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Pediatric conjunctival melanoma: A comprehensive case report and literature review

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ABSTRACT

Purpose: This case report aims to present a rare instance of conjunctival melanoma in a 5-year-old patient and contribute to the limited body of knowledge on pediatric conjunctival melanoma. The purpose is to understand the characteristics, diagnosis, and management of this uncommon malignancy in young individuals.

Observations: The case describes a 5-year-old female with a progressively growing pigmented conjunctival lesion. The lesion was observed to be located on the temporal conjunctiva of the right eye and displayed distinctive features, including feeder vessels. Imaging revealed specific dimensions of the lesion and ruled out deeper invasions. Histopathological examination revealed architectural and cytologic atypia, positive immunohistochemical staining for HMB-45, and a Ki67 proliferation index of 20 %, confirming the diagnosis of conjunctival melanoma.

Conclusions: Conjunctival melanoma, an uncommon malignancy even more so in pediatric patients, typically presents with pigmented growths and feeder vessels. This case underscores the need for thorough diagnosis and early intervention, as conjunctival melanoma can lead to devastating outcomes. The rarity of such cases limits our understanding of their etiology and progression. This case contributes to the literature on pediatric conjunctival melanoma and reinforces the importance of vigilance in detecting and managing ocular pigmented lesions in children.

1. Introduction

Ocular pigmented lesions include a broad range of entities, most melanocytic. Anatomically, these lesions can be divided into uveal, conjunctival, and scleral lesions. The uveal layer can present as a nevus and its malignant counterpart, melanoma. The conjunctiva and sclera have a more florid spectrum of lesions, including conjunctival nevus, primary acquired melanosis, benign epithelial melanosis, melanosis oculi, oculodermal melanosis, pigmented scleral spot, nevus, and melanoma.[1,2]

Conjunctival nevus arises from the proliferation of modified melanocytes arranged in nests. While it can be present from birth, it is typically identified during or after childhood. On the other hand, primary acquired melanosis and benign epithelial melanosis are attributed to conjunctival hyperpigmentation without melanocytic hyperplasia, as seen in ephelides. Conversely, Melanosis oculi and oculodermal melanosis (nevus of Ota) are characterized by an elevated number of fusiform melanocytes within the episclera and sclera. Lastly, pigmented episcleral spot occurs due to the translocation of uveal melanocytes to the episcleral space through a nerve loop.[1,2]

Conjunctival melanoma is an aggressive malignant tumor that originates from the uncontrolled proliferation of melanocytes on the basal layers of the conjunctival epithelium. This type of cancer can develop through various pathways, including from pre-existing nevi, areas of primary acquired melanosis, or it may emerge de novo.[3] Primary acquired melanosis accounts for approximately 75 % of conjunctival melanomas, followed by de novo cases and those originating from nevi.[4,5] It is important to note that pediatric conjunctival tumors are typically benign and rarely undergo malignant transformation.[6]

Conjunctival melanoma is an extremely rare malignancy in

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childhood and adolescence, with high mortality and the potential for devastating outcomes.[6] The low incidence of pediatric conjunctival melanoma makes published studies and reports on its presentation, management, and prognosis very scarce. An extensive literature search for articles in English or Spanish using the terms "pediatric conjunctival melanoma in children" (Pubmed; Google Scholar) and Boolean operators, combining "conjunctival melanoma" with terms like "childhood," "adolescence," "pediatric," and "children" (Pubmed) yielded 46 cases with detailed descriptions provided for only 22 of them (Table 1). We present a case of a successfully treated 5-year-old Mexican female with conjunctival melanoma.

2. Case report

A 5-year-old female presented with a pigmented conjunctival lesion in her right eye. The lesion had been present since birth and grew progressively over the past 2 years. The patient had no significant personal or family history of ocular or systemic diseases, nor were there any known risk factors. Visual acuity was 20/20 in the left eye and 20/40 in the right eye. Upon examination, a poorly defined oval pigmented brown lesion was observed, measuring 10 × 4 mm in the temporal conjunctiva of the right eye in contact with the scleral limbus (Fig. 1). The lesion exhibited two prominent tortuous episcleral feeder vessels in the inferotemporal quadrant. No intralesional cysts were observed.

Imaging with ultrasound bio-microscopy showed a 1.59 mm vertical x 6.38 mm wide medium reflective lesion on the corneal limbus, between the X and XI meridians. The lesion showed no deep invasion to the sclerae, ciliary body, or adjacent structures (Fig. 2).

The patient underwent a wide-excisional biopsy with 2 mm circumferential conjunctival margins. Additionally, lamellar sclerectomy, perilimbal lamellar keratectomy, and cauterization of feeder vessels were performed, followed by an autologus conjunctival graft from the ipsilateral (right) eye measuring 12 × 5 mm.

Histopathological examination of the excised lesion revealed an irregular brown/gray fragment with a soft consistency, measuring 0.7 × 0.6 × 0.2 cm (thickness), with a central homogeneous brown lesion. Microscopic analysis demonstrated a proliferation of epithelioid cells in nests and cords lacking maturation (Fig. 3A), with severe architectural and cytologic atypia characterized by nuclear pleomorphism and prominent nucleoli invading in a depth of 0.614 mm. The lesion exhibited pagetoid spread and moderate lymphocytic peritumoral infiltration. Immunohistochemical staining for HMB-45 was positive (Fig. 3B), and the index proliferation measured by Ki67 was 20 %. The diagnosis was established as conjunctival melanoma with clear margins.

