Ocular Oncology and Pathology

Case Series

Ocul Oncol Pathol 2024;10:227–233
DOI: 10.1159/000541063

Received: September 8, 2023
Accepted: January 19, 2024
Published online: September 27, 2024

Two Cases of Intraocular Undifferentiated Pleomorphic Sarcoma

Sodaba Khatab[a] Johanna Maria Colijn[b] Nicole Naus[b]
Robert M. Verdijk[a, c, d] Gijsbert Hötte[a]

[a]Department of Oculoplastic, Orbital and Lacrimal Surgery, The Rotterdam Eye Hospital, Rotterdam, The Netherlands; [b]Department of Ophthalmology, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands; [c]Section Ophthalmic Pathology, Department of Pathology, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands; [d]Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

Keywords
Adult ocular oncology · Adult ocular tumours · Intraocular tumours · Ocular oncology · Orbital tumour · Sarcoma

Abstract
Introduction: Undifferentiated pleomorphic sarcoma (UPS), formerly known as malignant fibrous histiocytoma, is a high-grade soft tissue sarcoma arising from mesenchymal stem cells. UPSs are rare and account for about 5% of all soft tissue sarcoma. UPSs arising in the head and neck are especially rare, comprising 1–3% of all UPSs. ***Case Presentation:*** In this report, we describe 2 cases of intraocular UPS. Both cases concern 68-year-old males: one developing a UPS in an eviscerated socket after a chronic fibrinous inflammation and the other years after ocular trauma. ***Conclusion:*** Our cases may support the hypothesis of chronic inflammation playing a role in sarcoma formation as they are characterized by a longstanding history of (surgical) trauma with signs of chronic inflammation and phthisis bulbi.

Introduction

Undifferentiated pleomorphic sarcoma (UPS), previously known as malignant fibrous histiocytoma (MFH), is a mesenchymal neoplasm which shows no identifiable cellular differentiation when analyzed by presently available immunohistochemical technology. UPSs are rare and account for less than 5% of all soft tissue sarcomas (STSs). UPSs arising in the head and neck are extremely rare, comprising 1–3% of all UPSs [1–3]. In this report, we describe two rare cases of intraocular UPS.

Case Report

Case 1

The first case involves a 68-year-old male with a medical history of diabetes mellitus and coronary and carotid artery stents. His ophthalmic history included cataract surgery in the left eye 3 years prior, followed by multiple procedures to treat persistent and fulminant fibrin formation in the anterior chamber, including multiple YAG laser capsulotomies, IOL explantation, fibrinolysis, synechiolysis, and vitrectomy (Fig. 1a).

karger@karger.com
www.karger.com/oop

Correspondence to:
Robert M. Verdijk, r.verdijk@erasmusmc.nl

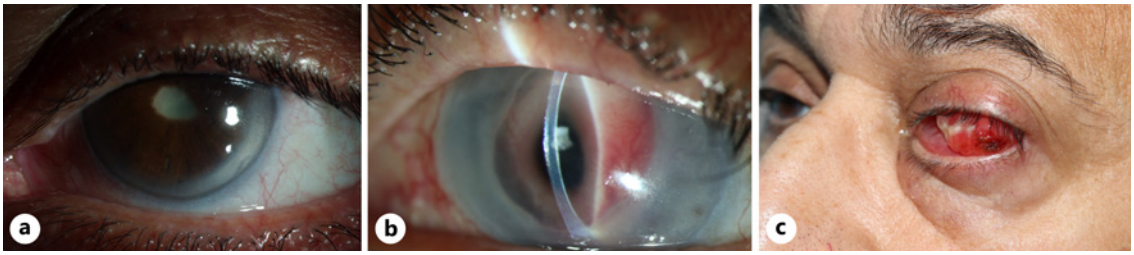

Fig. 1. Clinical photos of patient 1, left eye. **a** Pre-pupillary fibrotic plaque and posterior synechiae. **b** One year later, rubeosis of the iris and edema of the peripheral cornea. **c** Left socket: 6 months after evisceration, protrusion of the implant is noted with redness and swelling of the conjunctiva.

