OPEN ACCESS – CASE REPORT

Conjunctival Melanoma with Rhabdomyosarcomatous Differentiation: A Case Report

Angeline Llemit, Xavier George Cardos, John Patrick Padilla

Department of Pathology and Laboratories, Southern Philippines Medical Center, Davao del Sur, Philippines

ABSTRACT

This is a case of malignant melanoma with rhabdomyosarcomatous differentiation presenting as a conjunctival mass in a 50-year-old male. Melanoma cells were seen to react with desmin, myogenin and vimentin, indicating rhabdomyosarcomatous differentiation. This condition is very rare, with less than twenty cases reported in the literature, which contributes to the limitations in molecular characterization and standard treatment protocols for this entity. This condition has an aggressive course with a poor prognosis.

Key words: malignant melanoma, eye, rhabdomyosarcomatous differentiation, conjunctival melanoma

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 2 August 2024.
Accepted: 20 August 2024.
Published online first: 30 September 2024.
https://doi.org/10.21141/PJP.2024.12

Corresponding author: Angeline T. Llemit, MD
E-mail: angelinellemit@gmail.com
ORCiD: https://orcid.org/ 0009-0008-7964-404X

INTRODUCTION

Malignant melanoma is known to show a wide heterogeneity in its appearance, exhibiting non-melanocytic neoplastic components in its histology. This is termed divergent differentiation, showing elements such as skeletal muscle, smooth muscle, fibroblasts, nerves, cartilage and neuroendocrine components.[1] Melanoma with rhabdomyosarcomatous differentiation is a very rare entity, with less than twenty pathologically confirmed cases reported.[2] This is associated with a poor prognosis, with distant metastases seen in most documented cases.[3] This report describes a case of melanoma with rhabdomyosarcomatous differentiation in a 50-year-old male, presenting as a right conjunctival mass.

CASE

This is a case of a 50-year-old male who presented with a right conjunctival mass. Two months prior to admission, the patient noticed the development of a small, pigmented mass in his right eye following the accidental scratching of a pre-existing mole. The patient reported that this mole had been present since childhood and had remained unchanged in size and color over the years. However, in the intervening months, the lesion began to increase in size, prompting the patient to seek initial consultation at a local hospital, followed by referral to our institution for further evaluation. The patient was a farmer and had an unremarkable family history and past medical history.

Physical examination revealed complete ptosis of the right eye with reduced visual acuity (OD: 20/100, OS: 20/50), and a visible pigmented mass located at the superior fornix (Figure 1). There was no mass, ptosis, or restricted range of motion in the extraocular muscles of the left eye. The skin showed no pallor or suspicious lesions. Additionally, no cervical lymphadenopathy was present. The rest of the physical findings were unremarkable. The patient was then admitted to our institution with the diagnosis of "consider conjunctival melanoma."

