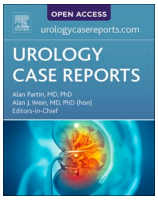
Urology Case Reports 56 (2024) 102814

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr



Oncology

A rare vision: First reported case of bilateral uveal metastasis from prostate cancer in the Middle East

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A B S T R A C T

We present the first reported case in the Middle East of bilateral uveal metastasis from prostate cancer in a 74-year-old man. Initially diagnosed in November 2016 with high-volume metastatic castrate-sensitive prostate cancer (mCSPC), his cancer progressed and was castrate-resistant. In December 2022, the patient presented blurry vision in the left eye and was diagnosed with left uveal metastase. Later his disease progressed to the right eye. This case shows the importance of considering ocular metastasis in patients with advanced prostate cancer, highlights the challenges in managing rare metastatic sites, and provides insights into treatment strategies for bilateral uveal metastasis.

1. Introduction

Prostate cancer (PC) is the most frequent form of cancer affecting men. While most of PCs are localized, some patients may develop or present with a metastatic PC. The bones are the primary site of metastases followed by distant lymph nodes, liver, lungs, brain and finally the digestive system.[1] Metastases to one ocular site is an exceptionally uncommon situation and it is very rare to have metastases in bilateral ocular sites (see Fig. 1) (Fig. 1).

This manuscript details a case study involving a 74-year-old male who presented with metassatic castrate sensitive prostate cancer and developed subsequently bilateral uveal metastasis.

2. Case presentation

We report the case of a 74-year-old man who visited us in November 2016 for examination of his prostate specific antigen (PSA) level without any other subjective symptom related to his prostate cancer. He was shown to have a PSA level of 196 ng/mL in a routine evaluation. His physical exam was normal, and the digital rectal examination revealed a slightly enlarged prostate. A prostate needle biopsy was performed, and pathological examination revealed a Gleason pattern 4 adenocarcinoma. His past medical history was unremarkable except for hypertension. An MRI of the abdomen and pelvis showed a prostatic tumor invading the seminal vesicle and the rectum with left pelvic lymph nodes and osteolytic lesions involving the right sacrum. PET-CT scan showed a hyperactive left apex primary, with contiguous extension on seminal vesicles, secondary hyperactive lymph nodes located on the left external iliac axis, mediastinum, and lung hilum lymph nodes with micronodular infiltrates compatible with a secondary lung origin and several bone metastases.

Based on the results, visceral metastasis and bone lesions, the patient was diagnosed with high-volume metastatic castrate sensitive prostate cancer (mCSPC) and started on androgen suppression with leuprolide (6-month depot) and docetaxel chemotherapy between January and April 2017. His PSA level reached 0,23 ng/mL in May 2017 and patient's disease remained stable. A PSMA PET-CT (prostate-specific membrane antigen positron emission tomography) scan in May 2017 showed a good therapeutic response of both primary tumor and related secondary disease.

Around the 2-year follow up, his PSA in October 2019 was found to be going up to 7,05 ng/mL and PSMA PET-CT scan showed progression of disease. He was started on enzalutamide 160 mg per day and was being followed with physical exams, PSA assessments and imaging. His PSA decreased to 0.04 ng/mL and remained stable until May 2021 when it increased to 1,4ng/mL. It is worth mentioning that after doing genetic tests, our patient was BRCA negative and dMMR or MSI stable.

A PSMA PET-CT scan done in May 2021 and compared to a previous examination in November 2020 showed a prostate with residual locally active disease, progression of the mediastinal lymph nodes, high uptake in the lung along the left lower lobe and the skeleton showed an early small bone metastasis with focal uptake at D10 body vertebrae. Therefore, the patient had metastatic castrate resistant prostate cancer (mCRPC) because of a rising PSA, new lesions, failing androgen deprivation therapy and docetaxel. The decision was made to start 21-day cycles of cabazitaxel chemotherapy in June 2021 but was stopped

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https://doi.org/10.1016/j.eucr.2024.102814
Received 17 June 2024; Accepted 30 July 2024
Available online 31 July 2024

after the 6th cycle in September 2021 because of chemotherapy related toxicities including febrile neutropenia, anemia, and thrombocytopenia. Since stopping chemotherapy in September 2021, he remained stable under androgen suppression (Goserelin) and was followed with regular PSA dosing and imaging.

In December 2022, patient started complaining of a blurry vision, an orbital and cerebral MRI showed left retinal detachment with subretinal hemorrhage in the left eye, posterior vitreous detachment, and small cilio-choroidal effusion (Figure, A). A PSMA PET/CT scan done afterwards showed findings compatible with progression of nodal disease in the chest with appearance of multiple metastatic lung nodules as well as appearance of a left orbital tumor. His left retinal metastases was treated in January 2023 with radiotherapy (2000 cGy in five fractions) and he was rechallenged with docetaxel 100mg (five 21-days cycles) between February and May 2023.

