Ovarian metastasis from renal clear cell carcinoma: a case report with an intraoperative, immunohistochemical study, and a review of the literature

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Summary

This case report refers to ovarian metastases from renal clear cell carcinoma (RCC) in a 46-year-old woman with a history of abdominal pain and urinary incontinence. A pelvic ultrasound revealed a heterogeneous, large, right-sided solid/multi-cystic ovarian mass, suggesting diagnosis of borderline or malignant epithelial ovarian tumor. At staging, abdominal CT incidentally revealed an enlarged left kidney with a lesion, consistent with renal carcinoma. At the time of surgery, a frozen section of ovarian neoplasm was performed to confirm diagnosis of primary epithelial borderline ovarian tumor or metastatic renal carcinoma. Macroscopically, the right ovary had been entirely replaced by a multiloculated cystic lesion with clear serous fluid, solid septa, and centrally, a solid gray area. Imprint cytology, performed during an intraoperative study of the lesion, showed cohesive clusters of neoplastic cells with clear abundant and vacuolated cytoplasm, pleomorphic, medium or large nuclei, and evident nucleoli. Histological examination revealed an epithelial neoplasm, characterized by large cells with clear optically empty cytoplasm that lined the alveolar and cystic spaces. A prominent vascular component with sinusoidal features was also present. These findings and the clinical data of the simultaneous renal lesion were consistent with an intraoperative diagnosis of ovarian metastatic renal carcinoma. Permanent sections revealed that the ovarian lesion showed the same pathological features as those observed in frozen sections. Immunohistochemical analysis of the ovarian tumor showing positivity for CD10 and renal clear cell marker (RCC Ma), while the presence of RCC in a nephrectomy specimen confirmed ovarian metastatic renal carcinoma. In conclusion, although ovarian metastasis of RCC is very rare, diagnosis can be made by careful histological examination, immunohistochemical study, plus clinical data.

Key words: Renal clear cell carcinoma; Ovarian metastasis; Intraoperative diagnosis; Immunohistochemical analysis.

Introduction

The most common sites for metastasis of a malignant tumor include the brain [1], bones [2], lungs [3], and liver [4-6]. Extragenital malignancies which commonly metastasize to the ovary include gastric, colorectal, breast carcinomas and lymphomas [7-8], and malignant tumor of the female genital tract [9].

Ovarian metastasis from renal clear cell carcinoma (RCC) are very rare with only 35 cases [10-35] in the English literature. The present case is the only example observed in the present Institution in the past 20 years.

Because of its rarity, ovarian metastasis of RCC represents a challenge in diagnosis and management. In fact, failure to recognize an ovarian metastatic extragenital tumor which mimics a primary Müllerian neoplasm could lead to misdiagnosis and inappropriate therapy. Thus it is very important to recognize this malignancy in clinical and pathological studies.

Herein, the authors report an additional case of ovarian metastasis from RCC, along with a review of the literature and histological differential diagnosis.

Case Report

A 46-year-old female was admitted to the present Institution with a history of abdominal pain and urinary incontinence. A pelvic ultrasound revealed a heterogeneous, large, right-sided solid/multi-cystic ovarian mass, suggesting a diagnosis of epithelial borderline or malignant ovarian tumor. At staging, abdominal CT incidentally revealed an enlarged left kidney with an intensely enhancing, heterogeneous nodular lesion located at the upper pole of the left kidney, consistent with renal carcinoma. At the time of surgery, a frozen section of ovarian neoplasm was performed to confirm the diagnosis of primary epithelial borderline ovarian tumor or metastatic renal carcinoma. Macroscopically, the right ovary had been entirely replaced by a 15-cm multiloculated cystic mass (Figure 1a). On cut sections, clear serous fluid was drained from the cystic spaces and thin golden-yellow solid septa and a central solid gray area were observed (Figure 1b). Imprint cytology, performed during an intraoperative study of the lesion, showed cohesive clusters of neoplastic cells. The cytoplasm was abundant, clear, and vacuolated. The nuclei were moderately pleomorphic, medium or large and centrally located, with evident nu-
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cleoli (Figure 2a). Histological examination revealed an epithelial neoplasm, characterized by large cells and a clear, optically empty cytoplasm with sharp borders and relatively uniform nuclei, which contained occasional prominent nucleoli. In some areas, these neoplastic cells were arranged in small nests. In other areas, the neoplasm showed alveolar and cystic spaces lined by clear cells similar to those of the solid areas. In both the alveolar and nodular areas, there was a prominent vascular component, with thin walls and sinusoidal features (Figure 2b). These findings and the presence of simultaneous renal lesion were consistent with the intraoperative diagnosis of ovarian metastatic renal carcinoma. Permanent sections stained with hematoxylin and eosin revealed that the ovarian lesion showed the same pathological features as those observed in frozen sections, with areas of alveolar and cystic spaces filled by eosinophilic material and lined by clear cells similar to those of the solid areas (Figures 3a and b). The intraoperative diagnosis was also confirmed by immunohistochemical analysis which revealed positivity for CD10 (Figure 3c) and renal cell carcinoma marker (RCC Ma) (Figure 3d). The patient then underwent left nephrectomy to define the nature of the nodular lesion. Macroscopically, the kidney showed a well-circumscribed, yellow, ovoid nodule of 5 cm in diameter, located at the upper pole (Figure 4a). The tumor had not invaded the renal capsule, perinephric fat, or pelvic walls. There was no adenopathy, ipsilateral adrenal gland involvement, or renal vein tumor thrombus.