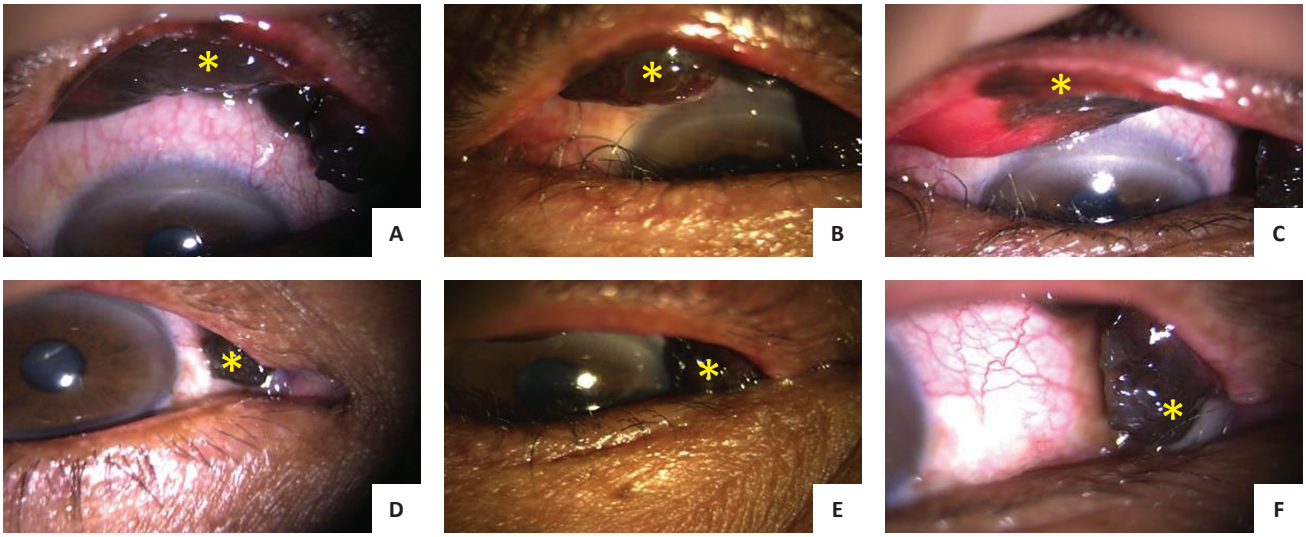

Figure 1. Examination of the patient's right eye reveals **(A)** a brown, fleshy, mass arising from the superior conjunctival fornix. **(B)** The mass spreads along the superior palpebral conjunctiva, and **(C)** extends toward the posterior lid margin. It further protrudes outward, reaching **(D)** the plica semilunaris and **(E, F)** the caruncle. *(Yellow asterisks indicate the relative location of the mass.)*

CT scan of the patient's eye mass revealed an irregular, ill-defined soft tissue lesion located at the right supraorbital region anterior to the globe approximately measuring 0.95 x 1.1 x 1.4 cm. The patient then underwent exenteration of the right eye, with an uneventful postoperative course.

The specimen submitted for pathology consists of the entire right eye with attached periorbital cuff, muscle and fascia that entirely measures 4.5 x 4 x 3 cm (Figure 2). The optic nerve measures 0.2 x 0.3 cm. The cut section of the eye reveals a tan, ill-defined mass (2 x 1.3 x 1.2 cm) at the palpebral conjunctival area (Figure 3). The mass is 2.2 cm from the optic nerve, 0.6 cm from the superior margin, 2 cm from the inferior margin, and 0.2 cm from the anterior margin.

Histologic examination of the eye mass shows nests of atypical cells consisting of pleomorphic polygonal cells with eccentric, hyperchromatic, vesicular nuclei and large, prominent nucleoli. The cytoplasm is abundant and eosinophilic with varying degrees of pigmentation visible. Tumor cells are seen invading the stroma, and 10 mitotic figures were seen per 10 high-power fields. Lymphovascular invasion was not identified (Figure 4).

The biopsy was signed out as "consistent with malignant round cell neoplasm, consider (1) melanoma, (2) rhabdomyosarcoma" with suggestions for immunohistochemistry with myogenin, desmin, vimentin, S100, HMB-45, and MART-1 for additional evaluation. No definitive post-surgical plan was made pending final identification of the malignancy, and the patient was lost to follow-up after discharge.

Immunohistochemical examination of the specimen was done, and the neoplastic cells showed diffuse positivity for melanocytic markers S-100, and Melan A (Figure 5). The neoplastic cells were also focally positive for skeletal muscle markers myogenin, desmin and vimentin (Figure 6), indicating rhabdomyosarcomatous differentiation.

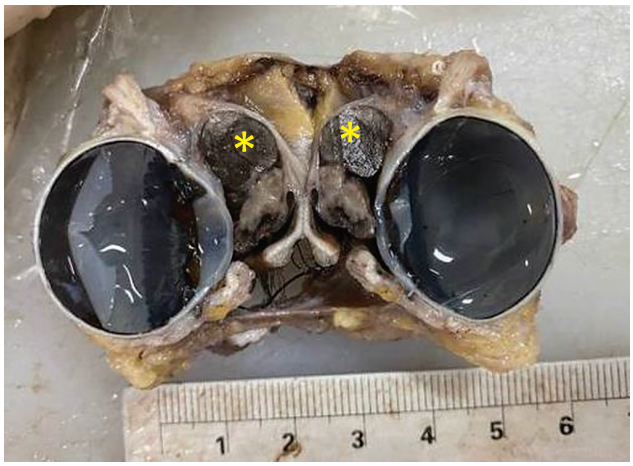

Figure 2. Cut section of the patient's exenteration specimen. The mass is seen occupying the superior palpebral conjunctiva *(yellow asterisks)*.

Figure 3. A mass is seen at the palpebral conjunctival area of the eye *(yellow asterisk)*.

