absence of any relevant systemic disease. We also review pertinent published reports in which similar pathologic processes have been documented.

CASE

A 62-year-old man, a known case of diabetes mellitus,

hypertension, and renal impairment, was admitted to the hospital with recent episodes of gross hematuria. An abdominal magnetic resonance imaging revealed a large cortical mass in the upper pole of the right kidney, which was suspicious for kidney carcinoma. A core biopsy of the mass revealed renal cell carcinoma (clear cell type). Several nonnecrotizing epithelioid granulomas were seen scattered within the tumor. Special stains for fungal or mycobacterial organisms (Gomori methenamine silver and Ziehl–Neelsen stains) were negative. A radical nephrectomy was performed.

The nephrectomy specimen revealed a 9-cm well-circumscribed mass replacing the upper pole. The tumor was golden-yellow at the periphery, with grayish-white to dark red and hemorrhagic areas toward the center (**Figure 1**). Histological examination showed clear cell renal cell carcinoma (Fuhrman grade 3). Large numbers of epithelioid granulomas were present scattered throughout the tumor (**Figures 2 and 3**). Most of the granulomas lacked central necrosis; however, foci of coagulative necrosis were present in occasional granulomas (**Figure 4**). These granulomas were mostly associated with necrotic tumor and were not considered to have caseation necrosis, since outlines of tumor vasculature were still recognizable within the necrotic areas. Again, stains for acid-fast and fungal organisms were negative. Some of the granulomas contained mul-

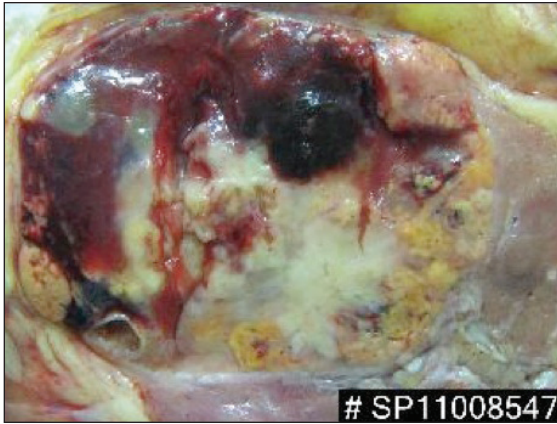


Figure 1. Cut surface of the tumor with yellow areas at the periphery and grayish-white to dark red areas with hemorrhage.

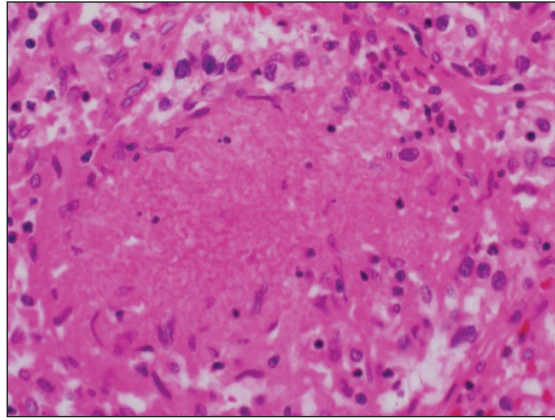


Figure 4. High-power view of a necrotizing granuloma with coagulative (noncaseating) necrosis.

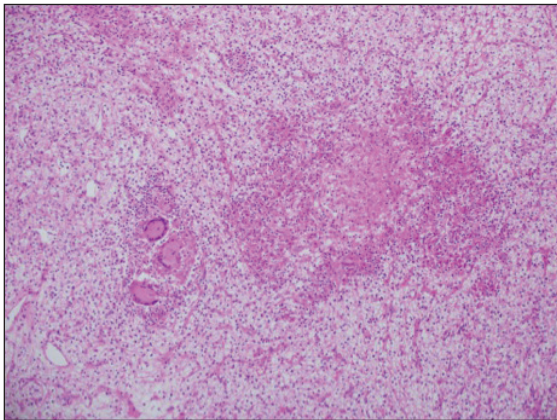


Figure 2. Clear cell renal cell carcinoma in the nephrectomy specimen with multiple epithelioid granulomas.

