CASE REPORT

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Metastatic renal cell carcinoma to the earlobe 27 years after nephrectomy

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Abstract

We present a case of a nodule on the earlobe of an elderly patient, without any known clinical history. Microscopic examination revealed a tumor with morphology reminiscent of metastatic clear cell renal cell carcinoma. The results of an extensive immunohistochemical (IHC) examination confirmed our initial diagnosis and further investigation of the patient's medical history revealed that a unilateral nephrectomy had been performed 27 years prior to the current tumor. We are reporting this case to emphasize the long interval between the primary tumor and its metastasis in an extremely unusual site, with a brief discussion on the ability of this particular neoplasm for extremely late metastasis to any site on the human body. Also, we are highlighting the extensive step-by-step IHC examination to confirm the diagnosis in routine pathology.

Keywords: clear cell renal cell carcinoma, late metastasis, cutaneous, PAX-8, cytokeratins AE1/AE3.

Introduction

Clear cell renal cell carcinoma (CCRCC) is the most common tumor of the kidney [1] and the pathologists one are most familiar with worldwide regarding this organ. It is included in the list of neoplasms, among other malignancies, which are notorious for their ability to metastasize at almost any site on the human body, even many years after the initial diagnosis and treatment of the primary tumor, melanoma being another very well known example [2].

Aim

Therefore, we decided that it would be of interest to present this case, which, although not unique, is still extremely rare and could be of assistance to any pathologist also encountering such an unexpected case as this.

Case presentation

An 85-year-old woman presented with a small nodule on her earlobe that had been there for a couple of years and which the surgeon decided to excise and send to our Laboratory.

Macroscopically, the nodule was about 1 cm wide, firm and brown, without any remarkable macroscopic features and was submitted to histopathological (HP) examination.

The specimen was fixed in 10% phosphate-buffered formalin and HP examination was performed in 4 μm Hematoxylin–Eosin (HE)-stained sections. In addition, for the differential diagnosis an extensive immunohistochemical (IHC) examination was followed in 4 μm tissue sections. A two-step IHC staining was performed using Biotin complex EnVision™+ System (Dako Cytomation, Carpinteria, CA, USA).

Under the microscope, the tumor consisted of well-demarcated cells, with abundant clear or slightly eosinophilic cytoplasm, round nuclei with fine chromatin and visible nucleoli, which were arranged in small nests spread on a highly vascular stroma (Figures 1 and 2). The tumor bore a striking and indisputable resemblance to a CCRCC.

Immunohistochemically, the tumor cells were positive for vimentin and, to a lesser extent, for cluster of differentiation (CD) 10 and epithelial membrane antigen (EMA), but, in contrast to our expectations, they were totally negative for cytokeratins (CKs) AE1/AE3. Further IHC investigation, which included antibodies against S-100 protein, melan-A, human melanoma black-45 (HMB-45), alpha-smooth muscle actin (α-SMA), p63, CD34, chromogranin, synaptophysin, monoclonal carcinoembryonic antigen (mCEA) and thyroid transcription factor-1 (TTF-1), was performed in order to exclude other possible entities, such as balloon cell melanoma, myoepithelioma, paraganglioma, metastatic thyroid carcinoma and skin adnexal or vascular tumors; the results proved to be totally negative for the above IHC markers.

In our attempt to have a detailed history, the surgeon who performed the excision informed us that the patient had indeed undergone unilateral nephrectomy for a kidney tumor 27 years prior to the present case, without reporting any remarkable incident that could be attributed to the neoplasm in the intervening time period.

We were also very glad to find that the clinician knew

the hospital where the prior surgery had taken place, which enabled us to finally find not only the slides but also some of the blocks from the primary neoplasm. The examination of HE slides confirmed that they represented CCRCC of low grade [*International Society of Urologic Pathologists*/*World Health Organization* (ISUP/WHO) score 1–2] and stage (no evidence of renal sinus or renal vein penetration, neither were there metastasis to lymph nodes or the adrenal gland on the available slides) (Figure 3).

