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Primary intraretinal clear cell sarcoma presenting as an amelanotic circumpapillary tumor

Megan S. Steinkerchner [a], Shizuo Mukai [a], Anna M. Stagner [b,*]

[a] Retina Service, Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, 02114, USA
[b] David G. Cogan Laboratory of Ophthalmic Pathology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, 02114, USA

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ABSTRACT

Purpose: To report a novel case of clear cell sarcoma presenting as an intraocular mass in a young adult female.
Observations: A 34-year-old female presented to the Retina Service as an emergency department referral for an intraocular lesion noted in the left eye. The patient endorsed progressively decreased vision in the left eye for three months duration. Fundus examination of the left eye was notable for a circumpapillary, retinal amelanotic mass with vitreous seeding. Due to concern for retinoblastoma and poor visual potential, the decision was made for primary enucleation. Initial histopathologic and immunohistochemical analyses demonstrated a primitive-appearing, epithelioid to spindled, intraretinal malignancy, with expression of all melanocytic markers by immunohistochemistry. Molecular genetic testing detected an *EWSR1::ATF1* fusion. The patient was diagnosed with clear cell sarcoma of the eye and systemic work up revealed no additional disease burden.
Conclusions and importance: Clear cell sarcoma is a soft tissue sarcoma that can present within the eye and should be included in the differential diagnosis of amelanotic intraocular (intraretinal) tumors, including those in adults with clinical appearances similar to retinoblastoma.

1. Introduction

Clear cell sarcoma (CCS), previously known as malignant melanoma of soft parts, is a rare sarcoma that represents 1 % of all soft tissue sarcomas [1] This soft tissue sarcoma typically presents as an indolent, painless mass infiltrating tendons and aponeuroses within the deep tissues of extremities in the young adult population. The mesenchymal neoplasm exhibits staining for melanocytic markers with immunohistochemical analysis and for this reason, presents a diagnostic challenge due to its significant overlapping morphologic and immunohistochemical features with melanoma, particularly with deep (i.e., arising in the subcutis or muscle and not within the epidermis/dermis) or metastatic melanomas. [2] Although 95 % of clear cell sarcoma cases arise within the extremities, the tumor can originate within visceral locations such as the kidney, gastrointestinal tract, and within the head and neck, including the orbit. [3] In this report, the authors describe, to their knowledge, the first case of intraocular clear cell sarcoma presenting as a circumpapillary, amelanotic retinal tumor in a younger adult.

2. Case report

A 34-year-old, Caucasian female presented to the Massachusetts Eye and Ear Retina Service as an emergency department referral due to concern for an intraocular tumor of the left eye. The patient endorsed a three months duration of progressively worsening vision and floaters in the left eye. She had not received a fundus examination in over 10 years and ocular history included refractive error of both eyes. The patient had no past medical history of a malignancy, and there was no family history of intraocular tumors, including retinoblastoma.

Upon initial ophthalmic examination, the Snellen visual acuity (VA) was 20/25 in the right eye and 20/150 in the left eye. Examination of the right eye was unremarkable. The left eye was notable for 1+ mixed pigmented cells in the anterior vitreous. Fundus examination of the left eye disclosed a 5.5 × 6 mm amelanotic, circumpapillary retinal tumor obscuring the optic disc that extended nasally with foveal involvement. The white retinal tumor displayed prominent dilated internal vasculature and vitreous seeding, most dense near the tumor (Fig. 1A). B scan ultrasonography showed a dome-shaped retinal lesion with low medium internal reflectivity overlying the optic nerve and macula that measured 3.51 mm in height (Fig. 1B). Fluorescein angiography revealed intrinsic

* Corresponding author. 243 Charles Street, Boston, MA, 02114, USA.
E-mail address: astagner@mgh.harvard.edu (A.M. Stagner).

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circulation within the retinal tumor (Fig. 1C) and optical coherence tomography revealed the lesion as primarily intraretinal in origin (Fig. 1D). Orbital imaging was recommended for further evaluation and the patient was discussed at multidisciplinary tumor board regarding possible management which included a biopsy, radiotherapy, and primary enucleation. The differential diagnosis of the retinal tumor included retinocytoma with malignant transformation into retinoblastoma, amelanotic uveal melanoma extending into the retina, or metastatic cutaneous melanoma; retinal astrocytoma or combined hamartoma were considered much less likely. The patient was lost to follow up for two months and returned for repeat evaluation with worsening vision and photosensitivity of the left eye. MRI brain and orbits revealed a retinal mass within the left eye near the optic disc, without obvious intraorbital or optic nerve involvement or a retrobulbar mass. VA in the left eye had deteriorated to counting fingers; no discernible changes in the retinal tumor were seen funduscopically at that time, although increased vitreous seeding was present. Due to the concern for retinoblastoma and poor visual potential, along with patient preference, the decision was made for primary enucleation of the left eye.

