

## A Case Report of Choroidal Metastasis from Renal Cell Carcinoma during Sunitinib Treatment: A Tumor “Pharmacologic Sanctuary”?

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### Abstract

**Background:** Choroidal metastasis from Renal Cell Carcinoma (RCC) is very rare and only one case during Sunitinib treatment has been published until now.

**Case presentation:** In February 2015, a 61-year old, Caucasian man was hospitalized for acute dyspnea. In 2006, he underwent right nephrectomy for clear-cells RCC. Chest CT-scan showed multiple lung and lymph node metastases. Histological examination confirmed metastasis from clear-cells RCC. According to Motzer and Heng classification, the patient was classified as intermediate risk and, from March to July 2015, he received a total of 3 cycles of Sunitinib treatment. Despite a relevant tumor response in lung and lymph node metastases, he presented a brutally, unexplained, blurred vision in his right eye secondary to a choroidal metastasis. An external radiotherapy was administered without any relevant, clinical benefit. Considering tumor response in the other metastatic sites, Sunitinib treatment was continued and it is now ongoing.

**Conclusion:** RCC-associated choroidal metastasis is extremely rare. In contrast with another case responding to Sunitinib therapy, our patient presented a significant tumor response to Sunitinib in the extraocular metastatic sites and a choroidal progression, suggesting that the choroid could be a potential tumor “pharmacologic sanctuary” for this drug.

This case also raises the question of how to treat patients presenting an isolated disease progression in the sites which are very difficult to be reached by systemic treatment.

**Keywords:** Choroidal metastasis; RCC; Sunitinib

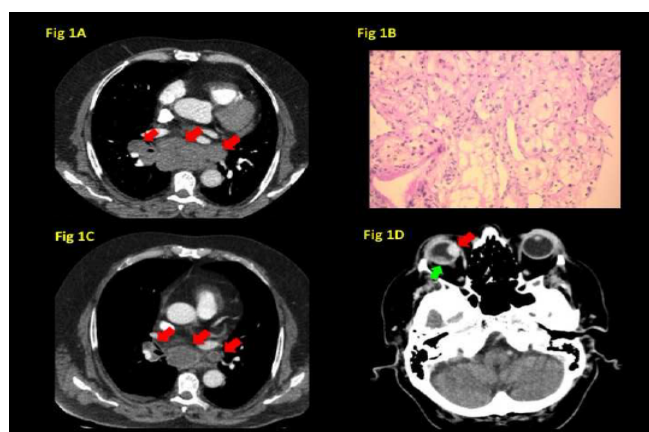
### Introduction

The incidence of intraocular metastasis is between 2% and 9%, according to the international literature, the leading causes being lung and breast cancer in men and women, respectively [1,2]. Renal cell carcinoma (RCC) is the thirteenth most common cancer in the world; its main secondary locations are lung, liver, bone and subcutaneous tissues.

We present a case report describing a patient with a metachronous choroidal metastasis (CM) from a RCC during Sunitinib therapy.

### Case Report

In July 2006, a 52-year-old, Caucasian man was surgically treated for clear-cells RCC (stage I). The follow-up was uneventful until February 2015 when he was hospitalized for acute dyspnea. Laboratory tests were in the normal range. Chest CT-scan showed a distal, bilateral, pulmonary embolism associated with multiple lung and lymph node metastases (Figure 1A, red arrows). PET-scan confirmed the metastatic lesions. A CT-guided, percutaneous biopsy of a mediastinal lymph node was performed. Histology showed the presence of malignant epithelial cells with clear cytoplasm and small nuclei, arranged in a compact-alveolar (nested) or acinar growth pattern interspersed with intricate, arborizing vasculature. Immunohistochemical staining was positive for AE1/AE3, CD10 and vimentin and negative for TTF-1 and cytokeratin 7. This pattern was consistent with a metastasis from clear-cells RCC (Figure 1B). According to Motzer/Heng classification, the patient was classified as intermediate risk



**Figure 1:** (A) Chest scan: Bulky, mediastinal, lymph node metastases at the diagnostic (red arrows). (B) Histology: Tumoral epithelial cells with a clear cytoplasm and a small, round nucleus, arranged in compact-alveolar (nested) or acinar growth pattern separated by a delicate branching network of vascular tissue, consisted with a metastasis from a clear-cells RCC (hematoxylin and eosin stain, original magnification x 20). (C) Chest scan after 3 cycles of oral Sunitinib: Tumor response with a significant reduction of mediastinal lymph node metastases (red arrows). (D) Brain scan: Choroidal RCC metastasis (red arrow) associated with a secondary retinal detachment (green arrow).

