Granulomatous Inflammation after brachytherapy for uveal melanoma

Date of meeting	May 26th-27th2022
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Case number	B-2114143
Material distributed	1, H&E

Clinical History:

A 71-year-old Caucasian male was referred to the University Hospitals Leuven in January 2022 for enucleation of his right eye.

Four years prior, the patient was diagnosed with a choroidal melanoma (classified as T3a) (10-2018). For this diagnosis, he received brachytherapy (Iodium 125 plaque for a total of 70 Gray, 11-2018), which successfully stopped the tumor growth, but lead to a retinal detachment with complete loss of visual acuity. Intra-ocular pressure remained within the acceptable range under topical therapy.

A follow-up MRI scan revealed a lesion of suspected relapse (11-2021). Further systemic workup showed no evidence of lung or liver metastases.

The patient´s medical history includes arterial hypertension, liver steatosis, and chronic obstructive pulmonary disease.

Ophthalmic pathology

Macroscopy:

Right eye measuring 23x22x23mm. No evidence of extra-ocular extension of the tumor. Temporal zone completely scarred. Optic nerve measuring 12x5x5mm: atrophic aspect. Cornea measuring 12x11mm, transparent with prominent arcus senilis. Pupil: constricted, 1.5mm. Mature brown cataract. Complete retinal detachment.

After horizontal lamellation a choroidal tumor was observed:

1. temporal white nodulus 8x4mm
2. peripapillary white lesion 12x8mm

Microscopy:

The anterior segment shows a normal cornea with thinned endothelium and a closed anterior chamber angle due to tissue overgrowth between iris and cornea. The iris shows superficial neovascularization along with diffuse focal lymphocyte infiltration. There is no evidence of trabecular invasion.

The posterior segment shows a pigmented choroidal lesion (4x5mm) of mixed cellular appearance:

1. densely pigmented epitheloid large cells with pleiomorphism and round large nucleolus with conspicuous atypia.
2. large spindle-shaped cells with little pigment and large oval nuclei with signs of pleiomorphism.

MelanA staining was positive, confirming the melanocytic origin of the tumor. The tumor nests are surrounded by infiltrating lymphocytes (CD 3 T lymphocytes). The Ki67 staining in this zone shows 1-

5% tumor cells in active cell cycle in hot spot areas. Mitoses (Phosphohistone H3 staining) were rarely detected (1-6 cells per 10 HPF (x20)). There was no recognisable intravascular infiltration.

Away from the tumor, the choroid shows marked infiltration by lymphocytes, plasma cells and scattered eosinophils, along with clusters of histiocytes. Throughout the choroidea there are more than 40 positive cells in 1 HPV.

The retina was completely detached, funnel shaped with only a few nuclear layers still recognizable. We saw atrophy of the inner and outer layers, as well as gliosis located in a tissue zone extending from the ora serrata (cyclic membrane). Subretinal eosinophilic material with blood residues were also detected.

No extra/intrascleral extensions were detected. However, the sclera and episclera show several zones of granulomatous inflammation in the regions adjacent to the tumor. These zones consist of large multinucleated giant cells accompanied with focal Schaumann and asteroid bodies surrounded by follicular reaction with T-/B-lymphocytes and plasma cells. The plasma cells stained positive for IgG and half of them for IgG4. PAS staining shows no clear patterns in terms of loops/networks in the tumor and is negative for fungi. Polarized light highlighted irregular material in selected giant cells.

The optic nerve shows pronounced atrophy with no signs of tumor infiltration.

Discussion:

This case represents a rare evolution after unsuccessful brachytherapy for choroidal melanoma showing choroidal, scleral and episcleral non-necrotizing granulomatous inflammation.

Non-necrotizing granulomatous inflammation is caused by a variety of conditions including infection, autoimmune, toxic, extra-corporal foreign-bodies and neoplastic conditions. The tissue reaction pattern narrows down the pathologic and clinical differential diagnosis. [1]

1. *Infectious granuloma after brachytherapy for choroidal melanoma*
There is one case published with documented fungal granulomas post brachytherapy in an eye with choroidal melanoma [2]. Due to the geographical relationship between the granuloma and ruthenium plaque, Ocera et al suggested intraoperative implantation and subsequent fungal growth. However, our case did not show evidence of an infectious origin. PAS and Ziehl staining were negative.

