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ORIGINAL RESEARCH ARTICLE

Renal Cell Carcinoma and Metastatic Sites

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ABSTRACT

BACKGROUND: *Renal cell carcinoma accounts for about 3% of adult cancers. The most common type is a 70% clear cell carcinoma. Approximately 30% of patients have developed metastasis at the time of diagnosis, and metastasis develops following nephrectomy in one third.*

METHODS: *The study included the cases that were diagnosed by operation for primary or metastasis between 2014 and 2016, and that have been followed up by the Bezmialem Vakif University, Department of Medical Oncology. The sites of metastasis for metastatic RCCs and how long after the time of diagnosis metastasis developed were recorded. The demographic data and metastatic sites of the cases are listed.*

RESULTS: *The most common metastatic sites are the lung. However, the rare settlements reported in the literature are noteworthy.*

KEYWORDS: *Renal cell carcinoma, metastasis, paranasal sinüs*

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INTRODUCTİON

Renal cell carcinoma (RCC) accounts for about 2-3% of malignant tumors in adults and causes 2.4% of deaths due to cancer each year (1). The incidence is rising especially in developed countries, with 84,400 new RCC cases in the European Union and 34,700 deaths due to these cancers. (2). Although new tumor types have recently been described, the most common (75-80%) type seems to be clear cell carcinoma. Other common subtypes include papillary RCC (10%), chromophobe RCC (5%), and collecting duct carcinoma (2%) (1). Among the prognostic parameters, Fuhrman nuclear grading and grading according to TNM are the most important systems. At the time of diagnosis, approximately one third of the cases are localized in the kidney, while 30-40% of the cases develop metastasis after surgery (3). The most common sites of metastasis for RCCs include the lung, brain, and bone (4) Our aim is to evaluate the localization of metastatic renal cell carcinomas followed up by our center in the light of literature.

METHODS

The study included the cases that were diagnosed by operation for primary or metastasis between 2014 and 2016, and that have been followed up by the Bezmialem Vakif University, Department of Medical Oncology. The sites of metastasis for metastatic RCCs and how long after the time of diagnosis metastasis developed were recorded. The demographic data and metastatic sites of the cases are listed.

RESULTS

A total of 31 cases were present. 10 of the patients were female and 22 were male. The

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mean age range was 60.8 (31-80). The most common site of metastasis was the lung,

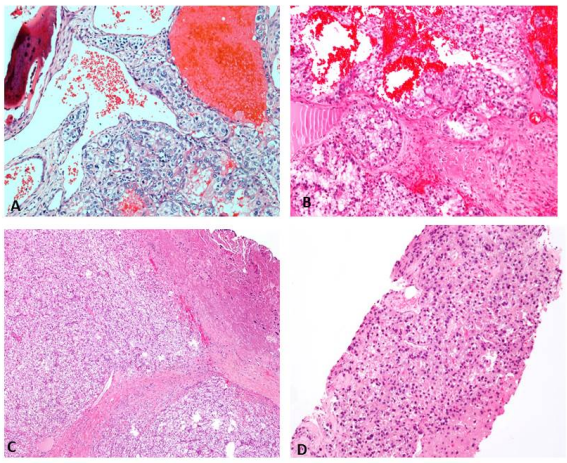

Figure 1: Renal cell carcinoma metastasis in the bone(A,B), intramuscular(C), liver(D) (HEX100).

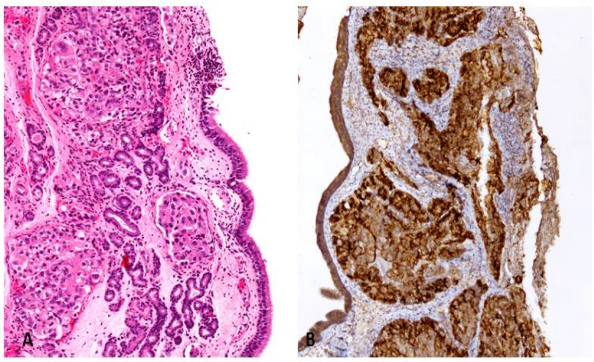

Figure 2: Renal carcinoma metastasis in the paranasal sinüs (HEX200) immuno hystochemical dİffuse staining (x200)

while the bone was the second most common site (Figure1, 2). In 20 of our cases, lung metastasis was present followed by bone and lymph node metastasis. There were two or more metastases in 20 cases. The elapsed time for metastasis was unknown in 4 cases. 10 of the cases followed up (37%) had a metastasis at the time of diagnosis. Pathologic staging could performed in 18 patients underwent nephrectomy. FG4 is 11%, FG3 is 61%, FG2 is 28% when compared according to nuclear Fuhrman grading (FG). E1 is 11%, E2 is 17%, E3 is 72% according to the TNM staging. Sarcomatoid differentiation was present in 4 cases. In biopsies taken from the metastatic sites, the tumor was in solid and trabecular pattern and consisted of eosinophilic and clear cytoplasm cells. Of course, the first thing that springs to mind was metastasis in patients with a history of RCC. However, it was necessary to be careful, since there was tumor diagnosis indicating clear cell change in almost all organs, even though RCC metastasis was included in differential diagnosis in cases with unknown primary. The patients detected to have focal or diffuse staining for RCC, CD10, PAX2, and PAX8 in immunohistochemical studies performed to determine the primary were considered as RCC metastasis. The present morphological and immunohistochemical results were evaluated together with radiological findings and interpreted as renal cell carcinoma metastasis.

