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Simultaneous occurrence of non-Hodgkin lymphoma, renal cell carcinoma and oncocytoma: A case report

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Abstract. We herein report the case of a 74 year-old woman with a diffuse large B-cell lymphoma and bilateral renal masses identified on computed tomography scans during the initial staging process. Following partial bilateral nephrectomy, histopathological examination revealed renal cell carcinoma (RCC) and oncocytoma in the left and the right kidneys, respectively. Shortly afterwards, lymphoma of the left palatine tonsil was diagnosed and the patient received chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP regimen), followed by radiotherapy. Due to metastasis of the RCC to the right breast, pancreas and the area of the left psoas major muscle, systemic treatment with pazopanib was commenced. To the best of our knowledge, this is the first reported case of simultaneous diagnosis of non-Hodgkin lymphoma (NHL), RCC and oncocytoma. The aim of this study was to review the related literature, discuss issues regarding the management of this unusual case and identify possible common etiopathological mechanisms underlying the simultaneous occurrence of NHL, RCC and oncocytoma.

Introduction

Non-Hodgkin lymphoma (NHL) accounts for ~4% of new cancer cases (1). Compared to the general population, NHL patients have a 1.88-fold higher risk of developing second malignancies (2). The incidence of concomitant appearance of NHL and renal cell carcinoma (RCC) was also proven to be higher than anticipated (3). The majority of reports on the association between lymphoid malignancies and RCC investigated treatment-related secondary RCC. Simultaneous occurrence, however, is an unusual phenomenon and the etiopathological mechanism underlying the coexistence has not yet been fully elucidated.

Renal oncocytoma is rare, accounting for only 3-7% of renal tumors (4). Thus, simultaneous diagnosis of oncocytoma, RCC and NHL is even more uncommon. We herein present the case of a patient diagnosed with these three malignancies presenting simultaneously. Written informed consent was obtained from the patient for the publication of the case details.

Case report

A 74 year-old woman, with a history of arterial hypertension (well-controlled by treatment), complained of a mass in the left side of the neck, sized ~8x2 cm. Fine-needle biopsy of the lesion was performed and the result was suggestive of malignant lymphoma. Further histopathological examination and immunophenotyping of the excised neck lymph node revealed non-Hodgkin lymphoma (NHL), specifically CD20-positive diffuse large B-cell lymphoma (DLBCL) (non-germinal center B-cell-like). No enlargement of other peripheral lymph nodes or B (systemic) symptoms were observed. During initial staging, a computed tomography (CT) scan of the abdomen and pelvis revealed bilateral lesions in the kidneys, sized 25x31x30 mm (right) and 53x42x46 mm (left), both suspicious for carcinoma (Fig. 1). Apart from leukocyturia (25-30/high-power field), the laboratory test results were within normal limits. Due to these findings, chemotherapy initiation was delayed. The patient underwent bilateral partial nephrectomy and the histopathological evaluation of the excised masses revealed an oncocytoma in the right kidney and an RCC (Fuhrman grade 2) in the left kidney. The patient became pyretic and enlargement of the left palatine tonsil was observed. Head and neck CT scans revealed a tonsillar tumor, sized 27x35x48 mm, without lymphadenopathy (Fig. 2). The histopathological examination of the tonsillar specimen confirmed DLBCL (clinical stage IA). One course of chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP regimen) was administered, followed by 3 courses of CHOP combined with rituximab (R-CHOP), started from the second course of CHOP, as soon as CD20

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Abbreviations: RCC, renal cell carcinoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; NHL, non-hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; PET, positron emission tomography; CT, computed tomography

Key words: renal cell carcinoma, oncocytoma, non-Hodgkin lymphoma, simultaneous neoplasms

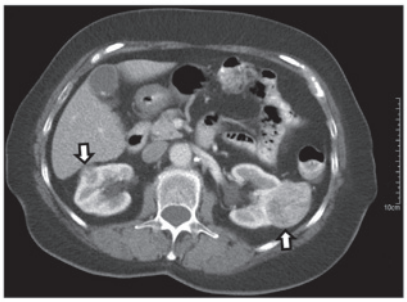

Figure 1. Bilateral neoplastic lesions in the kidneys (arrows; oncocytoma in the right and renal cell carcinoma in the left kidney) identified during initial staging of lymphoma.

