Renal Cell Carcinomas With Intratumoral Fat and Concomitant Angiomyolipoma

Potential Pitfalls in Staging and Diagnosis

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Abstract

Intratumoral fat and angiomyolipomas (AMLs) occurring within renal cell carcinomas (RCCs) have rarely been reported but may be mistaken for tumor invasion into perinephric or renal sinus fat or misdiagnosed as tumor exhibiting sarcomatoid differentiation. We report 16 such cases. In 14 RCC cases, there was intratumoral fat, 9 of which had fat located peripherally near the capsule (n = 6), renal sinus (n = 1), or both (n = 2). Inflammatory infiltrates and osseous metaplasia were identified in the intratumoral fat in 7 and 8 cases, respectively. Two cases had intratumoral AML foci located at the periphery of RCC. Intratumoral fat or AML at the periphery of RCC simulated the invasion into the fat, while the smooth muscle component of AML resembled spindle cell, or sarcomatoid, differentiation. Our study highlights the potential pitfalls in staging and diagnosis when intratumoral fat or AML is found within RCC.

Pathologic staging is one of the most important prognostic factors for renal cell carcinoma (RCC). If a tumor extends into perinephric or renal sinus fat, it is staged as pT3a. Sarcomatoid differentiation in RCC represents transformation to a higher grade and more aggressive form. Although not a component of the current TNM staging, it connotes poor clinical outcomes. The presence of fat within renal neoplasms has been reported mainly in the radiology literature in the context of radiologic differential diagnosis of angiomyolipomas (AMLs). The histopathologic features of RCC with intratumoral fat, however, have not been reported in the literature. RCC with intratumoral fat is important to recognize because it may be mistaken for tumor invasion into perinephric or renal sinus fat, which will lead to erroneous staging of RCC cases.

Although rare, AML and RCC are known to occur within the same kidney but separate from each other. However, RCC admixed with AML within the same lesion has never been reported. The presence of admixed RCC and the lipomatous component of an AML may lead to misinterpretation of RCC invading into fat and subsequently upstaging. Furthermore, RCC with admixed smooth muscle–predominant AML may cause diagnostic problems because it may be misdiagnosed as sarcomatoid RCC.

These issues have not been addressed previously. We report a series of 16 such cases to highlight the potential pitfall in staging and diagnosis associated with intratumoral fat and concomitant AML.

Materials and Methods

Nephrectomy specimens at the Cleveland Clinic, Cleveland, OH, from 1987 to December 2009 with a diagnosis of RCC
were reviewed. Cases with intratumoral fat or RCC with admixed AML were included in this study. They were assessed for the following morphologic features: histologic subtypes of RCC, location of the fat/AML within the RCC (periphery or center of the tumor) and relationship to perinephric fat and renal sinus, number of foci, size of the largest focus, presence of osseous metaplasia, and chronic inflammation. Immunostains for melanocytic markers (HMB-45 and melan A) were performed in cases with concomitant AML.

**Results**

Of approximately 5,800 nephrectomies reviewed between 1987 and 2009, 16 (0.3%) RCC cases had intratumoral fat (n = 14) or admixed AML (n = 2). The clinical, demographic, and morphologic features of the cases are summarized in **Table 1**. Of these 16 cases, 13 were clear cell RCC (CCRCC), 1 was papillary RCC, 1 was chromophobe RCC, and 1 was RCC, unclassified type. Of the cases, 13 cases were pathologic stage T1a and 3 were T3a (Table 1). In 14 tumors, there was intratumoral fat. Immunostains for melanocytic markers, including HMB-45 and melan A, were performed on 10 tumors with paraffin blocks available. The intratumoral fat in all 10 tumors was negative for both markers, confirming that the intratumoral fat was not fat-predominant AML. Of these 14 cases with intratumoral fat, 7 (50%) had a single focus of fat within the tumor, while the remaining 7 (50%) had 2 or more foci. The size of the foci of fat ranged from 0.1 to 1.8 cm. The mean and median sizes of the intratumoral fat foci, calculated based on the largest focus if multiple fat foci were present, were 0.97 and 0.65 cm, respectively. The fat was present as discrete foci or as scattered adipocytes within the tumor. Only the discrete focus of fat was considered for the calculation of the number and largest size of intratumoral fat in this study. Of 14 cases, 5 (36%) cases had fat at the center of the tumor **Image 1A**, 6 (43%) had fat at the periphery of the tumor, and 3 (21%) cases had fat located centrally and peripherally. Of the 9 cases with peripherally located intratumoral fat, it was found near the renal capsule in 6 cases **Image 1B** and **Image 1C**, near the renal sinus in 1 case **Image 1D**, and near both in 2 cases.

Osseous metaplasia with bone formation was identified in 8 (57%) of the 14 cases with bone formation intimately associated with the intratumoral fat **Image 2A**. A mixed chronic inflammatory infiltrate consisting predominantly of lymphocytes was also identified interspersed within the fat in 7 cases (50%) **Image 2B**. Such inflammatory infiltrates were present in 6 (67%) of 9 samples of intratumoral fat that was located at the periphery of RCC.