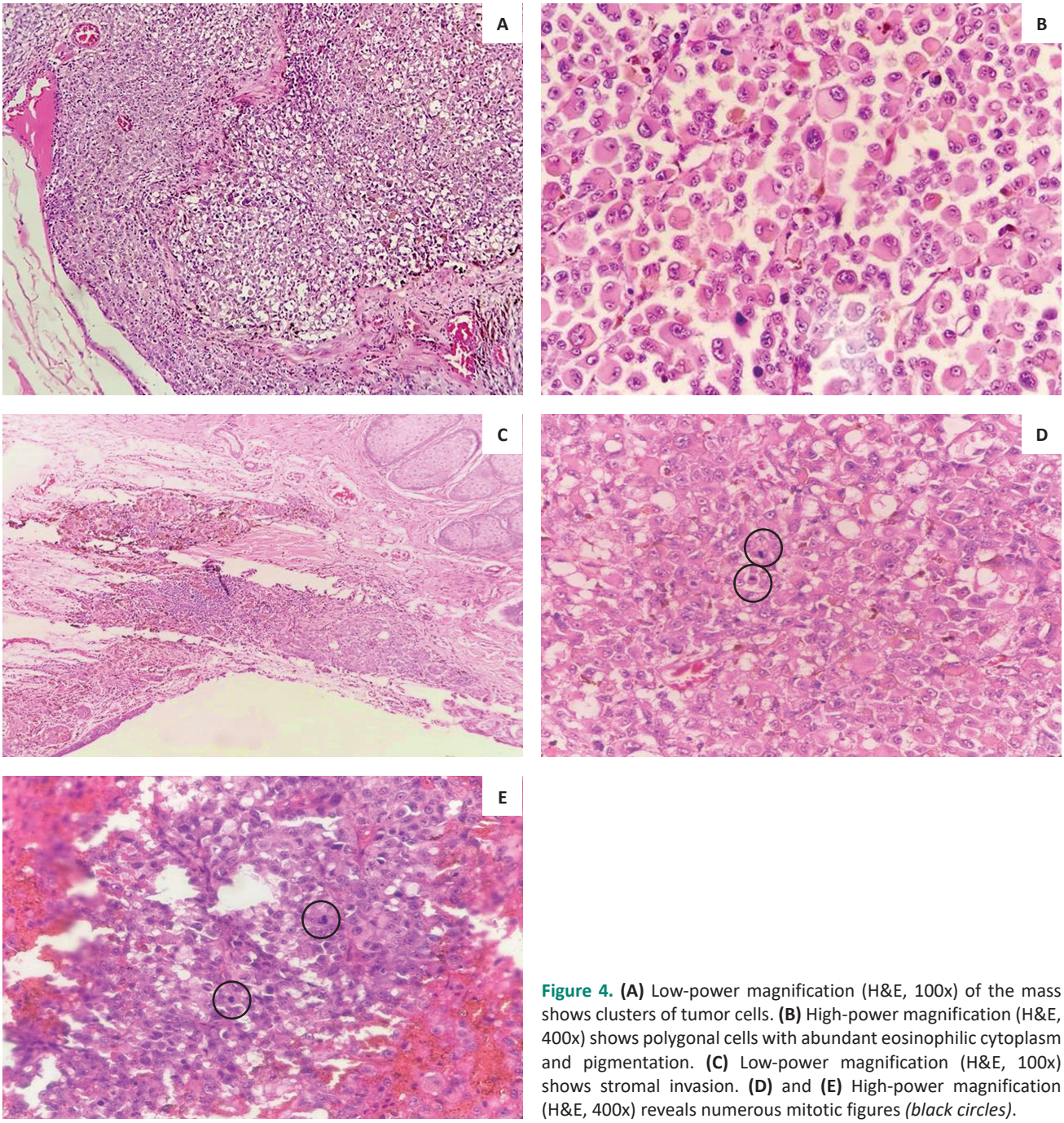

Figure 4. **(A)** Low-power magnification (H&E, 100x) of the mass shows clusters of tumor cells. **(B)** High-power magnification (H&E, 400x) shows polygonal cells with abundant eosinophilic cytoplasm and pigmentation. **(C)** Low-power magnification (H&E, 100x) shows stromal invasion. **(D)** and **(E)** High-power magnification (H&E, 400x) reveals numerous mitotic figures *(black circles)*.