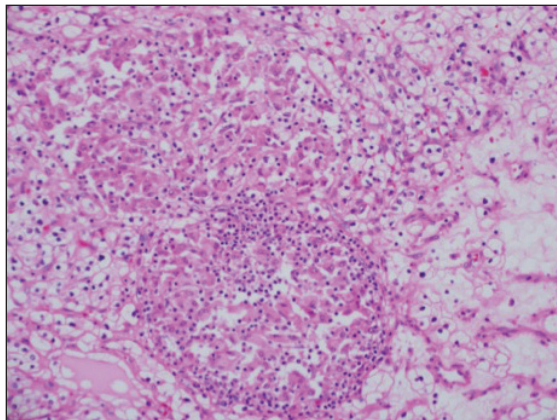


Figure 3. Clear cell carcinoma with nonnecrotizing granulomas.

tinucleated giant cells, including Langhans and foreign body types. The remaining part of the carcinoma contained scattered, focally dense aggregates of lymphocytes and plasma cells (**Figure 5**). More than 90% of the lymphocytes were immunoreactive for CD3 indicating T-cell lineage. These cells were present at the periphery of the granulomas and were scattered diffusely among the carcinoma cells (**Figure 6A**). CD20 positive B lymphocytes, however, were limited to small aggregates scattered randomly near the periphery of the carcinoma and were completely absent within the granulomas and in the adjacent areas of carcinoma (**Figure 6B**). Uninvolved renal parenchyma was completely free of any granulomatous reaction. The features of moderately advanced diabetic glomerulopathy (nodular type) and moderate arteriosclerosis were seen within the renal tissue. There was no evidence of interstitial nephritis or chronic pyelonephritis. Thorough clinical workup failed to reveal any evidence of sarcoidosis or any other systemic disease except for diabetes mellitus.

DISCUSSION

A granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelium-like cells (epithelioid cells), surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells. Granulomas form when the immune system attempts to wall off substances that it perceives as foreign but is unable to eliminate. There are two types of granulomas, which differ in their pathogenesis. Foreign body granulomas are incited by relatively inert foreign bodies. Typically, foreign body granulomas form around inert material such as talc, sutures, or other fibers that are large enough to preclude phagocytosis by a single

macrophage. The foreign material can usually be identified in the center of the granuloma, The second type of granulomas are Immune granulomas, which are caused by a variety of agents that are capable of inducing a cell-mediated immune response but are poorly degradable. In such responses macrophages engulf foreign protein antigen, process it, and present peptides to antigen-specific T lymphocytes, causing their activation. The responding T cells produce cytokines, such as IL-2, which activates other T cells, perpetuating the response. These cells also produce IFN- α , which is important in activating macrophages and transforming them into epithelioid cells and multinucleated giant cells, thus producing the phenotype of epithelioid granulomatous reaction.¹⁻³

The etiologic agents that induce a granulomatous reaction are quite diverse and may include infectious agents such as bacterial and fungal organisms. The morphologic patterns in the various granulomatous diseases may be sufficiently different to allow reasonably accurate diagnosis by an experienced pathologist. For example, granulomas with caseating necrosis are usually associated with infection by *Mycobacterium tuberculosis*. However, the morphologic appearance of the granulomas may be atypical so that an attempt to recognize the underlying etiologic agent may be necessary in every case. The offending agents may be identified by histological stains, microbiologic cultures, and serologic studies, or, in some cases, by using molecular techniques such as polymerase chain reaction.¹⁻³ In many granulomas, there may be no evidence of any of the above-mentioned infectious agents. Sarcoidosis is an example of a granulomatous disease in which no etiologic agent has so far been identified. Sarcoidosis is a multisystem, systemic disease in which nonnecrotizing granulomas are present in several organs including lung, liver, lymph nodes, spleen, and skin among others. In some patients granulomatous inflammation similar to that in sarcoidosis may be seen in a limited area, without evidence of any systemic disease. These changes are usually termed as SLR or sarcoid-like granulomas.^{4,6}

Sarcoid-like granulomatous reaction is most often seen in lymph nodes draining an area with a neoplasm. In some cases the nodes involved by the process may be distant from the site of the tumor. The involved lymph nodes are usually free of metastases, although occasionally, granulomas may be seen in relationship with metastatic neoplasm. SLR may also be seen in the vicinity of the tumor within the involved organ such as liver and lung. SLR to a tumor may in some cases be present within the tumor itself. In seminoma and dysgerminoma, this reaction is usually localized to the connective tissue septa within the tumor and is generally