On microscopic examination, this lesion was characterized by the same clear cells observed in multicystic ovarian lesion (Figure 4b). Thus, the final pathological diagnosis was RCC, Fuhrman grade 2, with metastasis of the right ovary (Stage TNM: pT1b Nx M1). The patient refused other additional medical therapy. After six months from diagnosis, the patient is free of disease. In fact, when she was readmitted for further examination, no abnormalities were found in either physical examination or imaging studies.

Discussion

RCC or hyper-nephroma is the most frequent neoplasm of the kidney accounting for 75% of renal neoplasms [36]. RCC is more frequent in males, with a 2:1 male to female ratio. The mean age at presentation is 50-70 years [37]. In most cases RCC is asymptomatic, since it grows as a retroperitoneal mass. This tumor, propagating into the renal
vene and inferior vena cava [37, 38] and reaching the right heart chambers [39], at presentation, in 20-30% of cases, is associated with distant metastases [37].

Despite the fact that this tumor is able to metastasize to different sites via hematogenous spread, only 35 cases of ovarian metastases from RCC have been reported in the English literature (Table 1)[10-35]. In addition, in a series of 147 cases of ovarian metastatic from extragenital neoplasms collected in a single institution over eight years, Li et al. did not find any examples of RCC with ovarian metastasis [40].

In the present institution, this case is the only example observed in the past 20 years. Moreover, most case reports of ovarian metastasis from RCC described in the literature are single cases, except for a small series reported by Young et al. [16], Insabato et al. [22], and Liang et al. [35] (Table 1). The first group of authors described three cases [16], while Insabato et al. [22] and Liang et al. [35] described three and seven cases, respectively (Table 1). Other clinical and pathological features of all these reported cases are listed in Table 1.

The age of the patients varied from 17 to 75 years. In some cases, ovarian metastases of RCC were synchronous with kidney cancer [15, 21, 26, 31, 35], in others they were observed before a primary renal tumor [16, 17, 35], and in a few cases even several years after the primary tumor diagnosis [20, 23, 32]. The follow-up in some cases has not been reported, nor has the therapy which the patients received (Table 1). In other cases, the death of the patients occurred only a few months after the diagnosis of ovarian metastatic RCC and when the neoplasm had already spread to other organs (Table 1) [10, 22, 26, 33].

According to many authors, RCC rarely metastasizes to the ovary since, fundamentally, this malignancy is more frequent in men than women, in addition it arises during the post-menopausal age, when the ovary has undergone vascular sclerosis [12]. Initially, it was suggested that ovarian metastasis from RCC was more frequent when the primary tumor is located in the left kidney, because of the renal-ovarian axis, a vascular mechanism that refers to the finding that the left renal vein does not drain into the inferior vena cava, but into the left ovarian vein [41]. Moreover, according to this hypothesis, left ovarian metastatic renal carcinoma can be observed when a primary tumor is located in the ipsilateral kidney. However, in the present case with left RCC and right ovarian metastasis, as well as other cases described in the literature, have demonstrated that this tumor, when located in the left kidney may metastasize to the contralateral ovary [16, 28, 30, 34, 35], as well as potentially spreading to the ipsilateral ovary [10, 15, 16, 22, 24, 26] and to both ovaries (Table 1)[17, 18, 33].