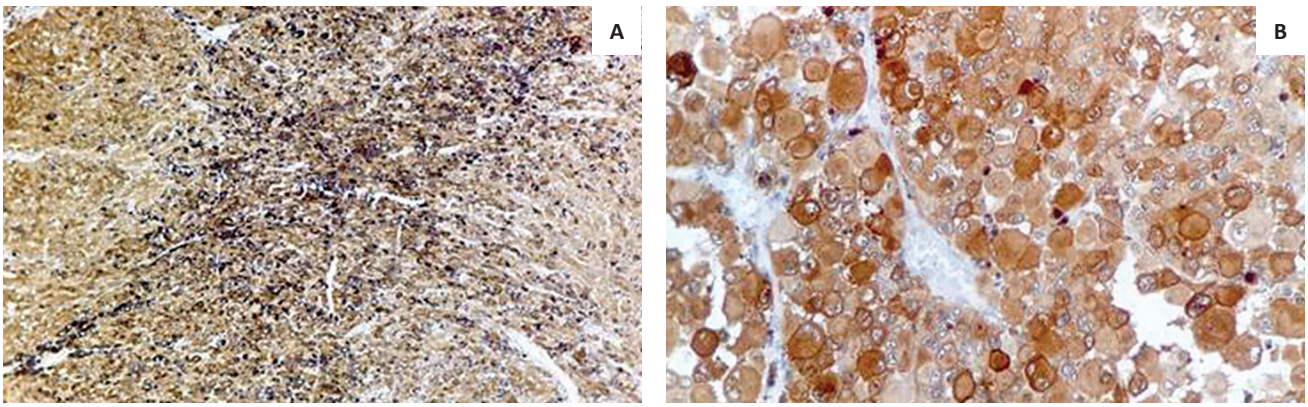

Figure 5. Immunohistochemistry was diffusely positive for **(A)** S100 and **(B)** Melan-A.

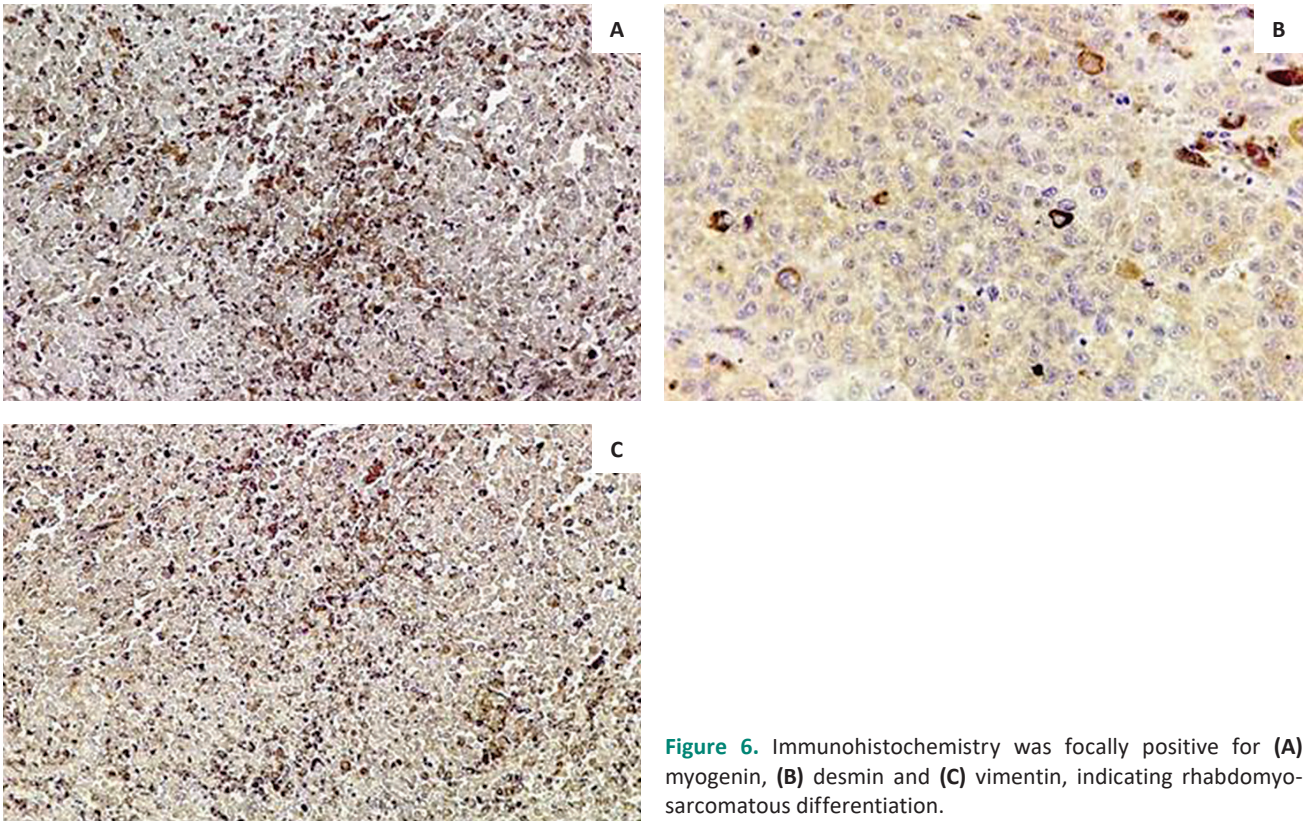

Figure 6. Immunohistochemistry was focally positive for **(A)** myogenin, **(B)** desmin and **(C)** vimentin, indicating rhabdomyosarcomatous differentiation.

