Iris metastasis from endometrial carcinoma: A challenging diagnosis and individualized eye-sparing treatment

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ARTICLE INFO

Keywords: Gynecological cancer, Chemotherapy, Iris

ABSTRACT

A woman in her 70’s with a history of recurrent oral aphthosis and two years earlier of resected stage IA low risk endometrial adenocarcinoma, presented with blurred vision and a painful mass of the right eye that had developed in two months. PET/CT imaging detected a nodule in the right lung. Because of diagnostic uncertainties between inflammatory disease (Behçet syndrome) or cancer, a biopsy of iris and pulmonary lesions were performed and lead to histologically documented metastases from endometrial adenocarcinoma in both sites. After a multidisciplinary team discussion excluding disfiguring local therapies (radiation therapy or surgery), systemic chemotherapy with carboplatin and paclitaxel was performed, leading to radiological complete response that is sustained at 12 months after the end of treatment. This case shows that chemotherapy should be considered as a valid organ-sparing treatment in the management of these uncommon metastatic sites.

1. Introduction

Uvea - composed of choroid, body ciliary and iris - is the most frequent site of intraocular tumors, mainly represented by metastases from the breast and lung, but have been described in endometrial cancers. Rich vascularization and favorable microenvironment explain the preferential neoplastic involvement of the uvea within the eye. However, the uvea remains an extremely rare site of cancer metastasis, that usually affect the choroid and infrequently the iris. The differential diagnosis include inflammatory diseases and benign neoplasms. Surgical enucleation and radiotherapy have been considered the standard of care for the treatment, while the employment of medical therapy for uveal metastases is limited to scarce case series and reports. However, to date, there are no guidelines for the management of iris metastases. Mathis et al., 2019 Jan; Liu et al., 2021 Jul 6.

We report the case of a woman who presented with an acutely symptomatic iris mass and pulmonary oligometastatic recurrence of endometrial adenocarcinoma, successfully treated with standard chemotherapy without mutilating surgery or radiation therapy.

2. Case report

A never-smoker woman presented with a two month history of a rapidly growing right iris mass, causing pain, ocular redness and blurred vision, despite systemic steroids and topical antibiotic therapy. Furthermore, her recent medical history was positive for chronic recurrent afebrile oral aphthous ulcers. Two years before the patient underwent to hysterectomy and bilateral salpingo-oophorectomy for a well differentiated FIGO stage IA endometriod adenocarcinoma of the uterus. No adjuvant chemotherapy and/or radiotherapy were administered, given the low risk of relapse according to the histopathological characteristics of the neoplasia. Cho et al., 2019 Jan and she was released into surveillance.

Ophthalmologic examination showed a pink flat alteration with irregular vascularization in the temporal quadrants of iris, as well as corectopia and anterior chamber hyphema. At baseline assessment the best visual acuity was 4/10 in the right eye and 9/10 in the left, while right ocular tone was 16 mmHg. Bulbar echography and orbit nuclear magnetic resonance documented a solid tissue with 8 mm full-thickness involvement of posterior pigmented epithelium. Optical coherence tomography (OCT) scan ascertained neither chorioidal nor retinal involvement. No other abnormalities were found both at the
physical evaluation and in the blood analysis, including inflammatory markers. Whole body $^{18}$F-FDG PET/CT imaging also revealed a pathological uptake (SUV$_{max}$ 20.2 g/mL) in a nodule of 27x26 mm in the lower lobe of the right lung (Fig. 1B).

Considering the rapid onset and the concomitant presence of oral ulcers, we firstly excluded a multi-organ inflammatory disease. Furthermore, a primary lung carcinoma with iris metastasis and a primitive malignant iris lesion were considered as potential differential diagnosis, thus leading to the decision of performing both a pulmonary and an iris biopsy.