**Table 1**

<table>
<thead>
<tr>
<th>Case No./ Sex/Age (y)</th>
<th>Primary Diagnosis</th>
<th>Tumor Size, Greatest Dimension (cm)</th>
<th>Fuhrman Grade</th>
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<tbody>
<tr>
<td>1/F/58</td>
<td>CCRCC</td>
<td>3.5</td>
<td>1</td>
</tr>
<tr>
<td>2/M/43</td>
<td>PRCC</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>3/M/50</td>
<td>CCRCC</td>
<td>2.6</td>
<td>2</td>
</tr>
<tr>
<td>4/M/54</td>
<td>ChRCC</td>
<td>1.9</td>
<td>2</td>
</tr>
<tr>
<td>5/M/76</td>
<td>CCRCC</td>
<td>4.5</td>
<td>3</td>
</tr>
<tr>
<td>6/F/43</td>
<td>CCRCC</td>
<td>3.2</td>
<td>2</td>
</tr>
<tr>
<td>7/M/71</td>
<td>CCRCC</td>
<td>2.6</td>
<td>3</td>
</tr>
<tr>
<td>8/F/49</td>
<td>CCRCC</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>9/M/56</td>
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<td>11.5</td>
<td>2</td>
</tr>
<tr>
<td>10/M/32</td>
<td>CCRCC</td>
<td>3</td>
<td>2</td>
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<tr>
<td>11/M/52</td>
<td>CCRCC</td>
<td>3.2</td>
<td>3</td>
</tr>
<tr>
<td>12/M/55</td>
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<td>13/F/88</td>
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<td>2.5</td>
<td>2</td>
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<tr>
<td>14/F/44</td>
<td>CCRCC</td>
<td>3.2</td>
<td>2</td>
</tr>
<tr>
<td>15/M/61</td>
<td>RCC, unclassified</td>
<td>2.2</td>
<td>1</td>
</tr>
<tr>
<td>16/F/58</td>
<td>CCRCC</td>
<td>1.7</td>
<td>2</td>
</tr>
</tbody>
</table>

AML, angiomylipoma; C, tumor capsule; CCRCC, clear cell RCC; CMRCC, chromophobe RCC; NA, data not available; PRCC, papillary RCC; RCC, renal cell carcinoma; S, renal sinus; +, present or positive; –, absent or negative.

When intratumoral fat was found at the periphery of RCC, adipocytes and cancer cells formed irregular, or “infiltrative,” interface with RCC and, therefore, created a false impression of cancer cells “invading” into fat (Image 1D).

Preoperative computed tomography (CT) scan results were available for 11 of 14 tumors with intratumoral fat (Table 1). Only 2 cases were documented to have “fat density” on the CT scan. Calcification was identified in 4 cases, including 1 with intratumoral fat density. The remaining 7 cases did not show intratumoral fat density or calcification.

Two cases of CCRCC had admixed AML **Image 3A** and **Image 4A**. In both cases, the AML was located at the periphery of CCRCC and the CCRCC and AML components were admixed together. The diagnosis of AML was confirmed by positive immunostains for melanocytic markers HMB-45 (Image 4C) and melan A. One case had a single focus of AML with a predominant spindle cell component (Images 4A-4C). The CCRCC cells infiltrated into the spindle cells and adipocytes and simulated desmoplastic reaction (Images 4A and 4B). The immunostain for HMB-45 highlighted the irregular and infiltrative interface between CCRCC cells and AML spindle cells (Image 4C). The second case had two foci of AML, one located near the capsule and the other near the renal sinus. The adipocytes of the AML formed an irregular or infiltrative interface with RCC cells and, therefore, simulated the invasion of RCC into perinephric fat (Image 3B). One RCC with intratumoral AML did not show fat density or calcification on preoperative CT scan.
Renal cell carcinoma (RCC) with intratumoral fat. Fat cells were found in the center of the tumor (A, H&E, ×40) or located peripherally, near the capsule (B, H&E, ×40; C, H&E, ×100). Residual atrophic renal tubules were present in the tumor capsule (C). Note the residual atrophic renal tubules outside the tumor capsule in C. D, Fat cells were present in a clear cell RCC that bulged into renal sinus and abutted large vessels (H&E, ×40). Note the tumor capsule was thin and there was no inflammation and desmoplastic reaction.
Discussion

The presence of fat in renal tumors has conventionally been associated with AMLs and is often considered as a diagnostic clue to AML in radiologic studies. However, intratumoral fat has been documented in other renal tumors, especially RCC, mainly in the context of radiologic studies. Between 1993 and 2009, 8 case reports documented 9 RCCs with intratumoral fat, 8 of which were confirmed by pathologic examination. Of these reported RCCs, 5 had documented fat in association with calcification or ossification or bone marrow elements. However, 4 cases of RCC had fat without calcification. All of these case reports discussed implications of the incidental occurrence of intratumoral fat in RCC for the radiologic diagnosis of AML.