Unfortunately, the patient was lost to follow-up after surgical management. The patient was then reported to have expired 11 months after the diagnosis was made.

DISCUSSION

Melanomas can arise in extra-cutaneous regions including the area in and around the eye. Conjunctival melanoma originates from the melanocytes in the basal layer of the conjunctival epithelium and accounts for about 5% of all ocular melanomas.[4] This entity is distinct from uveal melanoma despite both being referred to as "ocular melanomas."[5] Melanomas in this area can occur at any part of the conjunctiva, but often appear at sun-exposed areas such as the bulbar conjunctiva.[4,5] About 75% of cases arise from precursor lesions such as primary acquired melanosis (PAM) or a pre-existing nevus. The patient's tumor arose from a mole that had been present since childhood. *De novo* cases occur in 15–25% of cases.[4] The differential diagnosis for this tumor includes other melanocytic lesions such as PAM, conjunctival nevus and acquired melanoses, as well as malignancies such as pigmented squamous cell carcinoma, uveal melanoma, or metastatic melanoma from a cutaneous site.[6] The malignancies in the differential diagnoses are ruled out as there are no other body sites affected by a malignant tumor, as well as the absence of other component tumor cells in the mass (in the case of pigmented squamous cell carcinoma). The distinction of melanomas from other melanocytic lesions includes stromal invasion along with severe cytological and architectural atypia exceeding those expected in a nevus as essential criteria.[7] The prominent cytological atypia in the examined specimens rules out any benign lesions in the differential diagnosis and qualifies the tumor as a malignancy as opposed to a nevus with atypical features.

The biopsy was initially signed out as "consistent with malignant round cell neoplasm, consider (1) melanoma, (2) rhabdomyosarcoma" with suggestions for immunohistochemistry with myogenin, desmin, vimentin, S100, HMB-45, and MART-1 for additional evaluation. The presence of polygonal, eosinophilic cells in the specimen prompted the testing for muscle markers to rule out rhabdomyosarcoma.

This case of conjunctival mass on a 50-year-old male has shown positivity for desmin, vimentin and myogenin on the same area of tumor cells that has shown positivity for melanocytic markers S100 and Melan-A. This is consistent with the other documented cases of melanomas with rhabdomyosarcomatous differentiation, where foci of tumor cells were reactive to skeletal muscle markers (Table 1). Moreover, no other documented cases of melanomas with rhabdomyosarcomatous differentiation have been reported in the conjunctiva. This makes the current case possibly the first of its kind to be reported.

It should be noted that a melanoma with rhabdomyosarcomatous differentiation is distinct from a rhabdoid melanoma. A rhabdoid morphology in a tumor is described with features such as a polygonal shape, eccentric nuclei, large nucleoli, and abundant eosinophilic cytoplasm containing hyaline filamentous inclusions.[8,15] First described in a variant of Wilms Tumor, rhabdoid differentiation has been seen in other neoplasms and is thought to be a common endpoint of dedifferentiation of a variety of tumors.[10]