Subsequently, the patient had developed neovascular glaucoma and eventually phthisis bulbi (Fig. 1b).

Because of increasing pain, he was referred to the Department of Oculoplastic, Orbital, and Lacrimal Surgery. An uncomplicated evisceration procedure was performed and a spherical silicone implant was placed. Intra-operatively, severe fibrosis and calcification of the uveal tissue were noticed. The removed cornea and intraocular contents were sent for histopathology by a specialized ocular pathologist. It showed a bullous keratopathy and extensive retinal pigment epithelial proliferation with epithelial-mesenchymal transition and co-expression of smooth muscle markers, which was attributed to the history of intra-ocular inflammation.

Six months after the evisceration, the patient presented with progressive protrusion of the implant (Fig. 1c). B-scan ultrasound showed a mass anterior to the spherical implant with an irregular hyperechoic aspect. Magnetic resonance imaging (MRI) of the orbit showed a mass in the anterior orbit, extending into the intraconal space with low intensity on T1-weighted images, intermediate intensity on T2-weighted images and high contrast enhancement (Fig. 2).

Biopsy was performed and histopathological examination showed moderate cytological and nuclear pleomorphism with few mitoses and included spindle cells, epithelioid cells, and few histiocytes. Although some cytoplasmic vacuolation was noted no pleomorphic lipoblasts were found to support a diagnosis of pleomorphic liposarcoma. Immunohistochemical staining demonstrated strong immunopositivity for SMA and weak to moderate positivity for CD68 and caldesmon. The cells were negative for pankeratin, S-100, melan-A, desmin, MYF4, MyoD1, CD34, actin, and STAT6. In situ hybridization showed no MDM2 gene amplification or SS18 gene breaks. Using DNA methylation profiling, the tumor was classified as an undifferentiated sarcoma with a calibration score of 0.99 using the DKFZ sarcoma methylation classifier v12.2 (Fig. 3). The CNV plot showed a complex pattern of chromosomal losses and gains. RNA sequencing using a 40-gene panel did not reveal any fusions.

The patient was discussed in the national sarcoma network meeting and referred to the oncology head and neck surgery team. He underwent radiotherapy (50 Gy in 25 fractions), which failed to reduce the tumor size, followed by palliative exenteration. The final histopathological diagnosis was UPS. Revision of the histopathology from the eviscerated tissue corrected the original diagnosis to undifferentiated sarcoma.

Case 2

The second case concerns another 68-year-old male, with a general medical history of hypertension and eczema. His ophthalmic history started at the age of 13 when he suffered penetrating trauma of his left eye from a tree. Since then, he had no light perception and a distorted pupil. He had not received any surgery at the time, nor regular checkups by an ophthalmologist over the years.

He was referred because of leukocoria due to a growing white opacity in the anterior chamber of the left eye for 6 months. The eye had become more painful over time. By the time of presentation at the ophthalmology department, the intraocular lesions had already extended extraocularly. Examination showed complete opacification of the cornea that seemed to arise from the endothelium. Furthermore, two lesions were noted on the nasal conjunctiva, associated with deep vascularization and hyperemia (Fig. 4). The intraocular pressure was 27 mm Hg. Because fundoscopy was not possible, an ultrasound was performed, which showed a dense mass in the anterior chamber as well as under the nasal conjunctiva. Timolol and dexamethasone drops were started as well as lubricants to reduce the pain.