In the present article, we report 14 RCC cases with intratumoral fat, the largest study so far. The intratumoral fat was not fat-predominant AML because it was negative for melanocytic markers. The size of these intratumoral foci of fat varied from 0.1 to 1.8 cm. They were distributed randomly throughout the tumor. However, of the 14 cases with intratumoral fat,

![Image 2](https://academic.oup.com/ajcp/article-abstract/134/5/807/1769422/134580771769422) Renal cell carcinoma (RCC) with intratumoral fat. **A**, The intratumoral fat component had osseous metaplasia with bone formation and bone marrow elements (H&E, ×40). **B**, A clear cell RCC with intratumoral fat and mixed chronic inflammatory infiltrate, consisting predominantly of lymphocytes, and fibrosis surrounding the intratumoral fat (H&E, ×100).

![Image 3](https://academic.oup.com/ajcp/article-abstract/134/5/807/1769422/134580771769422) Renal cell carcinoma (RCC) with concomitant angiomyolipoma. **A**, The angiomyolipomatous component was present at the periphery of a clear cell RCC, with RCC cells intermingling with angiomyolipoma (H&E, ×40). This angiomyolipoma was positive for HMB-45 (not shown). **B**, A residual renal tubule was present at the periphery of the angiomyolipoma (H&E, ×100).
9 had fat at the periphery of the tumor, near the renal capsule, sinus, or both. In these cases, the intermingling of RCC cells with intratumoral fat at the periphery of the tumor created an irregular, or infiltrative, interface between the RCC and fat, which might have been misinterpreted as tumor invasion into perinephric or renal sinus fat and, therefore, might potentially create problems in the staging of the tumors. Mixed inflammatory infiltrates consisting of lymphocytes and plasma cells were identified in about 67% (6 of 9 cases) of intratumoral fat located at the periphery of the tumor in our study. The presence of mixed inflammatory infiltrates and fibrosis surrounding the intratumoral fat may further confuse the issue by raising the suspicion for desmoplastic response secondary to invasion by RCC. However, about 57% (8/14) of the cases in our study had osseous metaplasia associated with the intratumoral fat, including 6 cases with intratumoral fat located at the periphery of RCC and mixed inflammatory infiltrates (4 cases). This feature is helpful in differentiating intratumoral fat from perinephric and sinus fat invasion. Intratumoral bone is believed to occur as a reparative or metaplastic process secondary to ischemia, necrosis, or inflammation.

Our study reinforces the notion long held by radiologists that while the presence of fat density in a renal tumor provides a diagnostic clue to AML, it can rarely be seen in RCCs. Intratumoral calcification, on the other hand, is seen only rarely in AML and, therefore, provides a useful radiologic clue for RCC. In our study, fat density was seen in only 2 of 11 tumors with intratumoral fat, presumably owing to the small size of the fat foci. Intratumoral calcification, in contrast, was seen in 4 of 11 tumors, including 1 tumor that also had intratumoral fat.

Concurrent renal cell neoplasms and angiomyolipomas have rarely been reported. Jimenez et al reported 36 cases with coexisting renal cell neoplasms and AMLs. The
Intratumoral Fat in Renal Cell Carcinoma

Aron et al

Laboratory Medicine Institute, Cleveland Clinic, 9500 Euclid Ave, Clinic, Cleveland, OH. From the Pathology and Laboratory Medicine Institute, Cleveland diagnosis of RCC.

lesion can prevent potential erroneous staging and misdiagnosis of RCC. The intratumoral fat and admixed RCC and AML within the same renal sinus by RCC. Awareness of the rare occurrence of metaplastic process rather than invasion of perinephric fat/sinus invasion.

Another potential pitfall is the misinterpretation of smooth muscle–predominant AML intermingling with RCC as sarcomatoid differentiation in an RCC. Smooth muscle–predominant AML with a paucity of fat and vascular component may be difficult to recognize and may be mistaken for spindle cell, or sarcomatoid differentiation, in RCC. Smooth muscle–predominant AML can also show significant nuclear atypia with mitoses that may further complicate the issue. The presence of dysmorphic, thick-walled vessels will provide a clue to the right diagnosis. Immunohistochemical analysis for melanocytic markers (eg, HMB-45 and melan A) may be required to recognize the melanocytic differentiation and establish a diagnosis of AML in these cases.

The third potential pitfall is the interpretation of needle biopsy specimens from renal masses. AML in RCC could be sampled by needle biopsy without sampling admixed RCC, leading to an erroneous diagnosis of pure AML. Although the incidence of AML admixed in RCC is very low (<0.05%), pathologists should carefully examine all of the biopsy material so that any small RCC component is not missed.

Intratumoral fat and AML can rarely be found in RCCs and, when present, are often found at the periphery of RCC and can potentially be mistaken for invasion into perinephric or sinus fat and sarcomatoid differentiation. The intratumoral fat in an RCC may also lead to erroneous diagnosis of AML on preoperative CT scanning. The presence of osseous metaplasia within the fat suggests that the intratumoral fat is a metaplastic process rather than invasion of perinephric fat/sinus by RCC. Awareness of the rare occurrence of intratumoral fat and admixed RCC and AML within the same lesion can prevent potential erroneous staging and misdiagnosis of RCC.

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References