Suitable clinical data and the recognition of certain histological findings are essential for a correct pathological diagnosis of ovarian metastatic RCC. In the present case, the correct diagnosis had already been made on intraoperative frozen section examination, despite the presence of clear cells which might suggest other primary ovarian malignancies. In this case, the correct diagnosis of metastatic RCC of the ovary, on frozen section examination, was sug-
gested by the clinical data, which reported the presence of a probable malignant lesion in the contralateral kidney and by the recognition of peculiar cytological and histological features. On histological examination, the presence of cells with relatively uniform nuclei that contained occasional prominent nucleoli and a prominent vascular component, characterized by thin walls with sinusoidal features are mandatory for a correct diagnosis.

Table 1. — Clinicopathological features of RCC metastatic to the ovary.

<table>
<thead>
<tr>
<th>N</th>
<th>Authors</th>
<th>Age</th>
<th>Kidney</th>
<th>Ovarian lesion</th>
<th>Detection of ovarian lesion</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stadiem et al., 1937 [10]</td>
<td>39</td>
<td>L</td>
<td>L</td>
<td>21 mo later</td>
<td>S/RT</td>
<td>DOD 3 mo</td>
</tr>
<tr>
<td>2</td>
<td>Martzloff et al., 1937 [11]</td>
<td>66</td>
<td>R</td>
<td>R</td>
<td>6 mo later</td>
<td>Not listed</td>
<td>2 yrs alive</td>
</tr>
<tr>
<td>3</td>
<td>Bruegge et al., 1957 [12]</td>
<td>64</td>
<td>R</td>
<td>B</td>
<td>11 yrs later</td>
<td>Not listed</td>
<td>DOD 147 months</td>
</tr>
<tr>
<td>5</td>
<td>Stefani et al., 1983 [14]</td>
<td>68</td>
<td>R</td>
<td>L</td>
<td>3 mo later</td>
<td>S</td>
<td>2 yrs alive</td>
</tr>
<tr>
<td>6</td>
<td>Buller et al., 1983 [15]</td>
<td>52</td>
<td>L</td>
<td>L</td>
<td>Synchronous</td>
<td>Unknown</td>
<td>11 days alive</td>
</tr>
<tr>
<td>7</td>
<td>Young et al., 1992 [16]</td>
<td>48</td>
<td>R</td>
<td>L</td>
<td>Detected first</td>
<td>Not listed</td>
<td>8 yrs alive</td>
</tr>
<tr>
<td>8</td>
<td>Young et al., 1992 [16]</td>
<td>62</td>
<td>L</td>
<td>R</td>
<td>1 yr later</td>
<td>Not listed</td>
<td>3 mo alive</td>
</tr>
<tr>
<td>9</td>
<td>Young et al., 1992 [16]</td>
<td>48</td>
<td>L</td>
<td>L</td>
<td>Detected first</td>
<td>Not listed</td>
<td>Not listed</td>
</tr>
<tr>
<td>10</td>
<td>Spencer et al., 1993 [17]</td>
<td>40</td>
<td>L</td>
<td>B</td>
<td>7 mo before</td>
<td>S/RT</td>
<td>55 mo alive with widespread disease</td>
</tr>
<tr>
<td>11</td>
<td>Adachi et al., 1994 [18]</td>
<td>49</td>
<td>L</td>
<td>B</td>
<td>3 yrs later</td>
<td>S</td>
<td>6 yrs alive</td>
</tr>
<tr>
<td>12</td>
<td>Fields et al., 1996 [19]</td>
<td>54</td>
<td>R</td>
<td>L</td>
<td>3 yrs later</td>
<td>S</td>
<td>3 yrs alive</td>
</tr>
<tr>
<td>13</td>
<td>Vara et al., 1998 [20]</td>
<td>66</td>
<td>R</td>
<td>B</td>
<td>14 yrs later</td>
<td>S</td>
<td>16 yrs alive</td>
</tr>
<tr>
<td>14</td>
<td>Hammock et al., 2003 [21]</td>
<td>48</td>
<td>L</td>
<td>R</td>
<td>Synchronous</td>
<td>S/CMT</td>
<td>3 mo alive</td>
</tr>
<tr>
<td>15</td>
<td>Insabato et al., 2003 [22]</td>
<td>50</td>
<td>R</td>
<td>L</td>
<td>1 yr later</td>
<td>S</td>
<td>6 mo alive</td>
</tr>
<tr>
<td>16</td>
<td>Insabato et al., 2003 [22]</td>
<td>49</td>
<td>R</td>
<td>Unknown</td>