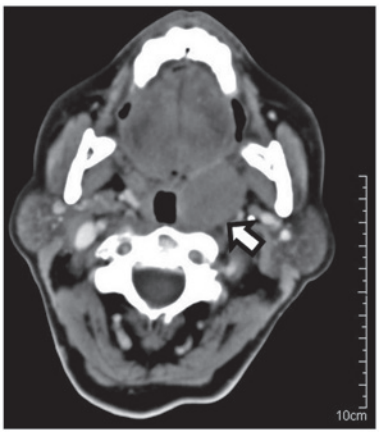

Figure 2. Diffuse large B-cell lymphoma of the left palatine tonsil (arrow) identified after bilateral partial nephrectomy.

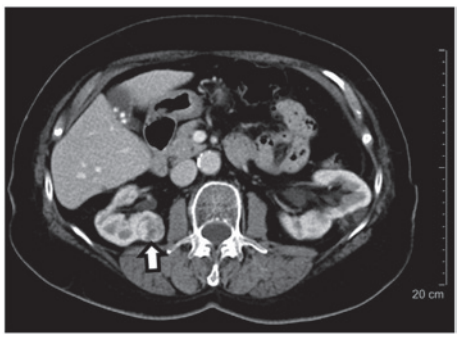

Figure 3. Follow-up abdominal computed tomography scan 2 years after chemoradiotherapy for lymphoma. An enlarging new lesion in the right kidney (arrow) was identified (renal cell carcinoma metastasis).

positivity was confirmed. Megavoltage 3D radiotherapy was next administered, involving the facial cervical portal, with an applied dose of 40 Gy in 20 fractions. Tumor regression was observed in post-treatment CT scans. Five months after treatment completion, a follow-up abdominal CT scan revealed a dense cyst-like area in the lower pole of the right kidney. After 1 year, the lesion became inhomogeneous and started to expand, eventually reaching 20x20 mm in size (Fig. 3), with simultaneous appearance of 5 nodal lesions in the pancreas (11-14 mm in diameter) (Fig. 4), as well as a focal change in the area of the left psoas major muscle, slowly enlarging over the course of observation to 27x19 mm (Fig. 5). Positron emission

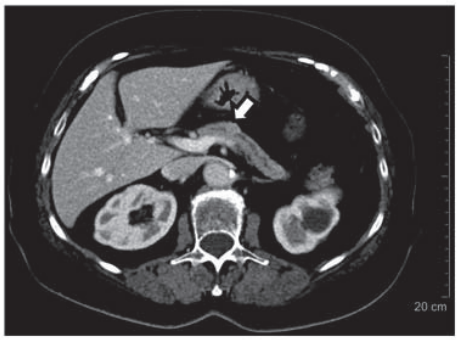

Figure 4. Renal cell carcinoma metastasis to the pancreas (arrow) was identified on a follow-up computed tomography scan performed 2 years after chemoradiotherapy for lymphoma.

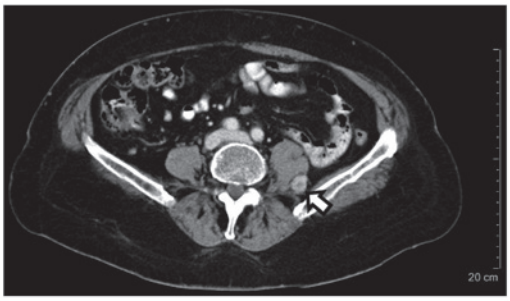

Figure 5. A new metastatic lesion from renal cell carcinoma in the left psoas major muscle (arrow) was identified on a follow-up computed tomography scan performed 2 years after chemoradiotherapy for lymphoma.

tomography (PET) did not confirm a proliferative process in the pancreas, while both lesions in the right kidney and near the psoas muscle were suspected of being neoplastic on PET scans. Both PET-positive lesions were surgically removed and found to be metastases from RCC. Shortly afterwards, two nodules in the right breast were identified on routine follow-up CT. Given the inconclusive result of fine-needle biopsy, the nodules were excised and were also found to be metastases from RCC. Due to the enlargement of the pancreatic lesions, suggestive of metastases, systemic therapy was initiated. Thus far, the patient has received 9 courses of pazopanib (400 mg per day), achieving stabilization of the pancreatic lesions. A total of 5.5 years after the diagnosis of RCC and DLBCL, the patient continues pazopanib treatment.

