Granulomata in Clear Cell Renal Cell Carcinoma: An Uncommon Presentation of a Common Cancer, Not Two Separate Entities

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ABSTRACT: Sarcoidal-like granulomata (SLG) are known to occur as a response to a variety of tumor types, including lymphomas, prominently seminoma, other miscellaneous carcinomas, and rarely in renal cell carcinoma. There have been a handful of previously reported cases in the literature of SLG occurring in association with RCC. Of those previously reported, none were associated with infection and only 3 patients had a history of sarcoidosis. The prognostic significance of SLG in RCC is unsettled and somewhat complicated by the relative rarity of its occurrence and the paucity of data therein. A case is presented of an otherwise histologically typical clear cell renal cell carcinoma with peri-tumoral and intra-tumoral SLG. Special stains were negative for organisms and past medical history was negative for sarcoidosis and connective tissue disease.

KEYWORDS: sarcoidal-like granulomata, granulomas in renal cell carcinoma, tumoral granulomata, renal cell carcinoma, clear cell renal cell carcinoma

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Case Report

A 65-year-old-male with an unremarkable past medical history presented with new onset hematuria. Urine cultures, cytology, and cystoscopy were unremarkable. The patient subsequently underwent a renal ultrasound, which revealed a Bosniak 2 cyst of the right kidney. Computed tomography–intravenous pyelogram (CT-IVP) showed a 2.6-cm partially exophytic heterogeneously enhancing mass in the upper pole of the left kidney, concerning for renal cell carcinoma (RCC). Multiple bilateral renal cysts were also noted, while subsequent chest radiographs were unremarkable for pulmonary lesions. A left robotic partial nephrectomy was performed which grossly revealed a solitary 2.4 cm tan focally hemorrhagic mass abutting the renal capsule. Histologic evaluation showed a clear cell neoplasm with acinar growth and delicate, chicken wire-type vasculature in a background of lobulated fibrosis and tumoral-associated inflammation containing granulomata (Figure 1A and B). Tumor foci of greatest nuclear pleomorphism contained nuclei with vesicular chromatin and conspicuous eosinophilic nucleoli visible at 40× magnification (Figure 2). Non-necrotizing sarcoidal-like granulomata (SLG) were present in both a peri-tumoral and intra-tumoral distribution and were accompanied by mixed inflammation of varying intensity, including pauci-inflammatory (Figure 3A) as well as heavily inflamed (Figure 3B). The latter contained actively forming SLG in association with neutrophils, eosinophils, lymphoctyes, and plasma cells (Figure 3B). The presence of reniform-shaped histiocytes with prominent nucleoli and associated eosinophils were not identified. The tumor was confined to the kidney, margins were uninvolved, and lymphovascular invasion was not identified. Special stains for microorganisms (Gram, PAS fungal, GMS, and Kinyoun) were negative, and a review of the patient's past medical history was unremarkable for connective tissue disease, pertinent travel history, or pulmonary symptoms. A diagnosis of *Clear Cell Renal Cell Carcinoma, ISUP (International Society of Urological Pathology) Grade 2*, was rendered, and the tumor was pathologically staged as pT1a (American Joint Committee on Cancer, eighth edition). Now 4 months post-nephrectomy, the patient is alive without evidence of disease.

Discussion

Prior to this report there have been 26 cases reported in the literature of SLG occurring in association with RCC.[1] Of those previously reported, 0 of 26 (0%) were associated with infection, 0 of 26 (0%) were associated with connective tissue disease, and only 3 of 26 (11.5%) had a history of sarcoidosis.[1] The histotypes of previously reported cases include 24 of 26 (92.3%) clear cell RCCs, including 1 with sarcomatoid differentiation, 1 of 26 (3.8%) clear cell papillary RCC (3.8%), and 1 of 26 (3.8%) chromophobe RCC. In 3 of 26 (11.5%), SLG were identified in regional lymph nodes draining tumor, while SLG involving perinephric fat and lung metastasis have also been reported. Only 1 of 26 (3.8%) had SLG unassociated entirely with primary tumor.