In May 2023, after a follow-up ophthalmology consultation, there was a suspicion of a right eye metastasis. An orbit MRI was made and compared to the previous one in December 2022. The result was in favor of a resolved left glob tumor but a new lesion of the upper outer quadrant of the right globe measuring on the post contrast images 10mm in length and 5mm in thickness, suggestive of a right orbital metastatic disease without a detached retina or hemorrhage and no retro-orbital tumor. At the same time a follow up PSMA PET/CT showed progression of metastatic bone and chest disease and a new metastatic lesion of the right globe.

It was therefore decided to switch the patient from docetaxel chemotherapy to 35mg Cabazitaxel chemotherapy (June 2023) and treat the right eye lesion with 3 bevacizumab monthly injections in the right eye.

3. Case discussion

Prostate cancer (PC) is the most frequent form of cancer affecting men. While most of PCs are localized, some patients may develop or present with a metastatic PC. The bones are the primary site of metastases followed by distant lymph nodes, liver, lungs, brain and finally the digestive system.[1] Metastases to one ocular site is an exceptionally uncommon situation and it is very rare to have metastases in bilateral ocular sites. PC can spread to the choroid through two pathways. In our case, the patient had lung metastases and then developed ocular metastases. Tumor emboli must have traveled through the pulmonary circulation to the ophthalmic artery via the carotid arteries and then the ciliary vessels and uveal tract. Alternatively, in the absence of pulmonary lesions, these metastases may disseminate into Batson plexus bypassing the pulmonary circulation.[2] Patients with eye metastases were always found to have widespread metastatic disease elsewhere. These tumors tend to be aggressive with poor prognosis because most of the reported cases of PC with bilateral uveal metastases had already metastasized to the bones or other organs before the eyes. Choroidal masses are frequently accompanied by a secondary retinal detachment as seen in our case.[3] This is why patients complain of decreased or blurred vision as a presenting symptom.[4] However, in our case, at the beginning the metastases were not causing any visual symptoms.

Although metastatic cancer to the orbit is a rare condition, many cancers can metastasize to the eyes. The primary tumoral leading to eye metastasis are: breast (37 %), lung (27 %), kidney (4 %), gastrointestinal tract (4 %), cutaneous melanoma (2 %), lung carcinoid (2 %), prostate (2 %), thyroid (1 %), pancreas (1 %), and other sites (3 %).[5] As the choroid is the best irrigated structure in the eye, it is the most frequent seat of metastasis (90 %), followed by the iris (8 %) and ciliary body (2 %). Other sites such as the retina, the optic disc, the vitreous and the lens capsule are rarely a site of metastasis (all combined <1–4%).[6]

The diagnosis of eye metastases is usually clinical and supported by radiologic evidence of metastatic cancer in other organs. Metastasis is identified as a solid, flat, plaque-like, mottled, yellow brown lesion that is commonly associated with serous retinal detachment. Biopsy should be considered in patients with less straightforward presentation. In case of doubt, diagnosis can be confirmed by several tools: fluorescent angiography, ultrasound, fine needle aspiration (FNA), MRI/CT scan and optical coherence tomography (OCT).

In two third of cases, detection of uveal metastasis occurs after discovering the primary tumor site. However, in some cases uveal