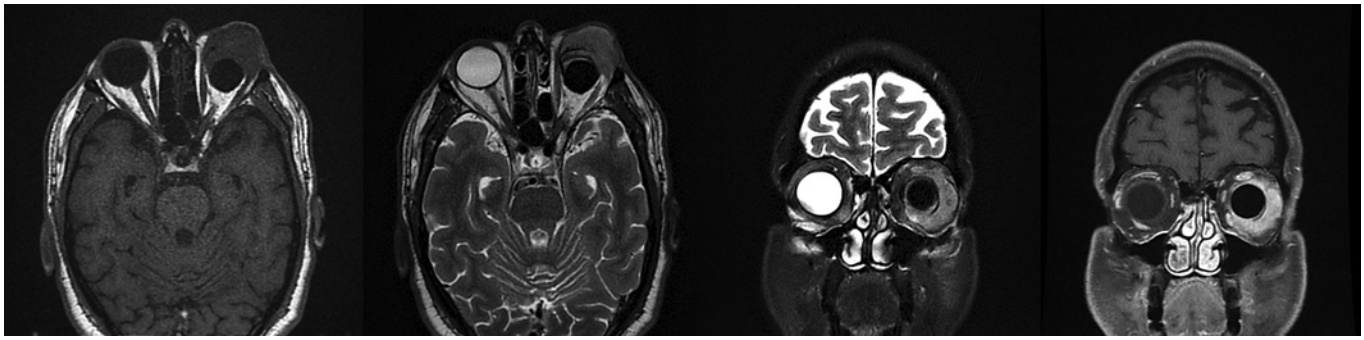

Fig. 2. Patient 1, MRI: mass in the left orbit, located anteriorly to the implant. The lesion demonstrates low intensity on T1-weighted images, intermediate intensity on T2-weighted images, and high contrast enhancement.

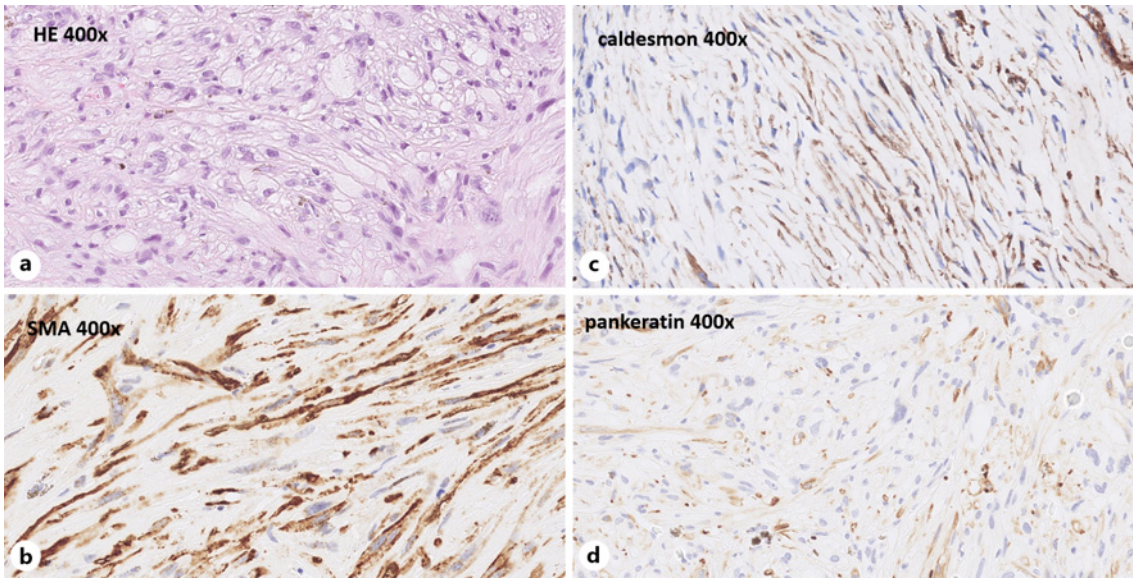

Fig. 3. Patient 1, histopathology of the exenterated tissue. **a** Cytological and nuclear pleomorphism, spindle cells, epithelioid cells, and histiocytes. SMA (**b**) and caldesmon (**c**) show moderate positive staining. **d** Keratin stain was interpreted as aspecific.

