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Molecular profiling of renal cell carcinoma presenting as iris metastasis

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ABSTRACT

Purpose: To describe a case of iris metastasis as the initial presentation of clear cell renal cell carcinoma, and to discuss molecular profiling of both the metastasis and primary kidney tumor.
Observations: We report a patient with blurred vision who underwent ophthalmic examination and was found to have an iris mass, which was excised and diagnosed as a metastatic clear cell renal cell carcinoma by morphology and immunohistochemical analysis. As a result of the pathology findings, computed tomography imaging was performed, revealing a right kidney mass, which was also resected and shown to represent a high-grade carcinoma confined within the renal fascia without lymphovascular invasion. Molecular testing of the primary and metastatic tumors using a custom next-generation sequencing panel revealed similar mutational profiles but disclosed a *TERT* promoter mutation in the primary neoplasm, not present in the metastasis, suggesting seeding of an early lower grade neoplastic cell clone within the iris.
Conclusions and importance: This report illustrates how pathological examination of a small iris lesion led to the discovery of a previously unknown systemic malignancy at a resectable stage. Molecular genetic profiling revealed that even lower grade clones within a high-grade neoplasm have metastatic potential.

1. Introduction

The iris is a rare location for metastatic spread of cancer, particularly without a known primary neoplasm. Iris metastases most frequently originate from the breast and lung and occur in the setting of preexistent metastatic disease to other organs.[1] Renal cell carcinomas may metastasize to virtually any organ,[2] but there are only very rare reports of iris metastases, typically involving widely disseminated disease.[3] Molecular studies to better understand the profile of metastatic renal cell carcinomas to the iris are lacking. We report a case of clear cell renal cell carcinoma (ccRCC) presenting as an incidental iris lesion during the workup for cataract and show that the metastasis likely originated from a lower grade clone within the high-grade primary tumor.

2. Case report

A 56-year-old man with hypertension and a 40-pack-year smoking history presented for evaluation of 3 months of painless blurred vision in the right eye. An iris lesion, not present 2 years earlier, was noted. Visual acuity was 20/70 on the right, improving to 20/40 with pinhole, and 20/20 on the left, with normal intraocular pressures. Slit-lamp exam (Fig. 1) revealed rare, pigmented cells in the right anterior chamber, posterior synechiae (nearly 360°), focal iris elevation and iridocorneal apposition at 5:00. There was nuclear sclerosis and pigment on the anterior lens capsule. Gonioscopy demonstrated focal angle closure at 5:00. Left slit-lamp and bilateral fundoscopic examinations were unremarkable. Ultrasound biomicroscopy (Fig. 1) showed a circumscribed 2.2 mm × 3.5 mm heterogeneously hyperechoic mass within the right iris associated with synechiae and mass effect on the crystalline lens. The patient was primarily concerned with visual improvement. Therefore, an excisional iris wedge resection, synechiolysis, pupilloplasty and cataract extraction with intraocular lens implantation were performed simultaneously for definitive diagnosis and vision restoration. Two months later, visual acuity improved to 20/20.

Histopathology revealed expansion of the iris stroma by nests of clear cells in a vascular background (Fig. 2). As the tissue was received in several small pieces, it was not possible to fully assess the surgical margins. Neoplastic cells were immunoreactive for pancytokeratins,

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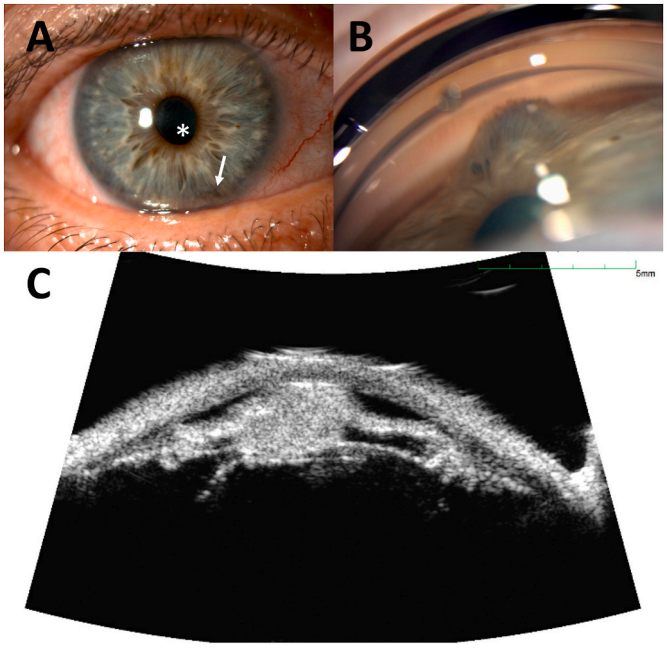