Table 1. Cases of malignant melanoma with rhabdomyosarcomatous differentiation

Reference	Clinical Information	IHC	Clinical outcome
Reilly, et al.[8]	59/M skin mass at anterior abdominal wall with right axillary lymph node metastasis	(+): Desmin, Myogenin, S100, HMB-45, Melan-A	Underwent surgery + adjuvant radiotherapy. Treated with vemurafenib with complete metabolic response. Small volume metastasis detected after 12 months.
Gharpuay-Pandit, et al.[9]	21/F submandibular mass (not biopsied) and cervical lymph node metastasis	(+): Desmin, Myogenin, MyoD1, S100, Melan-A	Underwent surgery + radiotherapy; developed chest metastasis and died of disease 10 months after presentation.
Gharpuay-Pandit, et al.[9]	90/M skin mass at the back of pinna	(+): Desmin, Myogenin, MyoD1, S100, HMB45 (-) Melan-A	Lesion was excised; Lost to follow-up.
Shenjere, et al.[10]	67/F Skin mass at chest	(+); Desmin, myogenin, MyoD1, S100, HMB-45, Melan-A	Underwent wide local excision; developed pulmonary metastasis; died of unrelated causes 2 years after diagnosis.
Shenjere, et al.[10]	51/F Mucosal melanoma at cervix with lymph node metastasis	(+): Desmin, Myogenin, S100, HMB-45, Melan-A	Underwent surgery + adjuvant chemotherapy. Developed widespread pelvic disease 10 months after surgery and considered for experimental treatment. Alive with disease.
Antonov, et al.[3]	75/M skin mass behind right ear with cervical lymph node metastasis	(+): Desmin, Myogenin, S100, Melan-A	Underwent wide local excision + chemotherapy. Developed chest metastases and died of disease 7 months later.
Kuwadekar, et al.[11]	72/M scalp mass	(+) Desmin, vimentin, myogenin (-) HMB-45, Melan-A	Underwent wide local excision. Re-biopsy was done 4 months post-op. Referred for external beam radiation therapy.
Campbell et al.[12]	52/F upper back mass with axillary lymph node and vertebral metastasis	(+) Desmin, myogenin, S-100, MART-1	Wide local excision + adjuvant chemotherapy. Died of disease 4 years after diagnosis.
Gupta, et al.[2]	72/M left lateral scalp mass	(+) Desmin, Vimentin	Wide local excision + immunotherapy and radiation; currently with disease.
Baltres, et al.[13]	2/F congenital nevus at lumbosacral region	(+) S-100, SOX10, HMB45, (+) myogenin, myo-D1, desmin, (+) hyperdiploidy with high-level gain of chromosome 8	Complete surgical excision + adjuvant chemotherapy. Pulmonary and hepatic metastases were found after treatment.
Tran, et al.[14]	96/M right forearm mass	(+) S-100, HMB-45, desmin, Myo-D1	Complete surgical excision. On adjuvant radiation therapy 5 months after excision.
Current case	50/M conjunctival mass	(+) Desmin, myogenin, vimentin, S-100, Melan-A	Exenteration, lost to follow up. Died 11 months after diagnosis.

Despite similar appearances, a rhabdoid melanoma lacks immunohistochemical markers for skeletal muscle (e.g., myogenin) and will only contain intermediate filaments (e.g., vimentin, desmin)[9,10]. Melanomas can also undergo transdifferentiation, in which a dedifferentiated melanoma acquires heterologous elements.[16] The loss of melanocytic markers in a transdifferentiated melanoma can obscure the diagnosis and may require molecular testing for confirmation. While a definitive progression sequence of malignant melanoma to produce rhabdomyosarcomatous elements has not been characterized, a proposed progression includes dedifferentiation of the melanoma and acquisition of nonmelanocytic phenotypes[14]. Sarcomatoid melanoma has been proposed as a "transition stage" of this tumor.[14]

The lack of funds and the patient being lost to follow-up has precluded molecular characterization of the current case. The molecular pathogenesis of melanoma has been extensively documented.[17] The use of *BRAF* and *NRAS* testing can be used to identify undifferentiated melanomas.[18] Conjunctival melanomas share similarities with cutaneous and mucosal melanomas at the molecular level, such as the presence of *BRAF*, *NRAS*, *NF1* and *KIT* mutations.[19] Only about one-third of conjunctival melanomas harbor a *BRAF* mutation, with the mutation itself associated with sun-exposed sites and as a target of therapy in primary and recurrent tumors[4]. *NRAS* mutations are common in conjunctival nevi but are only seen in 20% of conjunctival melanomas.[4] *NRAS* mutations in conjunctival melanomas are associated with an increased risk of metastasis and death.[20] *NF1* mutations are present in one-third of conjunctival melanomas but have no association with clinicopathologic features or prognosis.[4] Mutations in *KIT* are seen in conjunctival melanomas in non-sun-exposed areas. Like *NF1*, no association has been seen with *KIT* mutations and survival.[4]

Molecular markers sought as therapeutic targets for conjunctival melanoma include *BRAF*, *NRAS*, *NF1*, *KIT* and PD-1/PD-L1.[4,19,21] Other targets being explored for therapy include enhancer of zeste homolog 2 (EZH2) and the mTOR pathway.[21]