Anterior chamber tap resulted in a dry tap. The two lesions in the nasal conjunctiva were biopsied and histopathology was interpreted as a poorly differentiated adenocarcinoma of unknown origin. Immunohistochemistry showed no support for the origin of the lungs or prostate.

MRI of the orbit showed a retro-bulbar tumor with extension into the orbit and optic nerve (Fig. 5). PET-CT showed increased metabolic activity in the left orbit, but no lymphadenopathy in the neck or thorax.

The patient underwent an exenteration of the left orbit. Histopathology was strongly suspected for pleomorphic sarcoma (Fig. 6). Immunohistochemistry did not show a pattern suspect for metastatic disease to the eye with negative staining for pankeratin, BerEp4, P40, TTF1, CDX2, PSA, GATA3, PAX8, androgen receptor, SOX10, and HMB45. In situ hybridization did not show SS18 gene breaks. Based on the methylation array, the closest methylation pattern was of an undifferentiated sarcoma, albeit with a calibration score of 0.65 using the DKFZ sarcoma methylation classifier v12.2. The low score may be due to suboptimal DNA quality. The CNV plot showed a complex pattern with chromosomal losses of 1p, 9p, and 13q and gains of 5p and 7p as is frequently seen in undifferentiated sarcoma (Fig. 6).

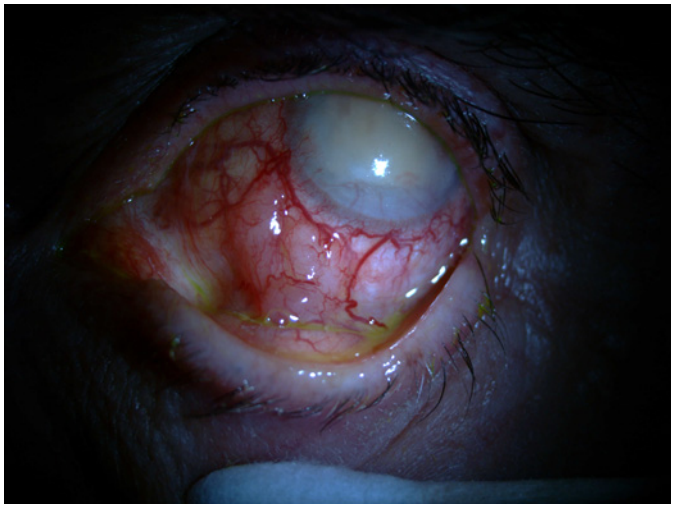

Fig. 4. Patient 2, left eye: opacity in the anterior chamber and conjunctival lesions and hyperemia.

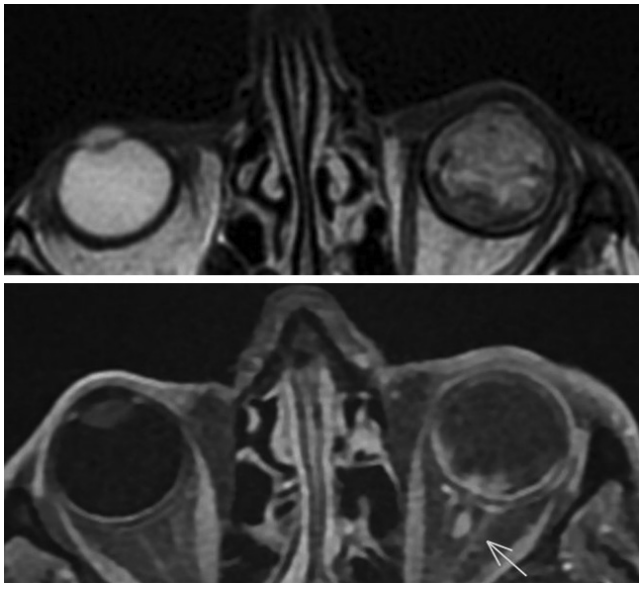

Fig. 5. Patient 2, MRI: tumor located at the posterior aspect inside the left globe (**a**) and the extension into the optic nerve (**b**) (arrow).