Histological analyses showed carcinoma with endometrioid architecture in both specimens (Fig. 2), thus supporting the diagnosis of iris and pulmonary metastases of endometrial adenocarcinoma. In addition, we requested and obtained the primitive uterine specimen from the institution of the primary surgery, and we performed a pathology review, which confirmed the diagnosis of endometrial carcinoma. Immunohistochemical and next-generation sequencing (NGS) assessments of metastases and primitive uterine specimen revealed PAX-8 expression, proficient DNA mismatch repair (pMMR), TP53 wild type status, absence hormonal receptors expression and CTNNB1 S33F, PIK3CA H1047Q, and KRAS G12V point mutations, overall consistent with the “copy number low” subgroup of endometrial cancers, as reported by the The Cancer Genome Atlas (TGCA) classification.(Cancer Genome Atlas Research Network et al., 2013 May 2).

Based on the histologic diagnosis, the patient was presented in a multidisciplinary discussion. Radiotherapy was excluded as an alternative due to the massive size of the lesion and presence of severe ocular pain. As for surgery, an eye enucleation was the only radical approach that could be performed, having ruled out any possibility of eye preservation. Therefore, taking into account the presence of another pulmonary metastasis, the rapid worsening of ocular symptoms, and in the perspective of an organ-sparing approach, a medical therapy was decided as the best option for the patient. The patient then started standard chemotherapy with carboplatin AUC5 and paclitaxel 175 mg/m$^2$ every 3 weeks for a total of 6 cycles.

The iris metastasis decreased and ocular pain resolved after one cycle of chemotherapy. Imaging after 3 cycles—including total body CT and orbital MRI—documented a complete response of the iris lesion and a partial response of the pulmonary metastasis. At restaging - after 6 cycles the complete response of the iris was maintained (Fig. 3A), and also the pulmonary metastasis disappeared (Fig. 3B).

During chemotherapy, periodical ophthalmological evaluations have been performed, which revealed a progressive normalization of the ocular tone, even if the visual acuity did not improve. Ultrasound biomicroscopy showed fibrotic involution of iris metastasis, conditioning lenticular-iridic synchiae, iris atrophy, and total cataract. In order to improve the residual visus, patient was referred to a high-expertise ophthalmological oncological surgery institute, where a cataract surgery has been evaluated, nevertheless it has been excluded since considered as a high-risk procedure.

At 19 months from the end of chemotherapy, the complete response of both iris and pulmonary lesions is maintained, and no new metastases have been detected.

3. Discussion

Uveal metastasis is the most frequent intraocular tumor, involving the choroid in 88–89 % of cases and less frequently the iris (9 %) or ciliary body (2 %).(Shields et al., 1997 Aug 1) Difference in relative blood flow and vessels permeability could explain the different incidence of metastasis between choroid and the rest of the uvea.(Weiss, 1993 Mar 1) In the iris tract, primary tumors, mainly represented by melanomas, are most frequent than metastases, which arises in 33 % of cases from breast cancers, in 27 % from lung cancers, and only in 2 % of cases from uterine cancers.(Liu et al., 2021 Jul 6; Shields et al., 2015 Jan) Typical clinical presentation is metachronous, unilateral, and consists of a pigmented mass associated with decreased visual acuity, pain, and ocular redness. Invasion of the irido-corneal angle and iris neovascularization frequently result in secondary glaucoma.(Shields et al., 2015 Jan) Differential diagnosis includes inflammatory disease and benign neoplasms such as iridocyclitis and melanocytic tumors respectively.(Shields et al., 1997 Aug 1; Shields et al., 2006 Nov 1) In our case, the acute clinical presentation - with a painful rapidly growing iris lesion - initially suggested an acute unilateral uveitis, which has been excluded by the ineffectiveness of steroids and antibiotic therapy. Meanwhile, the concomitant presence of oral ulcers and pulmonary involvement had fueled the hypothesis of a multi-organ inflammatory disease, such as Behçet syndrome, that was ruled out by the absence of other typical clinical findings, according to The International Study Group Criteria for Behçet Disease (ISBD) criteria.(Yazici et al., 2018 Feb).