Fig. 1. Clinical appearance of the iris mass. A. External photograph of the right eye demonstrates mild corectopia (asterisk) and a small area of iridocorneal apposition at the 5-o'clock position (arrow). B. Gonioscopy of the right eye reveals focal iris elevation and iridocorneal apposition. C. Right eye ultrasound biomicroscopy demonstrates an ovoid, well-circumscribed 2.2 mm × 3.5 mm heterogeneously hyperechoic iris mass, resulting in focal iridocorneal apposition and mass effect on the crystalline lens.

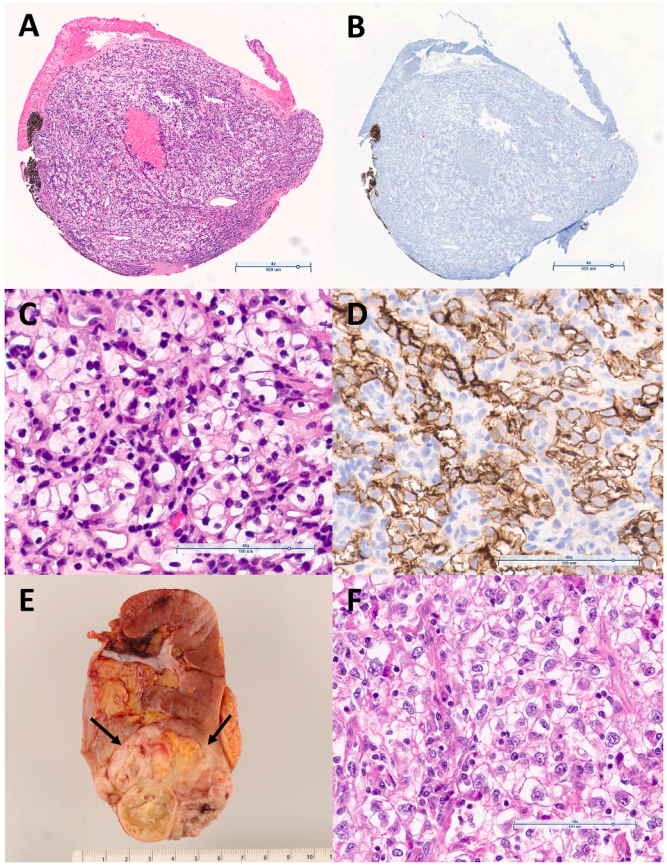

Fig. 2. Pathology of the iris metastasis and primary kidney tumor. A and C. The iris lesion consists of a proliferation of carcinoma cells with clear cytoplasm in a background rich in vessels, with near full-thickness replacement of the stroma to the iris pigment epithelium (H&E; A: 40X, scale bar size 500 μm; C: 400X, scale bar size 100 μm); B. Ki-67 showed a low proliferative rate (2%; red, Ki-67 immunostain, 40X, scale bar size 500 μm); D. Neoplastic cells exhibited strong membranous staining for carbonic anhydrase IX, an immunohistochemical marker of ccRCC (brown, CAIX immunostain, 400X, scale bar size 100 μm); E: Bisection of the radical nephrectomy specimen revealed a 5.8 x 5.2 × 4.8 cm lobulated heterogeneous yellow-white mass in the inferior pole of the kidney (arrows) with extensive areas of necrosis; F: Histology of the kidney tumor (H&E, 400X, scale bar size 100 μm) showed clear cells within a vascular background, but with more atypical nuclear morphology indicative of a higher grade neoplasm. Extensive necrosis (approximately 70% of tumor volume) and focal areas with rhabdoid and sarcomatoid differentiation, histological markers of poor prognosis, were also observed (not shown). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

AE1/3, Cam5.2, carbonic anhydrase-IX, CD10, and PAX-8, but negative for cytokeratins 7/20, SOX10, Melan-A, inhibin, synaptophysin, p40, TTF-1, consistent with metastatic clear cell renal cell carcinoma (ccRCC) (Fig. 2). The Ki-67 proliferation index was 2%.