After initial healing, our patient underwent radiotherapy 33 × 2 Gy. Six months postoperatively, MRI showed no signs of residual lesion and a facial prosthesis was fitted for cosmetic reasons. A year after surgery he developed an ulceration of the socket, but MRI showed no signs of local recurrence of the tumor. Necrosis of the orbital tissues was removed and he underwent reconstruction by the plastic surgeon. Imaging of the chest at the same time showed multiple intra-pulmonary and pleural noduli, highly suspected for metastatic disease. Three months later, this was confirmed on another CT scan of the chest by evident growth of the lesions, for which he will receive chemotherapy.

Discussion

UPS, formerly known as MFH, is a high-grade aggressive STS. After reclassification in 2002, the World Health Association (WHO) divided MFH into more specific diagnoses based on immunohistochemistry, with UPS representing the tumor not meeting any specific diagnostic criteria. Mesenchymal stem cells are the most likely origin of the tumor, which can affect soft tissues, bones, and retroperitoneum, and can metastasize to several organs. The extremities are the most commonly involved location (55%), followed by the trunk (35%), retroperitoneum (9%) and left atrium (1%) [4]. To the authors' knowledge, no prior intraocular cases have been published.

The estimated incidence of all UPSs is 30:1,000,000 and for head and neck approximately 1:1,000,000 [5–7]. Incidence is higher in males, especially white males, and increased with age [3].

In the field of ophthalmology, UPS is extremely rare. Reviewing the literature is difficult because up to 2002, UPS was grouped together with other sarcoma subtypes into the group of MFH. Since the reclassification, few case reports have been published, describing primary UPS in the orbit [8], or metastasis of UPS to the orbit [9]. Furthermore, two primary eyelid skin UPSs have been described [10, 11] and recently, a case report on epibulbar/conjunctival UPS has been published [12].

We found 1 case report describing UPS in a previously eviscerated socket after recurring inflammatory eye disease. However, in this case, the tumor was found 8 years after a bulbar evisceration had been performed. The case report does not mention if the eviscerated specimen from 8 years ago was sent for pathology, but given the time frame, it is unlikely that the sarcoma was already present at the time of the initial evisceration [13]. As for other types of sarcoma, intraocular localization has been rarely described in rhabdomyosarcoma [14] and synovial sarcoma [15, 16]. These diagnoses were excluded in our cases using molecular studies.

In general, evaluation and workup of UPS includes imaging of the primary tumor, lymph nodes, and distant metastases. A multidisciplinary team specialized in sarcoma should be involved in the treatment decisions. The standard of care for UPS is en bloc excision with microscopically negative margins. Adjuvant radiotherapy is

