Delayed Diagnosis of Lung Carcinoma Presenting as Choroidal Metastasis in a COVID-19 Patient and Initially Treated with Osimertinib

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Verzögerte Diagnose eines Lungenkarzinoms, das sich als choroidale Metastase in einem COVID-19-Patienten präsentierte und am Anfang mit Osimertinib behandelt wurde

Background

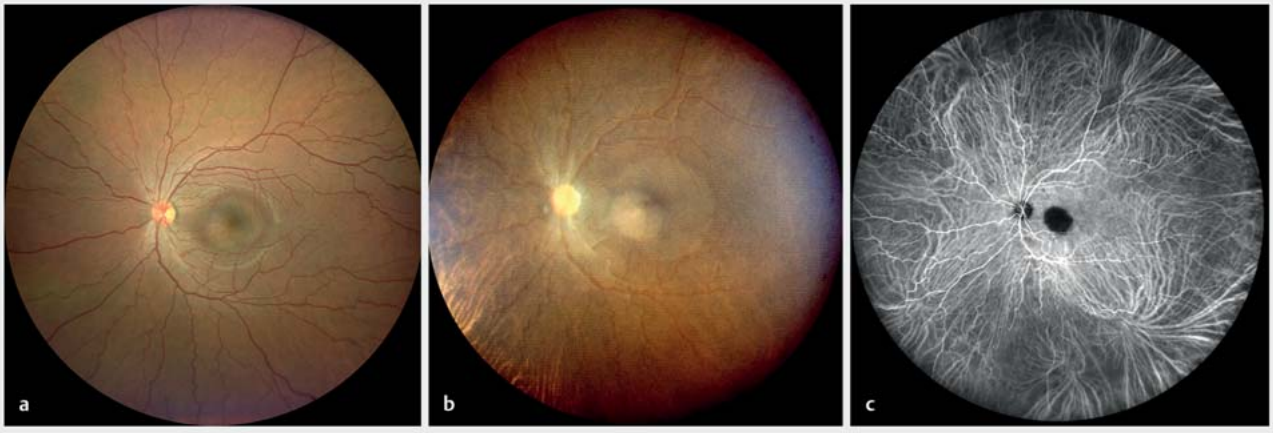
Until recently, management of choroidal metastases (CM) was based on a set of fairly reliable assumptions. For example, the observation that in patients who present with CM and no relevant oncological history, a chest computed tomography (CT) scan will diagnose lung carcinoma as the primary tumor in a majority of cases. Or the fact that external beam radiation therapy (EBRT) is the standard treatment for CM and is often urgently indicated because of the secondary exudative retinal detachment and risk of blindness [1].

The impact of the COVID-19 pandemic on cancer care has been widely commented, mostly with regard to the discontinuation in screening programs, the risk of iatrogenic infection of patients and staff, and the delay in diagnostic, therapeutic, and follow-up procedures, as well as the suspension of clinical trials [2]. As far as we are aware, there are no specific examples with regard to the effect of COVID-19 on CM management.

The arrival of systemic targeted therapies represents a more important and lasting game-changer, as they have improved life expectancy significantly in cancer patients who harbor the target mutation [1, 3], and specifically in lung cancer patients with EGFR (epidermal growth factor receptor) mutations [4–6]. However, for CM patients, this better prognosis implies that long-term radiation-induced side effects, in particular secondary ischemic retinopathy or optic neuropathy, become an increasing challenge. The use of targeted therapies as an alternative treatment for CM has been tried with first- and second-generation tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, and afatinib, but met with resistance problems [3–5, 7, 8]. Osimertinib is a third-generation TKI that inhibits EGFR TKI as well as EGFR T790M resistance mutations, offering an alternative treatment in lung cancer patients. Its efficacy in the setting of CM has only been reported upon in one case [4].