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and, from March to July 2015, he received a total of 3 cycles of Sunitinib therapy at the standard dose of 50 mg daily, following a "4 weeks on/2 weeks off" schedule. Whole-body CT-scan, realized after 3 cycles of treatment, showed a tumor response with an impressive reduction of lung and lymph node metastases (Figure 1C, red arrows).

However, a few days after this radiology restaging, the patient presented a brutally, unexplained, blurred vision in his right eye. The funduscopy revealed a hypopigmented, circumscribed, tumor, choroidal lesion associated with a secondary retinal detachment. A concurrent cataract did not allow us to take any picture of this lesion. At a new revision of the brain CT-scan images, an intra-ocular metastasis was identified (Figure 1D, red arrow), associated with a secondary retinal detachment (Figure 1D, green arrow). An external radiotherapy (30 Gy in 10 fractions) was administered without any relevant, clinical benefit. Considering tumor response in the other metastatic sites, Sunitinib treatment was continued and it is now ongoing.

## Discussion

CMs are very rare with a reported incidence of 2-9%, breast and lung cancers representing the most common source in 47-81% and 9-23% of cases, respectively [1-5]. However, gastrointestinal, kidney, prostate and skin cancers have all been reported to metastasise to the choroid [1-5]. Choroid represents the most common intraocular metastatic site with 69-88% of all published cases. In the majority of cases, CM is unifocal. Metastatic ocular lesions may be clinically silent, with only an estimated 12% involving the macula. At the time of diagnosis, 34% have an unknown primary [1-5]. The first CM case from RCC was described by Perl et al. in 1872 [6].

The underlying CM mechanism is still unclear. The eye is a particular site. Blood ocular barrier system includes blood-aqueous and blood-retinal barrier. Until now, there are no conclusive studies about physiological properties of this barrier and intraocular drug molecular bioavailability, particularly for cancer treatment [7]. Sunitinib is a small molecule that simultaneously inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, pathologic angiogenesis and metastatic progression. Sunitinib has been shown to inhibit a wide range of kinases and was identified as a potent inhibitor of platelet-derived growth factor receptor  $\beta$  (PDGFR $\beta$ ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-Like Tyrosine Kinase-3 (FLT3), colony stimulating factor receptor type 1 (CSF-1R) and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib and its primary active metabolite (SU012662) are metabolized primarily by the cytochrome P450 enzyme, CYP3A4. SU012662 comprises 23 to 37% of the total exposure [8].

To our knowledge, there are no data concerning intraocular diffusion of Sunitinib and its metabolites.

Clinically, the most common symptoms are blurring of vision, photopsia, floaters and pain whereas some patients may be asymptomatic. Typical ophthalmoscopic features include one or multiples creamy yellow choroidal lesions associated in some advanced cases with secondary retinal detachment [1-5]. The differential diagnosis includes choroidal melanoma, osteoma, hemangioma, neovascularization with disciform scarring, tuberculoma and posterior scleritis [1-5].

Several methods are available to directly characterize choroidal lesions, including ultrasonography, Fundus Autofluorescence (FAF) and Fine Needle Biopsy (FNAB). Ultrasonography differentiates between choroidal melanoma, metastasis, and hemangioma with 90% accuracy.

FAF may be used to aid in the evaluation of the tumor margin. In 17% of CM patients, a primary neoplastic source may never be found. In this population it would be beneficial to obtain a definitive diagnosis through FNAB, with a preservation of visual function [1-5].

Whole-body PET/CT can be useful for clinical evaluation of CM patients. It allowed the screening of the entire body and directed extraocular biopsy. Commonly used for tumor staging, PET/CT can play a pivotal role in the detection of the primary cancer [1-5]. CM from RCC on therapy, as in our case, remains very exceptional. Chin et al. [9] described a rapid involution of RCC-associated CM with oral Sunitinib, which is in contradiction with our case where we showed a tumor response of lymph node and lung metastases but an isolated choroidal tumor progression, the choroid representing probably a "pharmacologic tumor sanctuary" during Sunitinib treatment. We have no hypothesis that could explain this difference in efficacy of Sunitinib compared to the case described by Chin et al. [9].