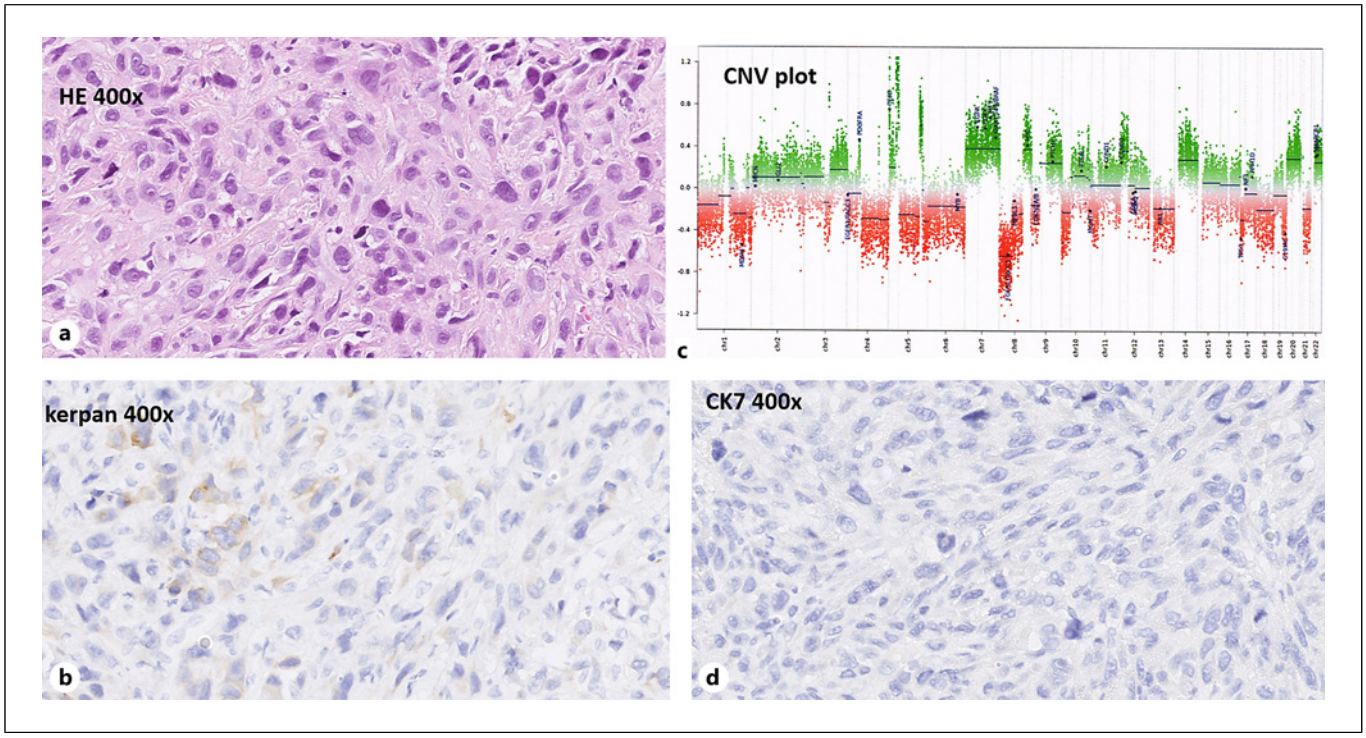

Fig. 6. Patient 2, histopathology of the exenterated tissue. **a** Cells with large nuclei, vacuolization, and inconspicuous nucleoli in ample eosinophilic cytoplasm. **b**, **d** Pankeratin shows weak positive staining; keratin 7 and other keratins were negative. **c** The CNV plot of the methylation profiling shows losses of 1p, 9p, and 13q and gains of 5p and 7p, a pattern that can typically be seen with pleiomorphic undifferentiated sarcoma.

indicated if resection margins are smaller than 1 cm or if the tumor involves bone, major blood vessels or nerves. Adjuvant chemotherapy is employed for advanced, widespread or unresectable UPS. Neoadjuvant (chemo-) radiation can be considered for the tumors deemed unresectable in order to reduce the tumoral mass and make them operable [17].

The 5-year overall survival rate for UPS is 56.3% [18]. UPS has a high rate of local recurrence and metastasis. Distant metastasis-free survival and local recurrence-free survival rates are 53.4% and 67.2%, respectively [18]. Approximately 5% of patients have metastases at presentation, with the lungs being the most common site [18]. The 5-year disease-specific survival and recurrence rates may be worse in radiation-associated UPS [19].

The differential diagnoses of UPS include sarcomatoid carcinoma (or spindle cell carcinoma), melanoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma, malignant peripheral nerve sheath tumor, giant cell lymphoma, or metastases [6, 7].

Histopathologically, UPS is diagnosed by excluding other well-classified STSs [1, 2].On light microscopy, UPS does not have a specific morphology. It is comprised of marked cytological and nuclear pleomorphism, often with bizarre giant tumor cells, spindle cells and rounded histiocyte-like cells [5].