Genetic studies specifically for melanomas with rhabdomyosarcomatous differentiation showed features shared with embryonal rhabdomyosarcoma, such as a hyperdiploid genome and a high-level gain of chromosome 8.[13] An *NRAS* mutation and "shared genetic alterations (loss of chromosome 1q31, amplification of 1q32, and gain of 12q23-qter)" has been found in both the melanoma and rhabomyosarcomatous tumor cells in two cases,[15,22] suggesting a clonal relationship between the two components. The rhabdomyosarcomatous cells were also shown to express rhabdomyogenic RNA transcripts, correlating with morphology and immunohistochemistry.[13]

Conjunctival melanoma by itself has a 10-year mortality rate of 25–35%. Prognostic factors include a *de novo* origin, non-bulbar conjunctival location, nodular growth, multifocal location, and lymph node spread. Increased mitotic rate, lymphatic invasion, and angiotropic metastases microscopically are also negative prognostic factors.[7] The presented case showed a non-bulbar conjunctival location and a mitotic rate of 10 mitoses per 10 high-power fields, but no lymphovascular invasion was identified.

Due to the paucity of cases, no standard treatment has been formulated for melanomas with rhabdomyosarcomatous differentiation. The cases documenting the disease used a combination of wide excision of the tumor with radiotherapy or immunotherapy (Table 1), with varying results. Survival from the time of diagnosis ranged from 7 months[3] to 4 years[12]. The presented case was lost to

follow-up, and the patient expired 11 months after the diagnosis was made. The disease remains to have a rapidly progressive course with a poor prognosis. Most of the documented cases rapidly developed distant metastases.[2]

CONCLUSION

This report discusses a case of malignant melanoma with rhabdomyosarcomatous differentiation located in the right conjunctiva of a 50-year-old male patient. Limited literature review has shown the aggressive nature of the entity in other locations, therefore, thorough examination and testing to identify and document this entity is necessary. Genetic studies have been performed but have limited value in diagnosing the entity and are more useful in identifying alterations targetable for immunotherapy. Due to its rarity, there is a lack of clinical trials aimed at developing standard treatment protocols, ultimately contributing to lower survival rates.

ACKNOWLEDGMENT

The authors acknowledge their Chairperson, Sheila May N. Ramos, MD, FPSP, Training Officers, Aije Hope D. Bruzon-Hortel, MD, DPSP and Ma. Theresa A. Fedoc-Minguito, MD, DPSP of the Department of Pathology and Laboratories of the Southern Philippines Medical Center, and Dr. Kristin J. Estores for her vital technical support during the completion of this paper.

ETHICAL CONSIDERATION

Patient consent was obtained for this case report.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