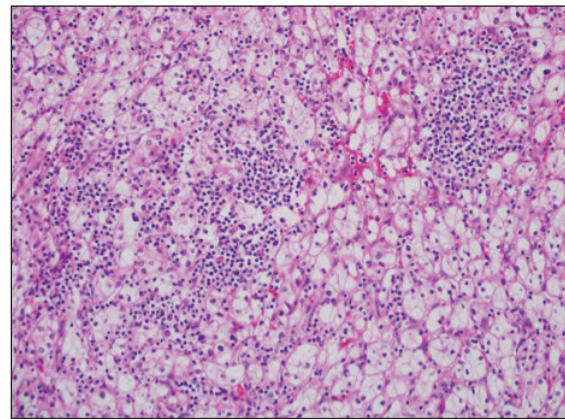


Figure 5. Clear cell carcinoma with diffuse lymphoplasmacytic infiltration.

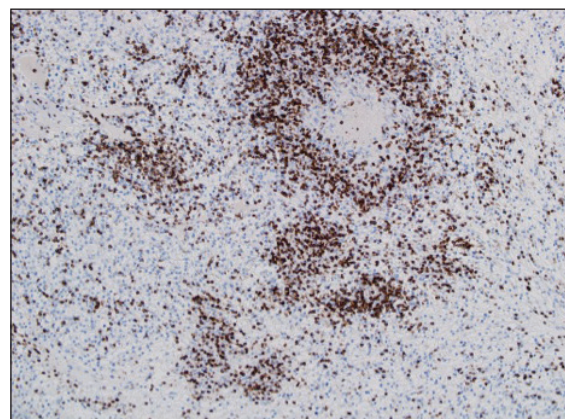


Figure 6A. A section from renal cell carcinoma with immunostaining for CD3, revealing large numbers of T-cells surrounding the granuloma and diffusely scattered in other parts of the carcinoma.

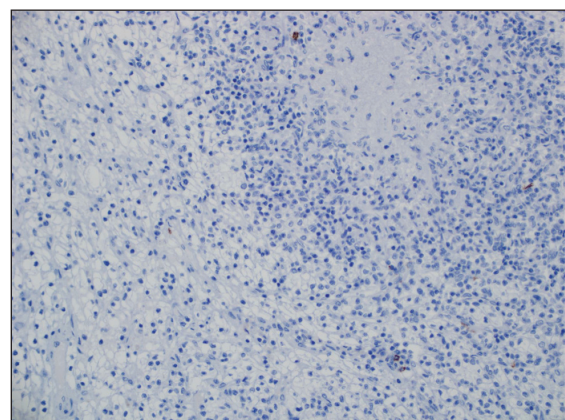


Figure 6B. CD20 immunostaining of the area shown in Figure 5 revealing the absence of B-cell.

Table 1. Cases of renal cell carcinoma with sarcoid-like reaction without evidence of systemic sarcoidosis.

Reference	Age/Sex	Other Location of SLR	RCC Type
Bottone et al (1993) ⁷	55/F	Liver, abdominal lymph nodes	Clear cell
Marinides et al (1994) ⁸	44/M	None	Papillary
Lucci et al (2002) ⁹	39M	None	Clear cell
Hes et al (2003) ¹⁰	73-85 2F/1M	None	Clear cell
Kovacs et al (2004) ¹¹	62/F	None	Clear cell
Piscioli et al (2008) ¹²	70M	None	Sarcomatoid
Narasimhaiah et al (2011) ¹³	44-65/3M	None	Clear cell
Present study (2012)	62/M	None	Clear cell

considered to be part of the morphologic spectrum of these tumors. Less commonly, other neoplasms may also display such a reaction within the stroma or among the tumor cells. There have been only sporadic case reports of such tumors, some of which have been carcinomas arising in a variety of locations such as breast, esophagus, lung, pancreas, stomach, bile duct, rectum, ovary, and kidney (reviewed in reference 3). Other types of neoplastic conditions involved by such a reaction are Hodgkin disease, non-Hodgkin lymphoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, melanoma, and leiomyosarcoma.⁴ The relative frequency of SLR, within the tumor or in lymph nodes, varies considerably among the various groups of neoplasms. In the study by Brincker, SLR was found to occur in 4.4% of carcinomas, in 13.8% of patients with Hodgkin disease and in 7.3% of cases with non-Hodgkin lymphomas.⁵