Histopathologic examination of the enucleated eye revealed a round, blue-cell tumor within the retina of the macula and adjacent to the optic nerve head, with an apparent microscopic connection to the choroid near the optic nerve head with a break in Bruch's membrane. Tumor invaded the pre-laminar optic nerve head up to the lamina cribrosa without definite post-laminar extension. At higher magnification, cytomorphologic examination revealed hyperchromatic, epithelioid to focally spindled cells, many with prominent nucleoli, with scant to moderate amounts of pale eosinophilic to amphophilic cytoplasm, growing in sheets and forming vague trabeculae with a focally myxoid background. Few mitotic figures were present, but no necrosis was seen within the tumor. Vascular pseudorosettes were present, but no true Flexner-Wintersteiner, Homer-Wright, or multilayered neuroepithelial/embryonal-type rosettes or fleurettes were identified (Fig. 2).

Immunohistochemical evaluation showed the neoplastic cells demonstrated diffuse staining for SRY-box transcription factor 10 (SOX-10), S100, and microphthalmia-associated transcription factor (MiTF), with staining of the majority of cells for Mart-1/Melan-A and HMB-45 (Fig. 3A–C). The tumor cells did not stain for preferentially expressed antigen in melanoma (PRAME) and had preserved expression of BRCA1-associated protein-1 (BAP1). V-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutant specific antibody for the V600E mutant was negative. Patchy staining for neuron specific enolase (NSE) and very focal staining for synaptophysin was noted. Expression of retinoblastoma protein (Rb) was preserved, as was expression of integrase interactor 1 (INI1), also known as SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) and brahma-related gene 1 (BRG1), by immunohistochemistry. No significant staining for CD99, desmin, paired-box gene 8 (PAX8), keratins, p63, or transducin-like enhancer of split 1 (TLE1) was seen in the evaluation for other sarcomas, primitive neuroepithelial or neuroectodermal tumors, or undifferentiated carcinomas. Ki-67 proliferation index was less than 5 %, relatively low for a small, round, blue-cell tumor and significantly lower than would be typical for retinoblastoma (Fig. 3D). Assays developed and performed at the Massachusetts General Hospital Center for Integrated Diagnostics using anchored multiplex polymerase chain reaction (PCR) technology with the ArcherDx platform and Illumina NextSeq next generation sequencing detected the presence of a fusion transcript involving *EWSR1* exon:8 and *ATF1* exon:4, without other reportable single nucleotide variants, insertions/deletions or copy number variants of known clinical significance, and with a low tumor mutational burden. Approximately 100 of the most common genes involved in cancer biology were interrogated, including of specific relevance to this case *RB1, GNA11, GNAQ, GNAS, BRAF* and *NRAS*.

The patient received a thorough systemic evaluation (whole body PET-CT and brain MRI) that revealed no additional sites of tumor burden, excluding a sarcoma metastasis to the eye. The patient was followed by the retina service for one year following the enucleation and the anophthalmic socket showed no evidence of disease clinically. CCS is a rare tumor in general and has not been described as a primary tumor in the eye, so the length of follow-up and use of imaging modalities is