Discussion

The differential diagnosis for bilateral solid renal masses encompasses RCC, lymphoma, angiomyolipoma, oncocytoma, adenoma and metastasis. The simultaneous occurrence of NHL in our patient was suggestive of lymphoma infiltration. On the CT scans, however, RCC appeared to be more likely. The risk of lymphoid malignancy in patients with RCC and, conversely, the rate of RCC in lymphoma patients, were found to be higher compared with those in the general population (2.67- and 1.86-fold, respectively) (3). In the literature, metachronous occurrence of these two diseases (lymphoma preceding RCC) is most often reported (5). Our patient was female; however, a male predominance has been

observed among patients diagnosed with both neoplasms (5). Although the development of a second tumor in lymphoma patients may be treatment-related or associated with immune dysregulation caused by lymphoma, the mechanism underlying simultaneous presentation of the two entities, as in our patient, has not been fully elucidated. Chromosome 3p and 17p deletions, shared by RCC and NHL, may be the underlying cause (5), as well as the overproduction of interleukin-6 by RCC that was shown to cause B-lymphocyte proliferation (6). Other similarities between the two malignancies include increased vascular endothelial growth factor production (7) and elevated levels of CD44, which is a molecule involved in cell proliferation. Interestingly, although a high CD44 concentration was also found in other tumors, the laboratory results of anti-CD44 therapy appear to be promising in RCC and NHL models (8). These findings not only provide new perspectives for targeted therapies in both neoplasms, but may also indicate the direction of research based on their common pathogenesis.

Oncocytoma and RCC have been found to share mitochondrial DNA alterations and a histological origin from the intercalated cells of the collecting tubules (4), which suggests their common pathogenesis. Vernadakis *et al* (9) have reported bilateral oncocytomas of the native kidneys in a renal transplant recipient. Due to the close association between oncocytoma and RCC, as well as reports on immunological disturbances in RCC and oncocytoma patients, the hypothesis of immune system involvement in the pathogenesis of these two tumors appears to be reasonable. No immunological disorders or defects were observed in our patient.

The significance of histopathological evaluation of renal lesions must be emphasized, as it helps differentiate between lymphoma infiltration and a primary renal tumor, but also distinguishes benign tumors (oncocytoma) from RCC, the latter being particularly important in clinical practice, since current imaging studies cannot credibly and accurately differentiate between RCC and oncocytoma (10). Kutikov *et al* (11) analyzed the records of 143 patients with renal lesions preliminary diagnosed on CT as RCC by experienced radiologists. On postoperative examination, 16.5% of the lesions sized 2-4 cm were found to be benign, while the result was 14.3% in masses sized >4 cm. In our patient, both lesions had a similar appearance on CT, namely hypodense, contrast-enhancing masses, without a central stellate scar (considered distinctive of oncocytoma), suggesting malignant processes and leading to prioritization of surgical intervention over chemotherapy for lymphoma.

Percutaneous core needle biopsy was not performed, due to strong suspicion of a malignant process. Renal mass biopsy is considered to be a standard of care when its result may allow sparing the patient unnecessary surgery (12) and it most often applies to small renal masses suspected as being benign tumors. However, discriminating between RCC and benign lesions in biopsy-derived material may be challenging, due to the considerable rate of false-positive and false-negative biopsy results (13).

In conclusion, to the best of our knowledge, this is the first case report on synchronous presentation of NHL, RCC and oncocytoma. It is of particular importance for the physicians to be aware that the occurrence of renal masses in NHL patients may not necessarily reflect lymphoma infiltration, but rather RCC or even a rare benign tumor. Since the credibility of imaging studies in differential diagnosis is limited, an appropriate histopathological evaluation is crucial. Given that the pathological mechanisms underlying the simultaneous occurrence of RCC, oncocytoma and NHL have not been clearly determined, further studies are required.

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