<td>7 mo later</td>
<td>S</td>
<td>DOD 6 mo</td>
</tr>
<tr>
<td>17</td>
<td>Insabato et al., 2003 [22]</td>
<td>17</td>
<td>L</td>
<td>L</td>
<td>2 yrs later</td>
<td>S</td>
<td>2 yrs alive</td>
</tr>
<tr>
<td>18</td>
<td>Valapiti et al., 2004 [23]</td>
<td>61</td>
<td>L</td>
<td>B</td>
<td>7 yrs later</td>
<td>S/interferon</td>
<td>9 yrs alive</td>
</tr>
<tr>
<td>19</td>
<td>Stolnicu et al., 2007 [24]</td>
<td>73</td>
<td>L</td>
<td>Unknown</td>
<td>5 yrs later</td>
<td>S</td>
<td>Unknown</td>
</tr>
<tr>
<td>20</td>
<td>Anagnostou et al., 2009 [25]</td>
<td>45</td>
<td>R</td>
<td>L</td>
<td>3 mo later</td>
<td>S/interferon</td>
<td>9 yrs Alive</td>
</tr>
<tr>
<td>21</td>
<td>Toquero et al., 2009 [26]</td>
<td>54</td>
<td>L</td>
<td>L</td>
<td>Synchronous</td>
<td>S/R</td>
<td>Other metastases 6 mo after ovarian metastasis and DOD 3 mo after</td>
</tr>
<tr>
<td>22</td>
<td>Guney et al., 2010 [27]</td>
<td>54</td>
<td>Not listed</td>
<td>B</td>
<td>39 mo after diagnosis</td>
<td>S/sunitibib</td>
<td>four yrs alive</td>
</tr>
<tr>
<td>23</td>
<td>Luyckx et al., 2011 [28]</td>
<td>75</td>
<td>L</td>
<td>R</td>
<td>1 yr later</td>
<td>Interferon</td>
<td>1.5 yrs alive</td>
</tr>
<tr>
<td>24</td>
<td>Deconne et al., 2011 [29]</td>
<td>63</td>
<td>R</td>
<td>Associated with Synchronous calcaneus metastasis</td>
<td>5 yrs later</td>
<td>S</td>
<td>11 yrs alive with metastatic gallbladder lesion</td>
</tr>
<tr>
<td>25</td>
<td>Udoji et al., 2012 [30]</td>
<td>45</td>
<td>L</td>
<td>R</td>
<td>5 yrs later</td>
<td>Not listed</td>
<td>2 yrs alive with metastatic rib lesions</td>
</tr>
<tr>
<td>26</td>
<td>Ibrahim et al., 2012 [31]</td>
<td>71</td>
<td>R</td>
<td>R</td>
<td>Synchronous, associated with Brenner and mucinous tumour</td>
<td>Not listed</td>
<td>Not listed</td>
</tr>
<tr>
<td>27</td>
<td>Bauerová et al., 2014 [32]</td>
<td>61</td>
<td>R</td>
<td>B</td>
<td>21 yr later with new RCC in L kidney</td>
<td>S</td>
<td>1 yr alive</td>
</tr>
<tr>
<td>28</td>
<td>Masago et al., 2015 [33]</td>
<td>35</td>
<td>L</td>
<td>B</td>
<td>18 mo later</td>
<td>S/sunitibib</td>
<td>DOD 3 months</td>
</tr>
<tr>
<td>29</td>
<td>Kostrzewa et al., 2015 [34]</td>
<td>51</td>
<td>L</td>
<td>R</td>
<td>4 yrs later</td>
<td>Not listed</td>
<td>Not listed</td>
</tr>
<tr>
<td>30</td>
<td>Liang et al., 2016 [35]</td>
<td>60</td>
<td>R</td>
<td>R</td>
<td>Synchronous</td>
<td>Not listed</td>
<td>40 months alive</td>
</tr>
<tr>
<td>31</td>
<td>Liang et al., 2016 [35]</td>
<td>48</td>
<td>L</td>
<td>R</td>
<td>14 mo later</td>
<td>Not listed</td>
<td>14 mo alive</td>
</tr>
<tr>
<td>32</td>
<td>Liang et al., 2016 [35]</td>
<td>45</td>
<td>R</td>
<td>L</td>
<td>30 mo later</td>
<td>Not listed</td>
<td>DOD 48 mo</td>
</tr>
<tr>
<td>33</td>
<td>Liang et al., 2016 [35]</td>
<td>43</td>
<td>R</td>
<td>R</td>
<td>20 mo later</td>
<td>Not listed</td>
<td>DOD 109 mo</td>
</tr>
<tr>
<td>34</td>
<td>Liang et al., 2016 [35]</td>
<td>52</td>
<td>L</td>
<td>R</td>
<td>10 mo later</td>
<td>Not listed</td>
<td>DOD 11 yrs</td>
</tr>
<tr>
<td>35</td>
<td>Liang et al., 2016 [35]</td>
<td>52</td>
<td>R</td>
<td>L</td>
<td>Prior to the diagnosis of RCC</td>
<td>Not listed</td>
<td>DOD 11 yrs</td>
</tr>
<tr>
<td>36</td>
<td>Present case</td>
<td>46</td>
<td>L</td>
<td>R</td>
<td>Synchronous</td>
<td>S alive</td>
<td>6 mo</td>
</tr>
</tbody>
</table>