A panel of immunohistochemical markers is used to exclude other malignancies. This panel includes keratins to exclude sarcomatoid carcinoma; S-100, melan-A, and HMB45 to exclude melanoma. Other STSs are excluded using the following markers: CD31 for angiosarcoma, CD34 for dermatofibrosarcoma protuberans, CD68 for histiocytic sarcoma, factor XIIIa for dermatofibromas and Bcl-2 for solitary fibrous tumors. Desmin, SMA and h-caldesmon are used to eliminate the diagnoses of pleomorphic leiomyosarcoma and pleomorphic rhabdomyosarcoma; S-100 and SMA to exclude pleomorphic liposarcoma. In case 1, the positive staining for SMA and weak positivity for caldesmon prompted a differential diagnosis of leiomyosarcoma. However, negative staining for both actin and desmin in combination with a methylation profiling match with undifferentiated sarcoma instead of with the well-recognized methylation profile of leiomyosarcoma resulted in a preferred diagnosis of pleomorphic undifferentiated sarcoma. In case 2 that developed metastatic disease to the lung extensive additional immunohistochemistry was performed

in order to exclude undifferentiated carcinoma especially because of the presence of epithelioid cells. In this case, the methylation profiling did not show a perfect match to undifferentiated pleomorphic sarcoma, most likely due to low quality of the DNA extracted. However, the CNV plot did demonstrate a profile that was supportive of this diagnosis. Especially relevant to the orbit is STAT6 staining to exclude malignant solitary fibrous tumor. Finally, Ki-67 is a useful marker to evaluate neoplastic cell proliferation, which correlates with the histological grade [20–22]. Fluorescent in situ hybridization studies may be used to exclude synovial sarcoma and MDM2 amplification to exclude liposarcoma. More recently, methylation profiling has proved valuable for the classification of poorly differentiated sarcoma [23, 24].

The exact pathogenesis of UPS remains unknown. Besides various genetic aberrations [25], radiation therapy is a known risk factor for STS. Around 1–3% of patients diagnosed with any sarcoma, had a history of radiation therapy. Specifically, in a series of 1,068 UPS cases, 5.1% of the patients had a prior history of radiation [3, 19]. There is also anecdotal evidence that UPS may arise at the site of chronic ulceration or scarring [5, 10].

Although the relation between past injury and the development of malignancies is controversial, there are several inflammatory pathways that may have a role in sarcomagenesis [26, 27]. There are case series suggesting repetitive insult to the musculoskeletal system contributes to sarcoma development [26], in particular after orthopedic implant placement [28–30]. Repetitive trauma has also been linked to the development of Marjolin's ulcer, which is a cutaneous squamous cell carcinoma that arises in the setting of previously injured skin, longstanding scars, and chronic wounds [31] and in Kaposi sarcoma [32].

Our cases may further support this hypothesis as they are characterized by a longstanding history of (surgical) trauma with signs of chronic inflammation and phthisis bulbi. Interestingly, post-traumatic ocular sarcoma has been well reported in cats [33–35].

In conclusion, UPS is an extremely rare tumor, which may develop in the context of a history of (surgical) trauma and longstanding intraocular inflammation. In our first case, signs of sarcoma were present in the evisceration specimen, which underlines the importance of histopathology of eviscerated material, even if a malignancy is not expected.

Statement of Ethics

This study protocol was reviewed and approved by Ms. Susan Marinissen the head of the Rotterdam Ophthalmic Institute (ROI) on April 4th. Written informed consent was obtained from the patients for participation and for publication of the details of their medical case or any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

We did not receive any funding for this article.

Author Contributions

Gijsbert Hötte, Nicole Naus, and Robert M. Verdijk contributed to the conception and design of a case series describing our patients with intraocular sarcoma and critically reviewed the manuscript multiple times. Sodaba Khatab, Johanna Maria Colijn, and Robert M. Verdijk contributed to the design, data collection, and drafting of the manuscript. Sodaba Khatab and Johanna Maria Colijn adjusted and reviewed the manuscript. All authors give their final approval for the version to be published and agree to be accountable for all aspects of the article.

Data Availability Statement

Patient data are saved in the electronic patient files and are not openly available. Further inquiries can be directed to the corresponding author. All data retrieved from existing literature are openly available.

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