Date of meeting: EOPS 2025 Basel, June 11th-14th 2025

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Case number: B-2128233
Material distributed: 1, H&E slide scanned

**Choroidal metastasis ofClear Cell Renal Cell Carcinoma**

**Clinical History:**
A 76 y old white man was referred to the ophthalmic oncology department for a choroidal tumor in the left eye with presumable diagnosis of melanoma. He complained of diminished vision for 3 months on the left side.
Vision in the left eye was 5/10. On fundus examination there was a mushroom shaped, amelanotic tumor in the superior sector reaching the upper optic nerve border with secondary neurosensorial detachment. Hemorrhages were present in the superior sector around the large vessels. Ultrasound revealed a hyper reflecting homogenous mass 7.2x14.2mm. MRI showed no scleral or optic nerve invasion. The right eye was completely normal.
General history revealed a clear cell renal cellcarcinoma (kidney resection:Grawitz tumor Fuhrmann grade 2), detected 9 years earlier with lung metastases 2 years later (completely removed). He was stable for 7 years with no recurrences on PET-CT scan, MRI and other screening methods. There was at that time no general or local chemotherapy or radiotherapy applied.
No other relevant general medical problems but successfully treated hypertension.
It was decided that the most likely diagnosis was uveal melanoma and because the tumor was close to the optic nerve, enucleation or proton beam irradiation was proposed and the patient choose for enucleation.

**Pathology: Macroscopy:**
The left eyeballof 23-24-23mm diameter did not show gross abnormalities. Diaphanoscopic examination revealed a shadow of 13-9mm next to the optic nerve in the superior sector. After sectioning a pale dome-shaped tumor was found in the superior sector of 8mm thickness. The retina was detached over most parts.

**Pathology: Histology:**
The anterior segment did not reveal abnormalities. In the superior sector the choroid was invaded by a tumor of sheets and cords ofmedium-sized clear epithelial arranged cells around the multiple fibro-vascular septae. The cytoplasm was pale and focal eosinophilic with multiple large and smaller clear oval spaces. There was discrete pleiomorphism. The nuclei were round with heterogenous chromatin distribution, slight pleiomorphism and atypia and prominent nucleoli. Between 5 and 10 mitosis per 20 HPF. Multiple T lymphocytes were invading the tumor, mostly in the peripheral parts of the tumor. The optic nerve was not invaded. No extra- or intrascleral invasion, or noduli were detected. There was a retinal

detachment present with discrete atrophy of retinal layers, and beginning of retinal invasion by sheets of tumorcells.

**Pathology: Immune-histochemical staining:**:
Positive stains; Prekeratin (AE1/AE3), CA9( membranous), PAX 8 (nuclear), RCC ( = renal cell carcinoma= antibody against surface membrane molecule of brush border of proximal renal tubules , cytoplasmic and membranous ), CD10 (cytoplasmic).
Ki 67 (Mib1): 30% positive cells.
PHH3 positive more than 10 cells per 20 HPF.
CD3 and CD8 were identical positive for T lymphocytes in basal and peripheral tumor sections.
Negative stains: CK20, CK7, MelanA, synaptophysin

**Discussion:**

This case reports of a choroidal metastasis 9 years after resection of a kidney because of clear cell renal cell carcinoma and after 7 years of complete remission; therefor the clinician missed initially the diagnosis.

Choroidal metastasis of lung carcinomas, and breast, kidney, GIT, thyroid, prostate, are well-known but seldom biopsied because of already known diagnosis and poor prognosis. This case is an illustration of a tumor in which the choroid was the first recognized metastasis after 7 years of disease free survival and still the only metastasis recognized by screening.The tumor was larger and thicker than most other choroidal metastatic tumors, mostly because of the location far from the macular region. In the more central regions of the fundus, vision decrease is faster remarked.

The chance of macular or temporal area involvement is very high (40%) which explains the high incidence of primary finding of eye involvement because of vision deterioration. Around 4-10% of eyes are generally involved in autopsy reports of metastatic diseases.

The invasion of the eye by metastases is a hallmark for far-advanced disease and the mean survival time after detection is variable in function of the primary tumor and the success of treatment with the newer specific anti-tumor agents and biologicals (4months to more than 25years). The choroid is the preferred location because of the high amount of vessels with a high flow rate of blood and metastatic tumor emboli.

In case of doubt, a small biopsy can easily be performed. The methods and technics to handle very small biopsies, small needle biopsies or cytology specimens with scarce cells differ in laboratories. The Cellient® automatic cell block system is a handy tool for small intra-ocular biopsies. The paraffine block offers the opportunity to 20 different (immuno)histochemical stains per block. DNA extraction can be performed as from other routine paraffine blocks; which opens possibilities for molecular technics as NGS and LPS.

RCC (Renal-cell carcinoma) is a kidney cancer that originates in the lining of the proximal tubules. In 70% of cases the type is clear-cell. In the USA 65 000 new cases are detected per year. Half are older then 65 year of age at diagnosis, 5-year survival was around 75 %. Newer insides and treatments increase the rates of survival.

RCC is in most cases sporadic, only Von Hippl-Lindau disease andtuberous sclerosis are known as genetic risk factors. CCRCC ( clear-cell renal-cell carcinomas) is associated with mutations in VHL, an essential component of the cellular oxygen-sensing pathway VHL is located on chromosome 3p and is inactivated by mutation in 52% of CCRCC. Defects of this complex activates VEGF,what is thena possible target for treatment. Most CCRCC have been shown PD-L1 expression on the tumor cell membrane and in the tumor-infiltrating mononuclear immune cells. This justifies the use of blocking antibodies against PD-1--PD-L1

After metastases are detected the median survival time was13 months, mean was 22months until 10years ago. Now the survival time had increased because of newer general treatments. The most common sites of spread are the lungs, bones and liver.This person survived for 7years after 1st lung metastasis, and has for so far knownonly 1metastasis in the choroid which was completely removed.

Spontaneous regression of choroidal metastasis from renal cell carcinoma had been 3 times described in the literature.

RCC is not sensitive to chemotherapy or radiotherapy, CCRCC is characterized by an intense neo-angiogenesis, disruption of cell metabolism and dysregulation of immune surveillance. Therefor newer drugs are already in clinical use: VEGF-blockers, mTOR inhibitors, and immune checkpoint inhibitors. Combinations trials, also combined with surgery promise much higher survival rates.Surgical resection of metastatic foci is a treatment option in patients with a solitary metastasis. More specific treatment is not yet approved.

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