After excluding an inflammatory disease, we discussed the potential oncological scenarios. A primary lung carcinoma with isolated iris metastasis and a primitive iris melanoma were both considered, given that the iris is a metastatic site for lung malignancies and that primitive malignant iris lesions are usually more frequent than metastases. Meanwhile a relapse of the primary endometrial carcinoma seemed unlikely, due to the histopathological staging. Therefore, given the

Fig. 1. Pre-treatment ophthalmological and imaging results. (1A): ophthalmological evaluation revealed a neovascularized iris lesion occupying the temporal quadrants of the right eye. (1B): $^{18}$F-FDG PET/CT scan showed an uptake in a nodule of the lower lobe of the right lung.
difficulty to distinguish between primary and secondary lesions, a fine-needle aspiration biopsy of both pulmonary and iris lesion was indispensable, as suggested by literature in such ambiguous clinical presentations. (Shields et al., 2006 Nov 1).

At the current state of knowledge, there are no standard treatment guidelines for uveal metastases, due to their rarity and the absence of randomized clinical trials. As reviewed by Mathis et al,(Mathis et al., 2019 Jan) local therapies such as radiotherapy, surgery or intravitreal anti-VEGF injections are preferred in isolated ocular relapses or oligometastatic diseases. Otherwise, life-threatening metastases can be treated with a combination of systemic and local palliative therapies.

Conventional external beam radiotherapy (EBRT) is the most chosen treatment for uveal metastases. It provides rapid tumor regression and improvement of ocular symptoms, however it does not control the metastatic spread and it increases the risk of developing ocular toxicity. (Kanthan et al., 2007).

Understanding the intraocular drug bioavailability is a major challenge, due to the complex anatomy and the dynamic physiological barrier of the eye. (Agrahari et al., 2016 Dec) Data regarding the use of systemic chemotherapy for the treatment of iris metastases are lacking, while the available literature mostly addresses choroidal metastases from breast and lung cancer. Aromatase inhibitors and traditional chemotherapy have achieved high response rate in the treatment of choroidal metastases from hormone-receptor positive breast cancer and non-small cell lung cancers (NSCLCs) respectively. (Manquez et al., 2006 Jun; Shah et al., 2014 Jan 1) Recent articles report excellent ocular response to small molecules such as alectinib, crizotinib, gefitinib and erlotinib. (Mathis et al., 2019 Jan) Otherwise, immunotherapy showed poor intraocular efficacy, highlighting the property of the eye as an immune-privileged site due to its anatomical, physiological and immunoregulatory processes that can limit the activity of the immune system. (Niederkorn, 2009 Sep 1).

To our knowledge, this is the fourth published case of iris metastasis from endometrial cancer, and the only one treated with first-line chemotherapy, resulting in a dramatic and sustained response and clinical benefit. (Planten, 1981; Capeans et al., 1998 May; Yoon et al., 2007 Jun).

In this case we faced an atypical rapid growing iris mass which represented a dual diagnostic and therapeutic challenge. Because of the morbidity related to therapeutic local procedures, the histological assessment of both metastases was required. Indeed, given the low risk of relapse of the primitive endometrial carcinoma (90.3 % 5-years recurrence free survival) (Bendifallah et al., 2017 Jan 1) and the potential plausible alternative differential diagnosis (primitive lung cancer and iris melanoma), the likelihood of endometrial cancer recurrence was low.

As regarding the treatment choice, a radical approach by local ablation of both metastases - either by radiation therapy and/or surgery – was rather considered by the multidisciplinary team. Radiation was excluded because of size of iris metastasis, and therefore a radical treatment would have implied pulmonary metastasectomy and eye enucleation. This approach, although supported by the limited extension...
of the oligometastatic relapse, was discouraged by the relatively short 2-years interval from primary surgery, and the patient desire of avoiding eye enucleation. In conclusion, the rapid worsening of ocular symptoms and the willingness of eye preservation led to the indication of a medical therapy.

This case highlights the importance of a multidisciplinary management to customize diagnosis and treatment, and the value of medical therapy as a valid alternative to radiotherapy and/or surgery for iris metastases, especially in the presence of extra-ocular involvement and in the perspective of an eye sparing approach.

A written informed consent was obtained from the patient for publication of this case report and accompanying images.

CRediT authorship contribution statement

Alberto Giuseppe Agostara: Conceptualization. Annabella Curaba: Conceptualization. Giulia Carlo Stella: Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

This study was supported by Fondazione Oncologia Niguarda Onlus, Milan, Italy Grant number: FONO2022-002.

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