Report of a Case

A 41-year-old black male presented a few months after the COVID-19 pandemic started at the Jules-Gonin Eye Hospital with a painless loss of vision (LE) for 2 months. The rest of his medical history was unremarkable. As a restaurant owner, he reported stress related with COVID-19 restrictions. On examination, Snellen best corrected visual acuity (BCVA) was 1.25 (RE) and 0.6 (LE). Subfoveal liquid in the left fundus evoked the possible diagnosis of a central serous chorioretinopathy (CSCR) (▶ **Fig. 1 a** and **Fig. 2 a**). The patient did not consent to fluorescein angiography (FA).



▶ **Fig. 1** **a**, **b** Panoramic color fundus pictures (Panoret-1000 camera). **a** Initial presentation: no obvious solid lesion could be observed. **b** Four weeks later: a single amelanotic choroidal lesion had appeared, provoking (**c**) on panoramic ICG-A, a masking defect, without evidence of any other lesions.

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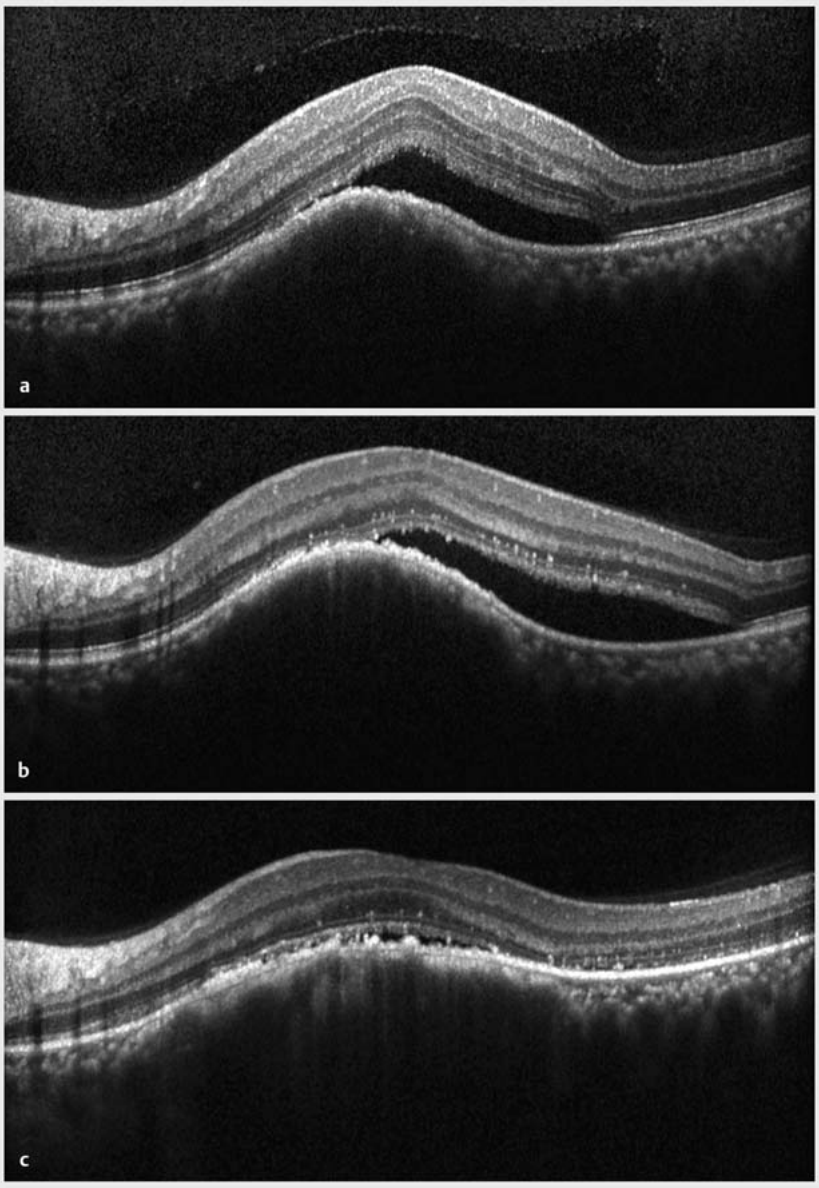