There is no international recommendation for CM treatment. The standard treatment remains external beam radiotherapy, applying 30 Gy in 10 fractions or 40 Gy in 20 fractions. The reported complete response and improved visual acuity rates are 80% and 57% to 89%, respectively [10,11]. Radiation therapy consistently shows rapid symptom alleviation, yield excellent local control and functional outcomes. However, there are only few reports on late toxicity after 6 months given the unfavorable prognostic of CM patients. Selected patients may live more than two years, underlying the need to better assess mean and long term outcomes. Some authors have favored exclusive systemic strategies with omission of irradiation. The current literature suffers from the scarcity of prospective trials. Duration of tumor response following systemic therapy is rarely reported but appears less favorable as compared to radiotherapy. Systemic treatments may be proposed for pauci-symptomatic CM in a polymetastatic context while radiation therapy remains necessary in symptomatic CM either upfront or as an alternating treatment. Focalized radiation like brachytherapy and proton therapy may be proposed for isolated CM with long disease-free interval between primary and CM, as these techniques have the potential to yield better tumor and functional outcomes in patients with long life expectancy [10,11].

The prognosis of CM patients is poor but is strictly correlated to the histology and the presence of concurrent extraocular metastases [1-6]. Our case also raises the question of how to treat patients presenting an isolated disease progression in the sites which are very difficult to be reached by systemic treatment. Based on tumor response of the other extraocular metastases, we decided to carry on Sunitinib therapy without changing systemic treatment, as we considered choroid as a "pharmacologic tumor sanctuary".

## Conclusion

To our knowledge, this is the only case of RCC-associated CM during Sunitinib therapy in a patient responding to the treatment in the other extraocular sites. This isolated choroidal tumor progression is probably related to a poor intraocular diffusion of Sunitinib and/or its active metabolites which do not reach a sufficient drug concentration leading to a tumor control at this site. Choroid could represent a "pharmacologic tumor sanctuary" to Sunitinib therapy.

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## References

1. Haimovici R, Gragoudas ES, Gregor Z, Pesavento RD, Mieler WF, et al. (1997) Choroidal metastases from renal cell carcinoma. *Ophthalmology* 104: 1152-1158.
2. Hammad AM, Paris GR, van Heuven WA, Thompson IM, Fitzsimmons TD (2003) Spontaneous regression of choroidal metastasis from renal cell carcinoma. *Am J Ophthalmol* 135: 911-913.
3. Kurashige Y, Otani A, Yoshimura N (2010) Choroidal metastasis of renal cell carcinoma: a case report. *Jpn J Ophthalmol* 54: 111-112.
4. Shoaib KK, Haq IU, Ali K, Mukhtar MA, Nazir M (2008) Choroidal metastasis from renal cell carcinoma presenting with cataract. *J Coll Physicians Surg Pak* 18: 380-381.
5. Srinivasan S, Gray DG (2003) Images in clinical medicine. Choroidal metastasis from renal-cell carcinoma. *N Engl J Med* 349: e22.
6. Perl M (1872) Contribution to pathology of tumours. *Virchow's Arch Pathol Anat* 56:445-448.
7. Patte M, Sillaire I, Pauchard E, Coulangeon LM, Kantelip B, et al.(2006) Blood ocular barrier physiology. Elsevier Masson Ophtalmology.
8. Motzer RJ, Hoosen S, Bello CL, Christensen JG (2006) Sunitinib malate for the treatment of solid tumours: a review of current clinical data. *Expert Opin Investig Drugs* 15: 553-561.
9. Chin EK, Almeida DR, Sacher BA, Boldt HC1 (2015) Rapid involution of choroidal metastasis secondary to renal cell carcinoma with oral sunitinib. *JAMA Ophthalmol* 133: 109-110.
10. Roy S, Madan R, Gogia A, Tripathy K, Sharma D, et al. (2015) Short course palliative radiotherapy in the management of choroidal metastasis: An effective technique since ages. *J Egypt Natl Canc Inst Jul* 31.
11. Jardel P, Sauerwein W, Olivier T, Bensoussan E, Maschi C, et al. (2014) Management of choroidal metastases. *Cancer Treat Rev* 40: 1119-1128.