Briefly, SLG formation is a T-cell-mediated response[2] in which tissue macrophages are recruited by CD8+ cytotoxic T cells in response to an antigenic trigger,[3] akin to sarcoidosis itself, and is considered a form of disease manifestation in many tumors. Thus in theory, an SLG response could be viewed as a natural antitumor response with the potential to confer a protective role; that possibility is discussed more fully below. SLG are not infrequently found in association with malignancy, albeit quite uncommonly in the kidney. Within surgical pathology, a foremost recognizable association of

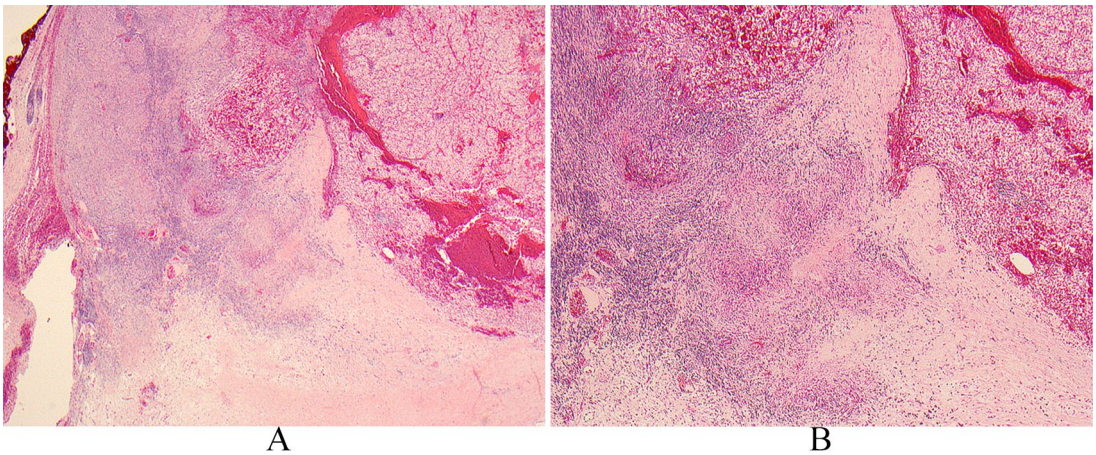

Figure 1. (A) Scar dividing lobules of clear cell RCC with peripheral involvement by granulomata and varying intensity of mixed inflammation (hematoxylin and eosin stain, 2× magnification). (B) Well-developed scar (hematoxylin and eosin stain, 4× magnification).

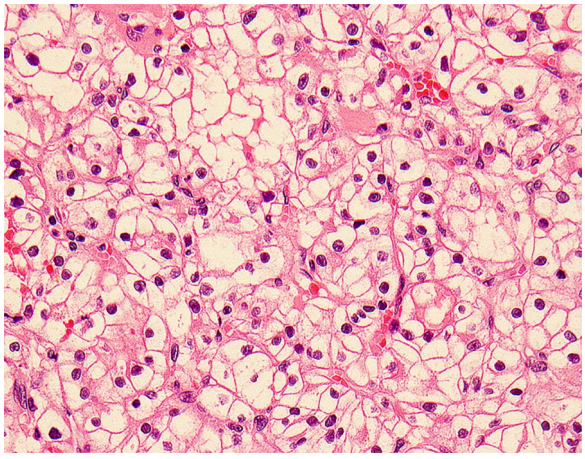

Figure 2. Tumor showing classic morphology of clear cell RCC, namely acinar growth with delicate chicken wire-like vasculature, and tumro cells with abundant clear cytoplasm. Nucleoli are prominent and eosinophilic at this magnification (40×), ISUP Grade 2 (hematoxylin and eosin stain, 40× magnification).

SLG-associated neoplasia occurs in seminoma, while SLG have also been observed in various carcinomas, lymphomas, and rarely sarcomas.[4] The exact stimulus for granuloma formation in RCC is unknown, with some speculation that intracytoplasmic glycogen may be the antigenic trigger,[1-3] which may partially explain the preponderance of reported cases involving tumor histotypes which contain abundant intracytoplasmic glycogen (25/26), usually clear cell RCC (24/26). The depth of that conclusion appears premature, however, given that only rare case reports and case series mention SLG in clear cell RCC, an otherwise common tumor. Operating under the assumption that intracytoplasmic glycogen is the antigenic trigger driving SLG formation in RCC, it could be reasonably surmised that this association should occur with a substantially greater frequency than currently recognized, given that there are roughly 48 000 new clear cell RCC cases diagnosed annually in the United States alone.[5] Contrast to seminoma, another tumor with abundant intracytoplasmic glycogen, with roughly 5000 new cases diagnosed annually in the United States, in which SLG are so routine, that the finding is entrenched within pathology textbooks as a classic manifestation of disease, while SLG in clear cell RCC have now been reported only 27 times.[1] It may also be plausible to surmise given that clear cell RCC as an individual tumor histotype comprises 65% of all RCC, the association may simply be a causation of prevalence. Still other possibilities exist for the formation of SLG in RCC, including prior sampling, history of trauma/surgery, concurrent dissemination of granulomatous infection, connective tissue disease, or sarcodosis, to name a few. In light of this, to the knowledge of the author, other than connective tissue disease and infection, these other possibilities remain unexplored.