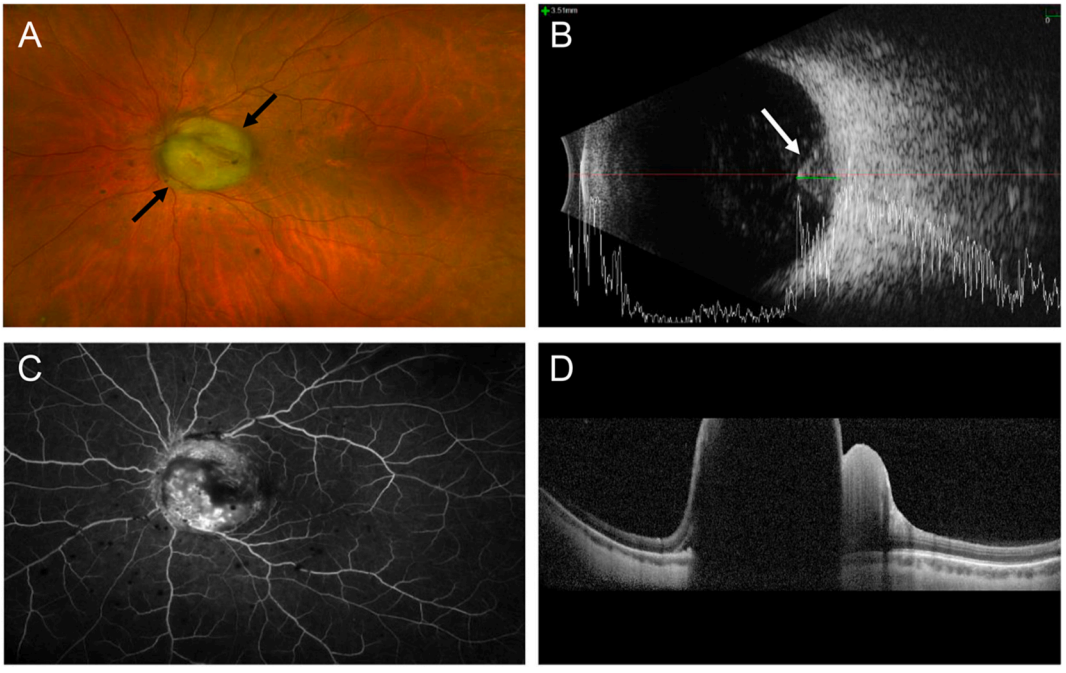

Fig. 1. **(A)** At initial evaluation, a wide field fundus photograph of the left eye showed a white, circumpapillary retinal mass (arrows) with vitreous seeding. **(B)** B scan ultrasonography showed a retinal mass 3.51 mm in height with low-medium internal reflectivity (arrow). **(C)** Fluorescein angiography demonstrated vessels within the lesion in the early venous phase, revealing intrinsic circulation within the tumor. **(D)** Optical coherence tomography (OCT) imaging revealed the lesion to be primarily intraretinal.