REFERENCES

1. Banerjee SS, Eyden B. Divergent differentiation in malignant melanomas: a review. Histopathology. 2008; 52(2):119-29. PMID: 17825057 DOI: 10.1111/j.1365-2559.2007.02823.x
2. Gupta A, Wagman R, Kuwadekar A, Scoppetuolo M, Dardik M, Smith F. Use of immunotherapy and radiation treatment in the management of metastatic melanoma with rhabdomyosarcomatous differentiation. Adv Radiat Oncol. 2019;5(1):134-9. PMID: 32051900 PMCID: PMC7004934 DOI: 10.1016/j.adro.2019.07.019
3. Antonov NK, Niedt GW. Malignant melanoma with rhabdomyosarcomatous differentiation. Am J Dermatopathol. 2016;38(6):456-60. PMID: 27205908. DOI: 10.1097/DAD.0000000000000478.
4. Chang E, Demirci H, Demirci FY. Genetic aspects of conjunctival melanoma: a review. Genes (Basel). 2023;14(9):1668. PMID: 37761808 PMCID: PMC10530751 DOI: 10.3390/genes14091668
5. Lin AY. Tumors of the conjunctiva. In: McKee's pathology of the skin. 5th ed. Elsevier; 2020.
6. Koç İ, Kıratlı H. Current management of conjunctival melanoma part 1: clinical features, diagnosis and histopathology. Turk J Ophthalmol. 2020;50(5):293-303. PMID: 33342197 PMCID: PMC7610047 DOI: 10.4274/tjo.galenos.2020.38096
7. Moulin, A, Verdijk, R, Jager, M, Brouwer, N, Ferreira, T. Conjunctival melanoma. In: WHO Classification of Tumours Editorial Board, eds. Eye tumours. Lyon (France): International Agency for Research on Cancer; 2023 [beta version ahead of print].
8. Reilly DJ, Volchek M, Ting JW, Allan P, Findlay MW. Rhabdomyoblastic differentiation in metastatic melanoma: making sense of a rare but complex form of mimicry. Int J Surg Pathol. 2014;22(6):520-4. PMID: 24275885 DOI: 10.1177/1066896913510031
9. Gharpuray-Pandit D, Coyne J, Eyden B, Banerjee SS. Rhabdomyoblastic differentiation in malignant melanoma in adults: report of 2 cases. Int J Surg Pathol. 2007;15(1):20-5. PMID: 17172493 DOI: 10.1177/1066896906295775
10. Shenjere P, Fisher C, Rajab R, Patnaik L, Hazell S, Thway K. Melanoma with rhabdomyosarcomatous differentiation: two further cases of a rare pathologic pitfall. Int J Surg Pathol. 2014;22(6):512-9. PMID: 24788528 DOI: 10.1177/1066896914531817
11. Kuwadekar A, Allard J, Dardik M, Smith F. Melanoma with rhabdomyosarcomatous differentiation. BMJ Case Rep. 2018. PMID: 29880623. PMCID: PMC6011467. DOI: 10.1136/bcr-2018-224263
12. Campbell K, Kumarapeli AR, Gokden N, Cox RM, Hutchins L, Gardner JM. Metastatic melanoma with dedifferentiation and extensive rhabdomyosarcomatous heterologous component. J Cutan Pathol. 2018;45(5):360-4. PMID: 29405341 DOI: 10.1111/cup.13122
13. Baltres A, Salhi A, Houlier A, Pissaloux D, et al. Malignant melanoma with areas of rhabdomyosarcomatous differentiation arising in a giant congenital nevus with RAF1 gene fusion. Pigment Cell Melanoma Res. 2019;32(5):708-13. PMID: 30945443 DOI: 10.1111/pcmr.12785
14. Tran, T, Linos, K, de Abreu, F, Carlson J. Undifferentiated sarcoma as intermediate step in the progression of malignant melanoma to rhabdomyosarcoma: histologic, immunohistochemical, and molecular studies of a new case of malignant melanoma with rhabdomyosarcomatous differentiation. Am J Dermatopathol. 2019;41(3):221-229. PMID: 30085960 DOI: 10.1097/DAD.0000000000000123
15. Abbott JJ, Amirkhan RH, Hoang MP. Malignant melanoma with a rhabdoid phenotype: histologic, immunohistochemical, and ultrastructural study of a case and review of the literature. Arch Pathol Lab Med. 2004;128(6):686-8. PMID: 15163228 DOI: 10.5858/2004-128-686-MMWARP
16. Ferreira I, Droop A, Edwards O, et al. The clinicopathologic spectrum and genomic landscape of de-/trans-differentiated melanoma. Mod Pathol.

2021;34(11):2009-19. PMID: 34155350 DOI: 10.1038/s41379-021-00857-z
17. North J, Bastian B, Lazar A. Melanoma. In: McKee's pathology of the skin, 5th ed. Elsevier; 2020.
18. Agaimy A, Specht K, Stoehr R, et al. Metastatic malignant melanoma with complete loss of differentiation markers (undifferentiated/dedifferentiated melanoma): analysis of 14 patients emphasizing phenotypic plasticity and the value of molecular testing as surrogate diagnostic marker. Am J Surg Pathol. 2016;40(2):181-91. PMID: 26448190 DOI: 10.1097/PAS.0000000000000527
19. Nahon-Estève S, Bertolotto C, Picard-Gauci A, et al. Small but challenging conjunctival melanoma: new insights, paradigms and future perspectives. Cancers (Basel). 2021;13(22):5691. PMID: 34830847 PMCID: PMC8616295 DOI: 10.3390/cancers13225691
20. Lally SE, Milman T, Orloff M, et al. Mutational landscape and outcomes of conjunctival melanoma in 101 patients. Ophthalmology. 2022;129(6):679-93. PMID: 35085662 DOI: 10.1016/j.ophtha.2022.01.016
21. Koç İ, Kıratlı H. Current management of conjunctival melanoma part 2: treatment and future directions. Turk J Ophthalmol. 2020;50(6):362-70. PMID: 33389937 PMCID: PMC7802095 DOI: 10.4274/tjo.galenos.2020.22567
22. Gattenlöhner S, Brocker EB, Muller-Hermelink HK. Malignant melanoma with metastatic rhabdomyosarcomatoid transdifferentiation. N Engl J Med. 2008;358(6):649-50. PMID: 18256407 DOI: 10.1056/NEJMc0707079