The involvement of renal cell carcinoma by SLR is rare with only a few cases reported in the published reports. The clinicopathologic details of these cases are given in **Table 1**. Of the 11 cases reported previously, 4 were female and 7 male patients.⁷⁻¹³ Their age ranged from 39 to 70 years. The histological type of carcinoma was clear cell in 9 cases, sarcomatoid renal cell carcinoma in 1 case, and papillary type in another case. In all cases the SLR was limited to the kidney except for 1 patient

reported by Bottone et al in which the granulomas were also present in liver and abdominal lymph nodes.⁷ In another case, reported by Campbell and Douglas-Jones, sarcoid-like granulomas were documented in renal carcinoma; however, this patient had a prior diagnosis of sarcoidosis.¹⁴ Therefore, this case was excluded from the review.

The etiology of cancer-related SLR is postulated to be secondary to an induced T-cell-mediated host response to soluble antigenic tumor factors.³ The antigenic factors may be either shed by tumor cells or released by tumor cells or released during tumor necrosis. These factors may be carried to regional lymph nodes, where SLR is usually manifested. Extensive T-cell infiltration within the carcinoma in our case is consistent with the primary role of T-cells in the initiation and perpetuation of the tumor cells injury, ultimately leading to granulomatous inflammation. It is not clear, however, why in many of the cases, SLR is seen in regional or distant lymph nodes while in some cases, like the present case, SLR is limited to the carcinoma.

In conclusion, a case of sarcoid-like granulomatous reaction involving renal cell carcinoma is reported. The granulomas were limited to the carcinoma, and there was no evidence of systemic involvement by sarcoidosis. Previously documented cases with similar findings are reviewed.

REFERENCES

1. Kumar V, Abbas AK, Fausto N, Caster JC. Acute and chronic inflammation in Robbins and Cotran Pathologic Basis of Disease. 2010, Chapter 2, eighth edition pp 44-77, Saunders Philadelphia PA USA.
2. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Eng J Med* 2007; 357: 2153-2165.
3. Kurata A, Terado Y, Schulz A, Fujioka Y, Franke FE. Inflammatory cells in the formation of tumor-related sarcoid reactions. *Hum Pathol* 2005;36:546-54.
4. Cohen PR, Kurzrock R. Sarcoidosis and malignancy Clinics in Dermatology 2007; 25:326-333.
5. Brincker H. Sarcoid reactions in malignant tumours. *Cancer Treat Rev* 1986;13:147-56.
6. Bhatia A, Kumar Y, Kathpalia AS. Granulomatous inflammation in lymph nodes draining cancer: A coincidence or significant association! *Int J Med Medical Sciences* 2009; 1: 13-16.
7. Bottone AC, Labarbera M, Asadourian A, Barman A, Richie C. Renal sarcoidosis coexisting with hypernephroma. *Urology* 1993;41:157-9.
8. Marinides GN, Hajdu I, Gand RO. A unique association of renal cell carcinoma with sarcoid reaction in the kidney. *Nephron* 1994;67:477-80.
9. Lucci S, Rivolta R, Fazi M. Sarcoidosis and clear cell carcinoma of the kidney: the sixth case? *G Chir* 2002;23:75-78.
10. Hes O, Hora M, Vanecek T, Sima R, Suic M, Haviček F, Beranova M, Michal M. Conventional renal cell carcinoma with granulomatous reaction: a report of three cases *Virchows Arch* (2003)443:220-221
11. Kovacs J, Varga A, Bessenyei M, Gomba S. Renal cell cancer associated with sarcoid-like reaction. *Pathol Oncol Res* 2004;10:169-71.
12. Pisciole I, Donato S, Morelli L, Nonno F, Licci S. Renal cell carcinoma with sarcomatoid features and peritumoral sarcoid-like granulomatous reaction: report of the case and review of the literature. *Int J Surg Pathol* 2008; 16:345.
13. Narasimhaiah DA, Manipadam MT, Aswathaman K, Krishnamoorthy S. Renal cell carcinoma associated with granulomatous reaction. *Saudi J Kidney Dis Transp* 2011; 22:1211-1214.
14. Campbell F, Douglas-Jones AG. Sarcoid-like granulomas in primary renal cell carcinoma. *Sarcoidosis* 1992; 10:128-31.