▶ **Fig. 2** **a–c** B scan OCT follow-up before and after treatment. **a** Initial presentation: subfoveal liquid in the left fundus evoked the possible diagnosis of a central serous chorioretinopathy. **b** Four weeks later: an increase in the curvature of the macula suggested a growing choroidal mass. **c** Four weeks after initiating osimertinib: the choroidal mass had regressed, and there was less subretinal liquid.

After 4 weeks, a single amelanotic choroidal lesion had appeared (▶ **Fig. 1b** and **Fig. 2b**), with a thickness of 1.6 mm on 20 MHz B-scan ultrasonography. The mass presented a few pinpoints at its surface on FA and provoked a masking defect on panoramic indocyanine green angiography (ICG-A) (▶ **Fig. 1c**). No other choroidal lesions could be identified in both eyes (BE). Suspicion of choroidal metastasis motivated a systemic workup, including a chest CT scan, which was reported to be "compatible with a recent COVID-19 pneumonia" that was not revealed during the initial medical history.

Three weeks later, the patient was admitted via the emergency department because of hemoptysis. The chest CT scan carried out upon admission revealed a pulmonary mass in the right middle lobe with mediastinal infiltration, multiple lymph nodes, and a suspected contralateral nodule. A bronchoscopy led to the diagnosis of a lung adenocarcinoma with EGFR mutations in exons 18 and 20. No distant metastases were detected other than in the left posterior choroid, for which EBRT was initially considered.

However, three months after initial presentation, a "pre-radiation" fundus control revealed the appearance of diffuse, multiple, minuscule, flat choroidal lesions (BE), only visible on ICG-A, compatible with miliary rather than oligometastatic lung cancer. The treatment strategy was adapted, and a palliative treatment with the EGFR TKI osimertinib was initiated.

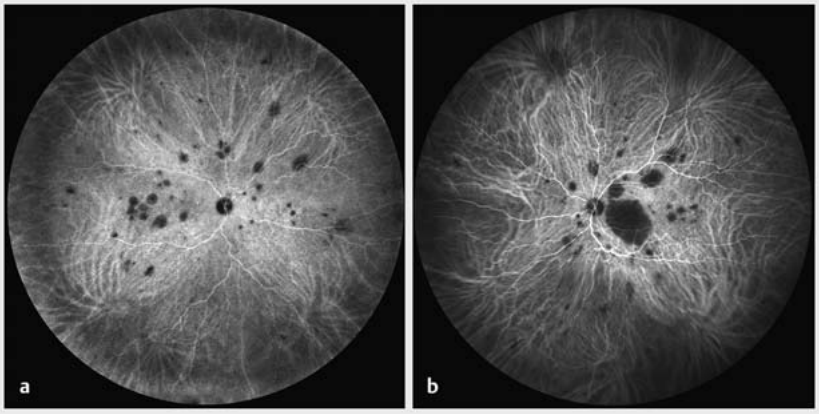
An ophthalmic checkup was performed 4 weeks after treatment initiation as a surrogate marker for the systemic treatment response. BCVA had improved to 0.9 (LE), with a regression of the main choroidal mass to 1.4 mm and less subretinal fluid (▶ **Fig. 2c**). On ICG-A, the multiple minuscule choroidal lesions (BE) were stable. On a PET-CT (PET: positron emission tomography) scan, the pulmonary mass had also regressed.

Seven months after first presentation, BCVA dropped again to 0.8 p (LE). After the initial treatment response to osimertinib, a diffuse increase in the size and number of miliary metastases could be observed on ICG-A (▶ **Fig. 3a, b**), and now also ophthalmoscopically. As an MRI did not reveal any brain lesions and the pulmonary mass was unchanged on the PET-CT scan, EBRT of BE (13 × 2.5/2 Gy) was performed.