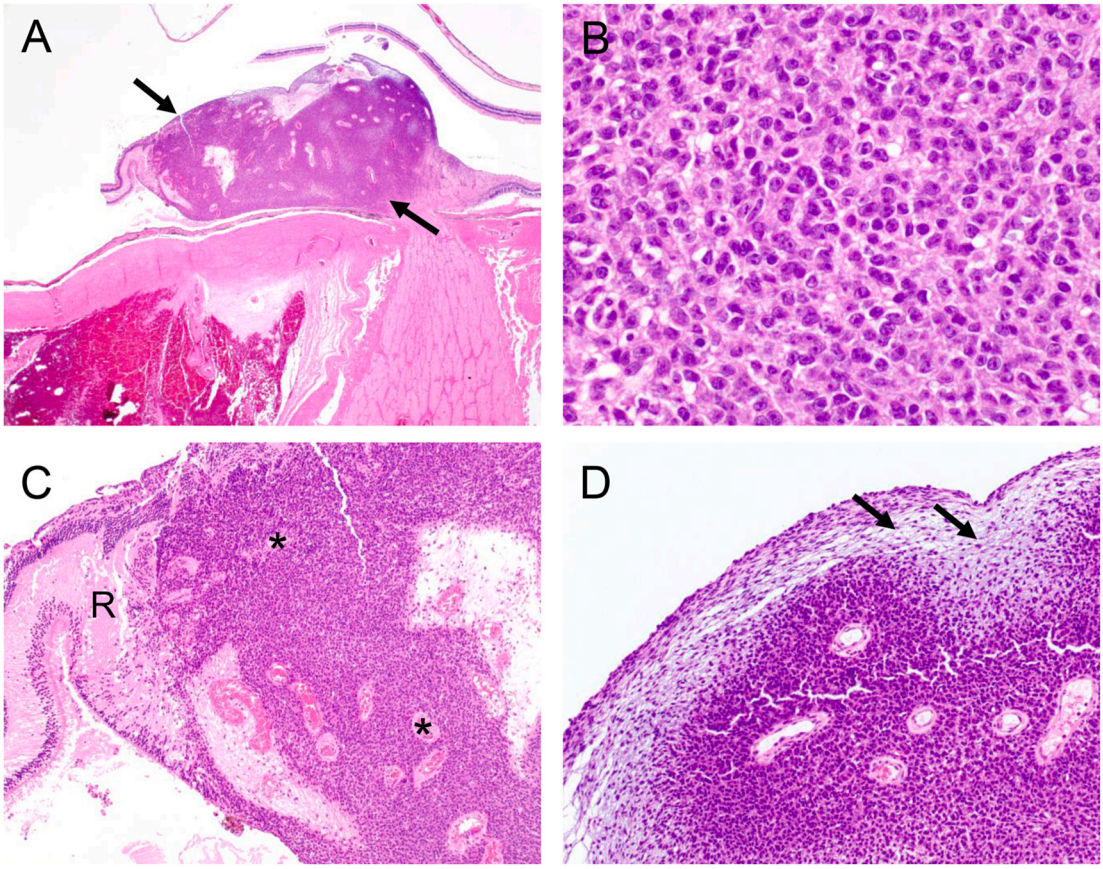

Fig. 2. (A) Hematoxylin and eosin (H&E)-stained section demonstrated a predominantly intraretinal neoplasm (arrows) comprised of primitive, round blue-cells (magnification 2x). **(B)** The epithelioid cells have prominent nucleoli and pale eosinophilic cytoplasm. Few mitotic figures are seen (magnification 40x). **(C)** Vascular pseudorosettes (asterisks) were present in the intraretinal tumor (R, retina; magnification 10x). **(D)** At its innermost aspect, the tumor was more spindled with a myxoid stroma (arrows) (magnification 20x). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

unclear, but the patient will continue to follow yearly with oncology near her home.

3. Discussion

Clear cell sarcoma is a rare, aggressive malignant neoplasm of the deep soft tissues, commonly originating in the extremities of the young adult, Caucasian population. CCS derives from neural crest cells in the mesenchyme and can present in locations including the upper and lower extremities, head and neck, and visceral sites such as the small intestine and pleura [3] The name clear cell sarcoma was derived from the often-seen histopathologic feature of clear cells (which are, ironically, not seen in the case presented herein) and prior to the introduction of advanced molecular diagnostics, the cancer was termed malignant melanoma of soft parts due to the identical immunohistochemical profile of CCS and melanoma. The tumor typically exhibits expression of the melanocytic markers HMB-45, Melan-A, and MiTF, along with the neural crest markers S-100 and SOX-10, in the majority of cases [4,5] A key genetic event in tumorigenesis is the chromosomal translocation (t12; 22) that results in the fusion of the Ewing's sarcoma breakpoint region 1 (EWS) and the cellular transcription factor (ATF1) in 90 % of cases [5] The EWSR1::ATF1 fusion oncogene constitutively induces the expression of MiTF in tumor cells, leading to tumor differentiation and melanocytic expression [6] The EWSRI and camp responsive element binding protein 1 (CREB1) translocation (t2;22) has also been shown to drive a minority of cases of CCS. [7]

CCS possesses a poor prognosis due to the early hematogenous spread to the lymphatic system and lungs. A previous case report by Nwanyanwu et al. noted choroidal metastases of CCS with concurrent spread to the thoracic vertebra, liver, spleen, and lymph nodes. [8] The patient described in the current report presented with an amelanotic retinal lesion and no other sites of tumor detection, suggesting the eye as the primary tumor site. Although primary intraretinal CCS has not been reported within the eye, previous cases of "primary intraretinal melanoma" or metastatic vitreoretinal melanoma without a known cutaneous primary may in fact have been CCS, prior to the availability of modern molecular diagnostic testing.

The clinical presentation of this case resembled retinoblastoma. Histopathologic examination along with appropriate molecular genetic studies were essential for diagnosis. Morphologically, retinoblastoma was not favored due to the absence of true rosettes, a relatively low mitotic rate/Ki-67 proliferative index with no apoptotic debris, and cytomorphology showing prominent nucleoli and significant pale eosinophilic cytoplasm, with cells focally set in a myxoid stroma; none of these features are typical of retinoblastoma. Similarly, medulloepithelioma was not favored due to the absence of multilayered rosettes, cysts, and neuropil. Sarcomas (e.g., Ewing's), central nervous system-type neuroectodermal tumors, metastatic disease, uveal melanoma, and metastatic cutaneous melanoma were considered on hematoxylin and eosin-stained sections. As with many fusion-driven sarcomas, cytomorphologically the cells of CCS characteristically have a uniform or monotonous appearance. Cytoplasm may be clear, but it is often pale eosinophilic and prominent nucleoli are common; mitoses are identifiable, although much less conspicuous than would be expected in metastatic melanoma or in many primitive small round blue-cell tumors including retinoblastoma. Although CCS and melanoma have identical