We decided to perform additional IHC examination for paired-box 8 (PAX-8) on the metastatic nodule, which resulted in intense and widespread nuclear positivity for the tumor cells (Figure 4).

The final diagnosis was compatible with metastatic CCRCC on the earlobe.

Almost two year after our diagnosis and despite the age of the patient, she was still alive, without any further suspicion of metastasis from the primary neoplasm.

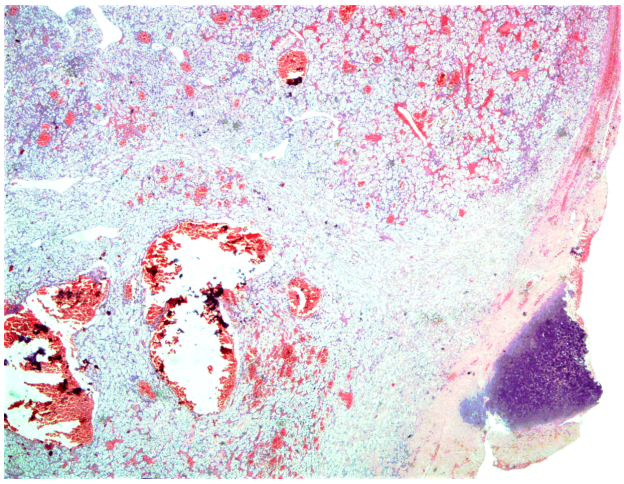

Figure 1 – ***Nested patterned neoplasm with vascularized stroma. Note a fraction of cartilage from the earlobe on the downright corner. HE staining, ×20.***

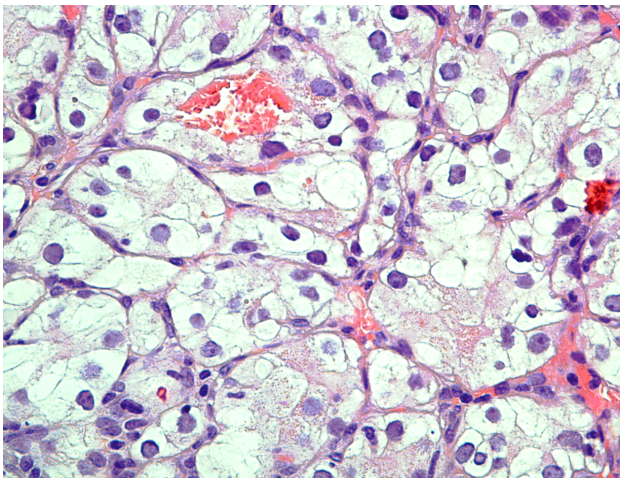

Figure 2 – ***Small nests of demarcated epithelial cell with clear cytoplasm, enlarged nuclei and sometimes-visible nucleoli. HE staining, ×400.***

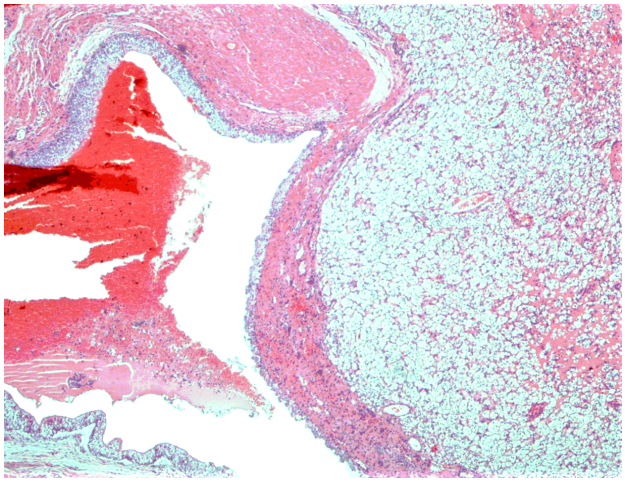

Figure 3 – ***Image of the primary tumor of the kidney. Note the absence of invasion to the renal pelvis. HE staining, ×20.***