Three months later, BCVA had recovered to 1.0 (BE), the main lesion in the left macula was less than 1 mm thick, and the retina completely reattached. However, a new PET-CT was compatible with a pulmonary progression and 1 month later, the appearance of brain metastases motivated the induction of a chemotherapy.

Discussion and Conclusion

Here we report on a 41-year-old male who presented a single choroidal metastasis as the first sign of his yet undiagnosed lung



▶ **Fig. 3** **a**, **b** Three months after starting osimertinib following an initially positive response, a diffuse increase in the size and number of miliary choroidal metastases could be observed on ICG-A in BE (**a**: RE and **b**: LE).

adenocarcinoma and who was ultimately treated with EBRT of BE. His history, instead of being a classic straightforward case, illustrates how both COVID-19 and the recently introduced targeted therapies influence and complicate the diagnosis and multidisciplinary management of metastatic lung carcinoma.

COVID-19 awareness, being ubiquitous, twice delayed the correct diagnosis in this case. First, by imputing the initial subfoveal liquid to "COVID-19 stress"-related CSCR. Of note, a literature search resulted in case reports about choroidal hemangioma, or even melanoma manifesting with CSCR [9], but not choroidal metastasis. Second, by interpreting the opacities on his chest scan as residual lesions of COVID-19 pneumonia instead of related to undiagnosed lung carcinoma, even in the presence of a suspected choroidal metastasis.

Coincidentally, with the treatment delay in this case, panoramic ICG-A allowed for recognizing a miliary rather than oligometastatic lung cancer and to adapt the treatment strategy accordingly, underlining the importance of ICG-A in CM management.

Before the era of targeted therapies, this patient with metastatic lung cancer would have been managed with combined chemotherapy, radiation therapy, and/or surgery, with a bleak prognosis. However, at the time, no targeted therapy was known to have been tried for EGFR mutations at exons 18 and 20. In consequence, the oncologists proposed to use the directly visible choroidal metastases as an initial monitoring tool to evaluate the efficacy of osimertinib, opening interesting new perspectives for future multidisciplinary management of CM patients. The fact that the systemic recurrence was only proven with a delay of 3 to 4 months following the fundus recurrence can be explained by the higher resolution offered by multimodal fundus imaging compared with that of PET-CT or MRI.

We observed an initial treatment response to osimertinib, followed by disease progression treated with EBRT. Dall'Olio et al. described in 2017 a complete response with a flat scar of a unique CM 4.5 months after initiating osimertinib in a 54-year-old white female with T790M-mutated non-small cell lung adenocarcinoma [4].

In conclusion, we report on a metastatic lung cancer patient presenting with a single choroidal metastasis, whose diagnosis was twice masked because of COVID-19 awareness and whose radiation therapy was preceded by an initially successful osimertinib targeted therapy.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors

Celine Noha Haeller[1], Lilly Khamsy[1], Jonas Kloepper[2], Luis Schiappacasse[3], Hasna Bouchaab[2], Solange Peters[2], Ann Schalenbourg[1]

1 Department of Ophthalmology, Jules-Gonin Eye Hospital, FAA, University of Lausanne, Lausanne, Switzerland
2 Department of Oncology, Medical Oncology Service, CHUV, University of Lausanne, Lausanne, Switzerland
3 Department of Oncology, Radiation Oncology Service, CHUV, University of Lausanne, Lausanne, Switzerland

Correspondence

Dr. Ann Schalenbourg
Department of Ophthalmology
Jules-Gonin Eye Hospital, FAA
University of Lausanne
Av. de France 15
1004 Lausanne
Switzerland
Phone: + 41 (0) 2 16 26 85 88
Fax: + 41 (0) 2 16 26 88 89
ann.schalenbourg@fa2.ch

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