Because of its rarity, ovarian metastasis of RCC represents a challenge in diagnosis and management. In fact, failure to recognize an ovarian metastatic extragenital tumor which mimics a primary Müllerian or other metastatic neoplasms with clear cells could lead to misdiagnosis and inappropriate therapy. Thus it is very important to recognize this malignancy in clinical and pathological studies.

Other lesions characterized by clear cells, which can mimic metastasis of RCC in the ovary, include primary ovarian neoplasms, such as clear cell carcinoma, dysgerminoma, steroid cell tumor, and clear cell variant of struma ovarii. Primary ovarian clear cell carcinoma is a high grade primary tumor, with peculiar features that are absent in metastatic RCC, such as the presence of large tumor cells with nuclei that protrude into the lumina (hobnail cells), and hyaline basement membrane [42]. Moreover, RCCs have a typical vascular framework with a sinusoidal pattern that is absent in ovarian clear cell carcinoma [16].

Macroscopically, a dysgerminoma is a solid, fleshy, lobulated lesion. On histological examination this neoplasm is characterized by nests of large vesicular cells with well defined cell borders, and a clear cytoplasm containing glycogen and central nuclei with one or more prominent nucleoli. These neoplastic elements are separated by fibrous septa containing lymphocytes or occasional granulomas [43].

Steroid cell tumors of the ovary usually occur in younger females (mean age 43 years) or occasionally before puberty [44]. These tumors are solid lesions and their clinical manifestations are quite characteristic, and include hirsutism and virilization. On microscopic examination, a steroid cell tumor shows irregular cords and nests of large rounded to polygonal cells. The cytoplasm of the tumor cells shows variable-sized clear vacuoles. The nuclei are monotonous, round, and centrally located with prominent nucleoli. On permanent histological section examination, also immunohistochemical analysis can help distinguish these from primary ovarian neoplasms and metastatic RCC. Cytokeratin 7 and CA125 are markers which are expressed in clear cell carcinoma, but are absent in RCC [17].

Dysgerminoma cells is characteristically immunoreactive for placental-like alkaline phosphatase (PLAP) [45, 46] and c-kit gene product (CD117) [47] which are negative in metastatic RCC. Steroid cell tumors are immunoreactive for alpha-inhibin, which is negative in RCC [44]. In this case the presence of cystic spaces lined by clear cells and filled by colloid-like eosinophilic material includes also differential diagnosis with clear cell variant of struma ovarii. Struma ovarii, as a monodermal variant of ovarian teratoma, is composed predominantly (over 50%) or entirely of thyroid tissue [43]. The diagnosis of this ovarian neoplasm was discarded due to the absence of concomitant thyroid tubular follicles, association with dermoid cyst and immunoreactivity to thyroglobulin [48].

In conclusion, although ovarian metastasis of RCC may be very rare, this case demonstrates that suitable clinical data and the recognition of certain cytological, histological, and immunohistochemical findings are useful for a correct pathological diagnosis.

References


[38] Niehans G.A., Manivel J.C., Copland G.T., Scheithauer B.W., Wick G. GIORDANO, A. PEZZUTO, E.M. SILINI 1027