Computed tomography (CT) scans of the chest, abdomen and pelvis were obtained to search for the primary neoplasm and for tumor staging. A 6.4 cm right lower pole renal mass involving the sinus and perinephric adipose tissue was discovered, without evidence of extrarenal disease on the CT scans. A radical nephrectomy was performed, revealing a high-grade (WHO/ISUP nuclear grade 4/4) ccRCC (Fig. 2) with focal sarcomatoid and rhabdoid features and extensive tumor necrosis without evident lymphovascular invasion. Given the inability to definitively confirm clean margins and the solitary site of metastasis, the eye was treated with I-125 plaque brachytherapy. The patient initially declined systemic adjuvant therapy, then received 2 cycles of immunotherapy (ipilimumab, nivolumab), discontinued due to side effects. There is no evidence of recurrent lesions 15 months after the initial diagnosis of the iris metastasis.

Molecular testing (Oncomine next-generation sequencing panel and complete Sanger sequencing of the *VHL* gene) demonstrated a partial overlap of tumor mutational profiles. Both primary and metastatic tumors harbored mutations in *VHL* (p.E160Sfs*10) and *SETD2* (p.K1405*), with an additional *VHL* mutation (p.G44D) in the metastasis. The primary exhibited *TERT* promoter mutation (C228T) and a second *SETD2* (p.S1374Afs*8) mutation, which were not present in the iris metastasis. No copy number variations were detected.

3. Discussion

This case exemplifies an unusual presentation of a previously unsuspected high-grade primary ccRCC following incidental discovery of an iris metastasis showing low-grade histology. Clear cell renal cell carcinoma (ccRCC) is the most common primary renal tumor, corresponding to more than 80% of cases. While up to half of ccRCCs are confined to the kidney at presentation, approximately 30% develop metastases.[4]

Although the iris metastasis was the only evidence of dissemination after extensive systemic workup, there were multiple histologic markers of poor prognosis in the primary neoplasm. Sarcomatoid or rhabdoid differentiation, defining features of the highest WHO/ISUP grade, independently confer 5-year survival rates of 15–20%. Necrosis (≥10%) also correlates with unfavorable outcomes.[4]

The molecular profiles of the primary and metastasis shared common mutations for ccRCC in *VHL* and *SETD2*. The *VHL* tumor suppressor gene, located in chromosome 3p, is mutated in the large majority of sporadic ccRCCs and all that occur in the familial von Hippel-Lindau setting. *SETD2*, which encodes a histone-3-lysine-methyltransferase, also in 3p, is mutated in 13% of ccRCCs.

Interestingly, the primary tumor exhibited the *TERT* promoter C228T mutation, which is associated with aggressive behavior in ccRCC,

glioblastomas, urothelial and thyroid carcinomas.[5] The *TERT* C228T may have been a late acquisition of the primary tumor after metastatic seeding, or the cell clone from which the iris metastasis derived may have originated in a heterogeneous tumor region lacking the mutation. In any event, the absence of *TERT* abnormality in the metastasis supports the notion that an aberrant VHL protein is sufficient to confer metastatic capacity in ccRCCs, as previously proposed in tumors with low grade histology.[6]

4. Conclusions

In this case, pathology from the excision of an iris lesion led to the detection of an asymptomatic high-grade renal cell carcinoma at a stage where the mass was still resectable, and not widely disseminated. Additionally, the histologic and molecular features of the iris metastasis are in keeping with a low-grade clone of the kidney primary, which could suggest a better prognosis for the patient considering that both tumors were resected and show no histological evidence of lympho-vascular invasion.

Patient consent

The patient gave written informed consent to publish the case (including publication of images).

Acknowledgments and Disclosures

The authors have no conflicts of interest or financial disclosures. The authors alone are responsible for the content and writing of this article. All authors attest that they meet the current ICMJE criteria for Authorship. The authors thank Dr. Raja Seethala and Dr. Sheldon Bastacky for surgical pathology consultation.

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