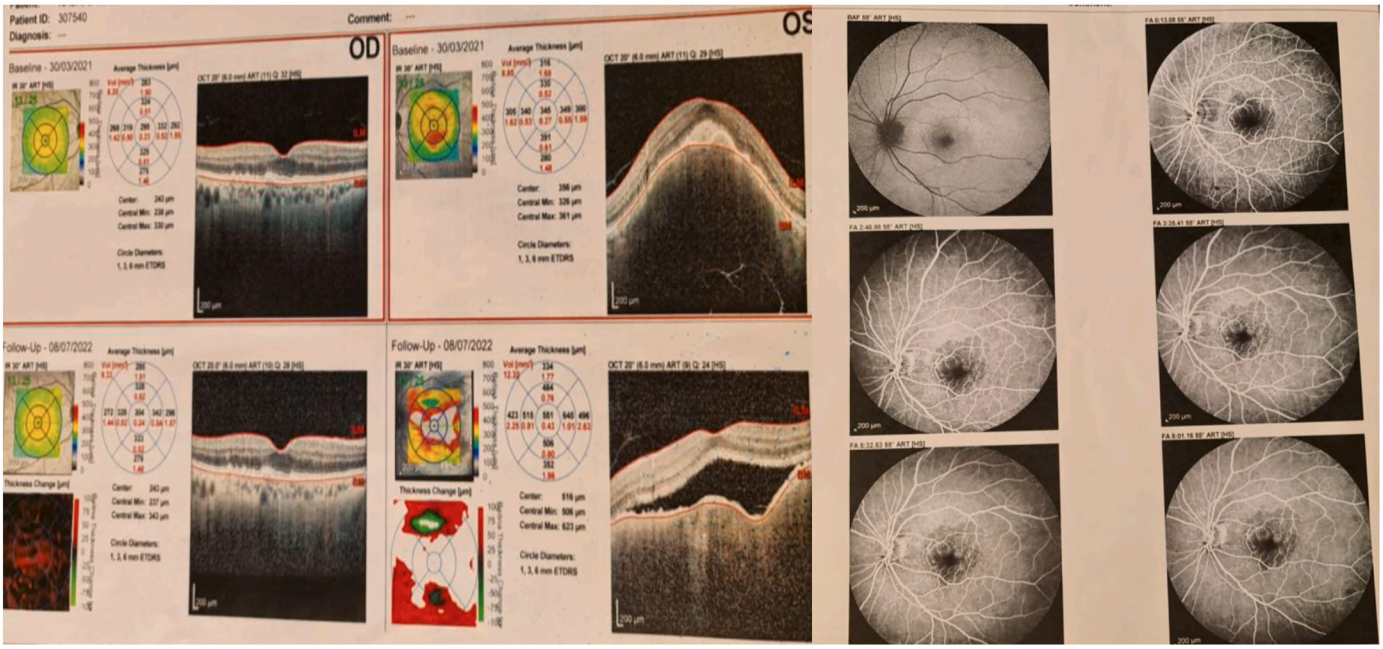

Fig. 1. Panel A (left side). Optical Coherence Tomography (OCT) of a 74-year-old man with uveal metastasis. OCT shows left retinal detachment with subretinal hemorrhage in the left eye and posterior vitreous detachment.
Panel B (Right side). Fluorescein angiography (FA) images of the eyes at different times showing areas of leakage and supporting the OCT findings. Top Row: initial FA images, showing the retinal blood vessels. Middle Row: mid-phase FA images, showing further details of the retinal vasculature. Bottom Row: late-phase FA images, showing areas of leakage indicating retinal pathology.

metastases are discovered before PC. Furthermore, bilateral metastases were found more frequently in females compared to males (21 % vs 11 %).[5] These metastasis manifest in multiple ways: limited ocular motility (54 %), proptosis (50 %), blepharoptosis (49 %), palpable mass (43 %), blurred vision (23 %), pain (17 %), visible lump (17 %), enophthalmos (11), diplopia (9 %). Even glaucoma can be present either due to direct invasion of the filtration angle or due to its obstruction by tumor cells.[7]

Treatment of uveal metastasis is typically palliative.[8] These tumors are very radiosensitive, and radiotherapy is preferred over surgery. External beam radiation therapy (EBRT) is an effective palliative treatment. If EBRT fails, plaque radiotherapy can be an alternative. Main differences between these two modalities are that EBRT is for outpatients during 3–4 weeks while plaque radiotherapy is for inpatients during 3–4 days.[9]

Radiotherapy is mainly delivered through a dose varying between 30 and 40 Gy (Gy) in 20 fractions (2Gy each). It is usually well tolerated and efficient with an overall response rate of around 90 % and a complete response rate of 61 %. Complications were rarely noted and very limited (cataract, radio-induced retinopathy and glaucoma) occurring in 6–42 months after the treatment.[9] Some studies might even suggest delivering a unilateral field with 40 Gy for unilateral choroidal metastasis without sparing the contralateral choroid as it seems to be effective in destroying possible contralateral micrometastasis and may lower the risk of late side effects as compared to bilateral fields. Further techniques showing promising results are being used, such as the association of radiotherapy and chemotherapy, however no sufficient data has yet been published for it to be introduced to the guidelines of treatment.

Finally, for metastatic prostate cancer (PC), ocular metastasis can be treated solely with radiotherapy, following the general treatment approach for all metastatic eye diseases, regardless of the primary cancer site or type. Alternatively, radiotherapy can be combined with androgen deprivation therapy (ADT), or ADT can be used alone if the metastatic prostate cancer is castrate sensitive. Once the cancer becomes castrate-resistant, ADT is no longer effective, and radiotherapy (either external beam radiotherapy [EBRT] or plaque radiotherapy) remains the last proven and effective treatment modality.[4] Moving on to the outcome, metastatic cancer to the eye and uvea is in most cases suggestive of a poor life prognosis: nearly half of the patients die after one year and the 5-year survival rate is around 25 %.[10] Even though there are some differences in survival chances depending on the primary tumoral site, all the statistics are pejorative and tend to high mortality rates.

CRediT authorship contribution statement

Ernest Diab: Writing – original draft, Writing – review & editing. **Lynn Abi Khalil:** Resources, Writing – review & editing. **Georges Baaklini:** Resources, Writing – original draft. **Antoine Chartouni:** Resources, Writing – original draft. **Joseph Kattan:** Supervision, Validation.

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