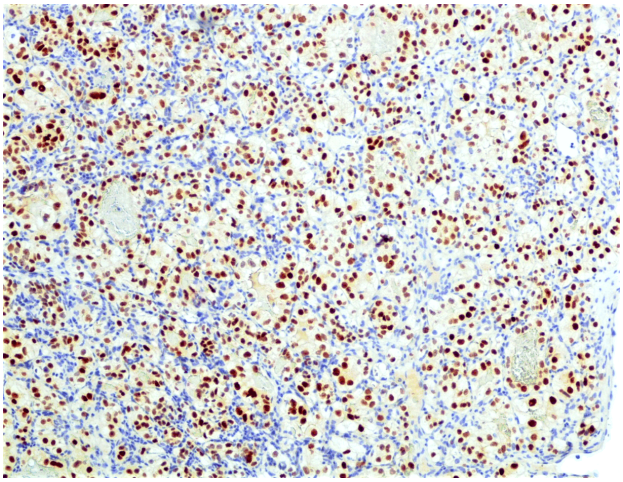

Figure 4 – ***Widespread nuclear positivity for PAX-8 on metastatic nodule to the earlobe. Anti-PAX-8 antibody immunomarking, ×100. PAX-8: Paired-box 8.***

Discussions

CCRCC accounts for the vast majority of kidney tumors. Its clinical behavior depends heavily on the pathological stage of the initial neoplasm and, secondarily, to the histological tumor grade, expressed on a scale of 1 to 4 by the ISUP/WHO scoring system [1]. It is well known that CCRCC has the potential for early or late metastases, the former being considered an indicator of a less favorable outcome, to almost any organ of the human body, the respiratory system comprising the majority of them. The record is currently been held by a recently reported case with a 37-year interval between nephrectomy and lung metastasis [3]. Cutaneous metastases are not encountered as often as one might expect, representing 6–11% of metastatic CCRCC cases, and about half of them are located on the scalp, sometimes representing the first manifestation of a concurrent primary neoplasm of the kidney [3].

Late cutaneous metastases are very rarely reported with the intervening time range between one to 10 years [4–7]. Our case represents a very long interval period of 27 years between primary CCRCC diagnosis and cutaneous metastasis appearance and even in a very unusual site of the human body, such as the earlobe.

Diagnosis can be made confidently, most frequently based on histology and a clinical history of nephrectomy

for a renal neoplasm, aided by characteristic IHC markers for more problematic cases. Regarding the latter, the use of PAX-8 (or PAX-2) is heavily recommended, and considered superior to traditional markers, such as CD10 or renal cell carcinoma (RCC), on the grounds of specificity and sensitivity to CCRCC [8, 9]. Although negativity for CKs AE1/AE3 could be considered to cast doubt on the validity of our diagnosis, this is not necessarily true, based on references [10], where it is stated that an appreciable percentage of metastatic epithelial renal neoplasms, especially chromophobe and clear cell, may lose their cytokeratin expression on the metastatic sites. This observation is supported by the concept that there is genomic and proteomic divergence among primary and secondary renal cell carcinomas, a fact that can explain many differences not only on morphology but also on the expression of a number of IHC markers among them [11].

Moreover, the mechanisms of tumor cancer cells dormancy seem to be of great importance for future therapeutic approaches [2, 12, 13]. We have to present such cases in order to comprehend and properly establish these mechanisms.

Conclusions

To our knowledge, the current case represents the longest interval period between primary CCRCC diagnosis and cutaneous metastasis appearance that has been recorded so far. Additionally, it is probably the first to demonstrate the earlobe as a potential very unexpected metastatic site for this tumor regardless of the intervening time. Careful HP examination, combined with thorough clinical information and the aid of targeted IHC studies guide to the correct diagnosis despite the rarity and unexpectedness of this condition.

Conflict of interests

None to declare.

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