2. *Foreign-body granuloma after brachytherapy for choroidal melanoma*
Foreign-body giant cells are histiocytic reactions due to inert material without an adaptive immune response, for example, suture, talc. A collection of histiocytes surround the foreign material and as single histiocytes are unable to phagocytize the foreign material alone.
A foreign body reaction to the primary treatment (local application of Iodium plaque and suture material) could explain the topographical relation of the granulomatous lesions with regards to the treated area. This hypothesis is supported by the birefringent nature of the observed granulomas and bears resemblance to a case published by Ayres et al.[3] In contrast, our case shows multiple smaller lesions rather than a single large granuloma.
Foreign-body granuloma formation has also been described in other organ systems after brachytherapy. Willems et al documented multiple peritoneal foreign-body granuloma after selective internal radiation therapy for intrahepatic cholangiocarcinoma. [4] Foreign bodies accompanied with granulomatous reaction were also observed in the prostatic ducts after brachytherapy with Iodine-125 for squamous cell carcinoma. [5] Even though microscopically our case showed no definitive foreign material, the described histopathology with presence of histiocytes and giant cells that are characteristically found in foreign body granuloma is congruent with this hypothesis.

3. *Immune generated granulomas after brachytherapy for choroidal melanoma*

Immune granulomas are histologically characterized as necrotizing or non-necrotizing. Non-necrotizing granulomas consist of a collection of epithelioid histiocytes and giant cells with minimal peripheral chronic inflammation, as in our case.

The typical example is sarcoidosis with its non-caseating epithelioid granulomas and multinucleated giant cells with intracytoplasmic inclusions such as asteroid bodies, crystalline inclusions and Schaumann bodies in a background of lymphoid cells, similar with our case.

However, the finding of Schaumann bodies is not specific for sarcoidosis as neither is the diagnosis of sarcoidosis determined solely by pathological appearance. [6]

Elevated ACE levels >50% above the upper limit of normal favour a diagnosis of sarcoidosis over granulomatous lesions.[1] Serum ACE levels were not yet known at the time of writing.

Thus, the focal presence of ocular non-caseating granulomas without other systematic manifestations does not support the diagnosis of sarcoidosis. In addition, the typical clinical presentation of ocular sarcoidosis is the manifestation of anterior/intermedia/posterior uveitis or chorioretinitis. Episcleral or scleral presentation as isolated manifestation for ocular sarcoidosis have not been reported.

Sympathetic ophthalmia must also be considered in our case. Penetrating eye injury, intraocular surgery or brachytherapy can cause an autoimmune hypersensitivity response at the uveal level in the traumatised eye, which is followed by a similar response against the fellow ("sympathising") eye. [7] The inflammation is usually granulomatous and the choroid is diffusely thickened with lymphocytes, nests of epithelioid cells and multinucleated giant cells, which often contain melanin pigment. The inflammatory process usually does not involve the choriocapillaris or the retina. Dalen-Fuchs nodules, which are clusters of epithelioid cells containing pigment lying between the RPE and Bruchs' membrane. [8]

Ahmad et al reported a case of sympathetic ophthalmia six month after ruthenium plaque brachytherapy for choroidal melanoma. [9] Margo et al published a case of early sympathetic ophthalmia after proton-beam radiation for choroidal melanoma. [10] They reported an infiltration of lymphocytes, epitheloid histocytes with multinucleated giant cells containing pigment in the tumor and surrounding choroid.

However, in our case, the granulomas are found at the level of epi-/sclera and did not show pigment-containing epitheloid, giant cells in the uveal tract or between RPE and Bruchs' membrane.

Additionally, the fellow eye did not show any clinical manifestations of sympathetic ophthalmia until today. The diagnosis is therefore rather unlikely for our case although there is a small probability of an unilateral sympathetic ophthalmia as early stage of disease as suggested by Albert et al. [11]

4. *Toxic granuloma brachytherapy for choroidal melanoma*

During brachytherapy normal tissue is inadvertently radiated. The impairment of soft tissue is related to the radiotherapy dose, radiotherapy projection, and the concurrent use of chemotherapy. Yang et al documented a nasopharyngeal granulomatous mass after radiotherapy for nasopharyngeal carcinoma as a delayed post-radiation side effect. They proposed that the mechanisms of nasopharyngeal granuloma may occur from vascular hyalinization, microcirculation disorder, immunodepression, inflammation, and fibroblast formation. [12]

Therefore, a granulomatous reaction as an accompanying reaction after scleral and episcleral radio-necrosis should also be considered as the aetiology for our case.

Conclusion: eyeball after radiotherapy: still active uveal malignant choroidal melanoma with granulomatous inflammation from uncertain origin.

Reference:

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