DISCUSSION

RCC accounts for about 3% of adult cancers and about 85% of renal tumors. Approximately 30% of patients have developed metastasis at the time of diagnosis, and metastasis develops following nephrectomy in one third (3). Because of the high incidence of renal involvement in RCCs, they cause vascular spread rather than lymphatic spread. Moreover, when there is an increase in intraabdominal and intrathoracic pressure, a backflow occurs from the venous system here towards the prevertebral and vertebral venous plexus (Batson venous plexus), thus the tumor cells skip the pulmonary capillary filtration and may metastasize to different anatomical regions despite the long time after resection (5). RCC metastases may be seen in all organs (6). The most common metastatic sites are the lung (33-72%), intraabdominal LN (3-35%), and bone (21-25%) (5). In 32% of our cases, there was metastasis in one site, while there were multiple metastases in about 2/3 of the cases. The rare metastatic sites reported in the literature include parotid, thyroid, forehead skin, paranasal sinuses, tongue (7), ulnar nerve (8), adrenal (9), colon (4) stomach (6), gingiva (12), hypophys (11).Considering renal cell carcinoma metastasis in any organ, it may be synchronous with the

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primary tumor of that organ. Synchronous tumors are most commonly associated with RCC. For example, bladder, prostate, colorectal, and lung tumors are most commonly synchronous with RCC (12).

In determining the biological behavior of RCCs, diagnostic, prognostic and predictive biomarkers maintain their popularity. Positron emission tomography (PET) is not used for staging or diagnosing localized RCCs. However, in advanced cases, they may lead to predict the lifespan (13). Lymph node involvement and distant metastasis in RCC are associated with poor prognosis and shortened lifespan (14). The most common clinical signs in metastatic RCCs are asthenia, bone pain, weight loss, fever, cough, neurological findings depending on the metastatic site. On the other hand, approximately 20% of cases have an asymptomatic or atypical localization (15). Our metastatic patient with paranasal localization also presented with the complaint of nosebleed. The radiological examinations revealed diffuse metastases in the paranasal sinus, frontal lobe, anterior ethmoid, nasal cavity, liver, adrenal, lung, humerus and muscle tissue. Metastasis of RCCs to the head and neck region is extremely rare (16). Therefore, a newly defined RCC-like clear cell carcinoma in the head and neck region should also be considered in differential diagnosis, and the presence of a mass in the kidney should be examined in such cases (17).The first treatment approach in a renal cell carcinoma patient should be determined according to disease stage, patient's age and comorbid condition. High-dose IL-2 is the recommended first line treatment in metastatic RCC (18). However, this treatment should be administered by experienced centers to patients with an appropriate performance score and without additional comorbid diseases and organ dysfunction in terms of toxicity management(19). With high-dose IL-2, long-term remission has been achieved in 10% of patients (18). Patients ineligible for high-dose IL-2 treatment should be evaluated in terms of eligibility for targeted antiangiogenic or PD-1 or PD-L1 pathway blocker treatment. The most commonly used drugs in the first line treatment are pazopanib and sunitinib. Both are vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) pathway inhibitors (20,21). These two drugs show similar efficacy in patients with good and moderate prognosis (22,23). In patients progressing after these treatments, immunotherapy, if not previously received, or axitinib, a VEGFR-1, 2, 3 inhibitor, is the appropriate treatment choice (24,25). Nivolumab, a monoclonal anti-PD-1 antibody, used as immunotherapy, and cabozantinib, which inhibits the AXL and MET genes associated with resistance to VEGFR and VEGFR inhibition, are appropriate treatment in progressive patients after targeted treatment (26-28).

Both nivolumab and cabozantinib have been found to be superior to single agent everolimus in the second line treatment, in terms of efficacy and survival (29). However, lenvatinib + everolimus is also an appropriate treatment alternative in progressive patients after antiangiogenic treatment, in case that these two drugs are not accessible (30).

The European Association of Urology (EAU) has shown in the RCC guideline panel that patients underwent complete metastasectomy had a longer lifespan than those who did not undergo or underwent partial metastasectomy (31). However, the decision for metastasectomy depends on patient's performance status, prognostic parameters, elapsed time until metastasis develop, site and number of metastasis (32).

In this study, we compared the sites of RCC metastases followed up by our department in company with the literature. In conclusion, renal cell carcinoma is full of surprises and it should be kept in mind that it may show up with metastasis anytime, anywhere, even if the primary has not been detected.

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