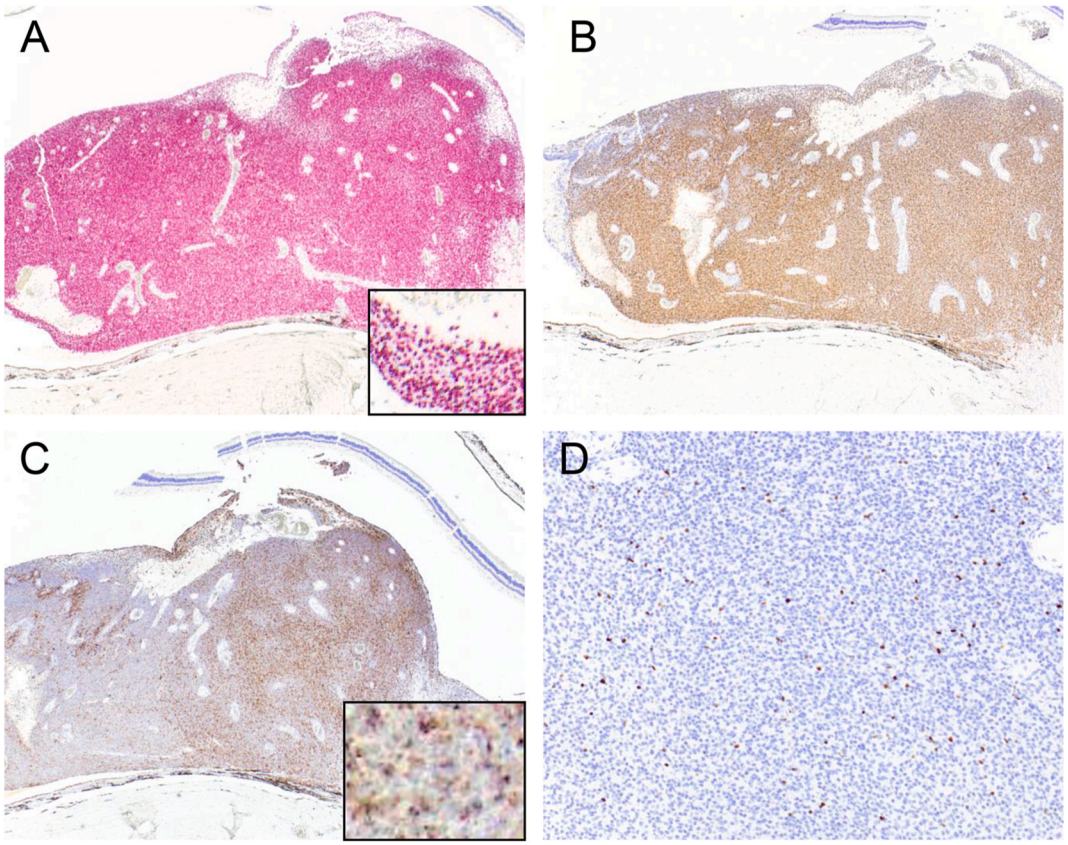

Fig. 3. (A) The tumor demonstrated diffuse nuclear staining for SOX-10 (red chromogen, magnification 4x, nuclear staining pattern shown in inset) and **(B)** MiTF (brown chromogen, magnification 4x). **(C)** There was variable staining for HMB-45 (brown chromogen, magnification 4x, cytoplasmic staining pattern shown in inset). **(D)** Ki-67 proliferative index was less than a few percent (brown chromogen, magnification 20x). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

or nearly identical immunophenotypes, molecularly, they are very different. Uveal melanoma is driven almost exclusively by initiating mutations in G-protein-coupled-receptor associated proteins (e.g., *GNAQ* and *GNA11*) and arises where the normal melanocytes reside in the eye (the uvea). Cutaneous melanoma, which is often vitreoretinal when it metastasizes and may have a regressed, unidentifiable primary, is driven by mutations in *BRAF, NRAS* or *NF1*, activating the MAP-kinase pathway, and often has a very high tumor mutational burden (TMB), as it is often related to UV-light exposure. In contrast, many sarcomas, like CCS, are driven by one oncogenic fusion that often defines the disease entity, with a low TMB.

4. Conclusions

This report of a novel case of primary clear cell sarcoma within the eye presenting as a circumpapillary retinal mass with vitreous seeding expands the differential diagnosis of a primary, primitive-appearing intraretinal tumor, especially if true rosettes are not present, and brings into question the diagnosis of “retinoblastoma” occurring in an adult, especially without molecular genetic proof of inactivation of the retinoblastoma gene.

CRediT authorship contribution statement

Megan S. Steinkerchner: Writing – original draft, Investigation, Data curation. **Shizuo Mukai:** Writing – review & editing, Supervision, Resources, Conceptualization. **Anna M. Stagner:** Writing – review & editing, Writing – original draft, Supervision, Resources, Conceptualization.

Patient consent

Informed consent was obtained from the participant for publication of the details of their medical case and any accompanying images.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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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.

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