The effect of SLG on prognosis is similarly uncertain. Theoretically speaking, applying the logic used in infection that granulomas are a protective response, a similar response to tumor should hypothetically infer host protection. This hypothesis also appears premature, as data in other cancers associated with SLG are either unsettled or contrarian to that supposition, although specific prognostic implications of SLG in RCC have not been studied to date.[6-11] At best, the prognostic significance of SLG in RCC appears unsettled and remains somewhat complicated by the relative rarity of its occurrence and the paucity of data therein.

Exceedingly rare reports of Langerhans cell histiocytosis (LCH) have been reported in association with RCC and merits brief mention.[12,13] In differentiating between LCH and an SLG response, the former are comprised of a biphasic population of morphologically aberrant histiocytes with benign-appearing eosinophils. Tumor nuclei of LCH are reniform in shape with vesicular chromatin, frequently containing a nuclear groove as well as nucleoli. Unlike the epithelioid histiocytes of SLG, tumor nuclei do not stream nor do they form a true syncytium. In challenging cases, the combination of S100 and CD1a or Langerin, CD207, positivity with co-expression of

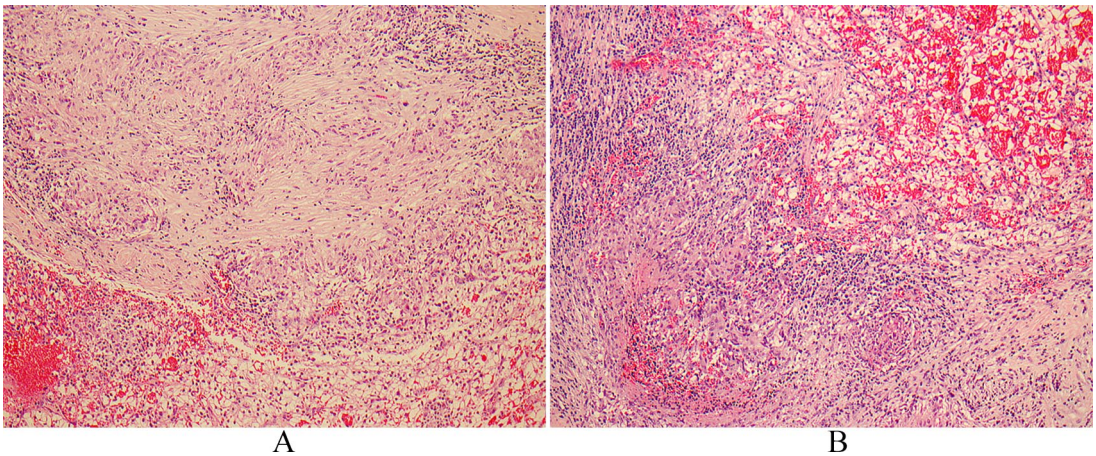

Figure 3. (A, B) Interface of tumor with sarcoidal-like granulomata. (A) Jagged tumor interface with exuberant well-developed pauci-inflammatory sarcoidal-like granulomata, as well as (B) granulomata with exuberant inflammation containing neutrophils, eosinophils, lymphocytes, and plasma cells (hematoxylin and eosin stain; 10× magnification).

CD68 helps confirm the diagnosis of LCH, as SLG express neither S100, CD1a, nor CD207.[14]

In conclusion, to date, RCC-associated SLG have not been associated with infection or connective tissue disease, and only infrequently with sarcoidosis. When faced with SLG in association with RCC, correlation with past medical and travel history is prudent, and in those without clinical suspicion or for whom no pertinent past medical or travel history is elicited, exhaustive staining for microorganisms seems to be of low utility. In this setting, SLG appear to represent an uncommon presentation of a common entity, rather than a collision of tumor with non-tumefactive-induced granulomatous disease.

Author Contributions

The sole author of this manuscript wholly contributed to its production.

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