During the one-week follow-up, the graft showed adequate scarring and granulation tissue. There were no signs of local recurrence. The patient was asymptomatic. Visual acuity was 20/20 in the left eye and 20/30 in the right eye.

Two-month follow-up showed no signs of local recurrence. The patient was asymptomatic. Visual acuity was 20/20 in the left eye and 20/25 in the right eye. The patient will use lubricating eye drops daily and will undergo close monitoring with follow-up every 6 months.

3. Discussion

The 2018 WHO classification for melanomas divides melanomas into nine different pathogenic pathways. These pathways are further grouped as melanomas typically associated with cumulative solar damage (CSD) and melanomas not consistently associated with cumulative solar damage (no CSD). The CSD group includes low-CSD melanoma (pathway I), high-CSD melanoma (pathway II), and desmoplastic melanomas (pathway III). No CSD group includes Spitz melanomas (pathway IV), acral melanomas (pathway V), mucosal melanomas (pathway VI), melanomas arising in congenital nevi (pathway VII), melanomas arising in blue nevi (pathway VIII), and uveal melanoma (pathway IX).[24] Although conjunctival melanoma is classified in pathway VI along with other mucosal melanomas, it constitutes a very heterogeneous group. Sun-exposed conjunctival melanomas, as in bulbar conjunctiva, can show strong UV mutation signature, and mutations in BRAF, NRAS, NF1, and TERT. These mutations are used to classify cutaneous melanoma and are strongly associated with cumulative solar damage.[25,26] BRAF is the most common mutation in cutaneous melanoma, and NF1 is the most common in conjunctival melanoma.[27] Other mutations like KIT, GNAQ, and GNA11 can be found in conjunctival melanomas, although less frequently, and are related to mucosal and blue melanomas.[24] Lesions in the sun-exposed bulbar conjunctiva run the increase in the incidence of conjunctival melanoma, indicating a potential link to increased UV radiation exposure. While UV radiation is indeed recognized as a risk factor for conjunctival melanoma, it is noteworthy that the condition can also develop in areas that are not directly exposed to UV radiation, such as the forniceal and tarsal conjunctiva. This suggests the existence of distinct pathways for the development of conjunctival melanoma, with some cases associated with cumulative solar damage and others unrelated to UV exposure. Therefore, UV exposure is not an absolute requirement for conjunctival melanoma, supporting the notion that different mechanisms contribute to the development of melanomas with and without cumulative solar damage.[28] In our study, the majority of patients (69 %, n = 16) included in Table 1 exhibited melanoma limited to the bulbar conjunctiva and sun-exposed areas. This finding is particularly intriguing in pediatric patients, as they typically have limited cumulative solar damage. The observed pattern suggests the existence of a distinct pathway for the development of conjunctival melanoma in pediatric cases, which differs from the mechanisms associated with cumulative solar damage commonly seen in adults. The most frequently reported mutations in adult cases are linked to solar exposure, which is an unlikely etiological factor in pediatric patients.

Mucosal melanomas constitute a very small percentage of 1.4 % of all melanomas, and conjunctival melanoma accounts only for 20 % of mucosal melanomas and 5 % of all ocular melanomas.[27–29] The incidence of conjunctival melanoma is increasing in different populations worldwide, in a similar trend to that of cutaneous melanoma. Contrarily the incidence of mucosal and ocular melanomas is considered stable.[5,30] The mean age at presentation is between 55 and 65, and its incidence increases with age. Conjunctival melanoma is extremely rare in patients younger than 20 years old; only 0.68 % of cases develop in patients younger than 14.[5,31]

Conjunctival melanoma usually presents as a pigmented lesion or mass with feeder vessels and progressive growth, the lesion can be present since birth. Differentiation from a benign lesion can be difficult; hemorrhage, large base, tortuous feeder vessels, adherence to the sclera, corneal invasion, multifocality, and the lack of cysts lesions support the diagnosis of melanoma.[24] It is usually asymptomatic but can present burning pain, dry eye, and variable symptoms caused by invasion (proptosis, chemosis, astigmatism, restricted ocular movements, etc.).[11,31] Our patient presented an asymptomatic pigmented lesion with 2 engorged feeder vessels and progressive growth; the lesion was detected 2 years before treatment. Excision biopsy with no-touch technique is the most favorable diagnostic and therapeutic approach for circumscribed conjunctival melanoma.[30] Lesions can be staged with optical coherence tomography, B-scan ultrasound, MRI, CT, or PET; abdominal and chest imaging is important to rule out metastatic disease.[31]

Guidelines on diagnosis and treatment of conjunctival melanoma are focused on adults, therefore the treatment for pediatric conjunctival melanoma is based on adult data. Excisional biopsy with no-touch technique consists of wide local excision, cryotherapy to conjunctival margins, and alcohol corneal epitheliectomy for corneal involvement.[30] This technique has been shown to reduce local recurrence.[32] Our patient underwent wide local excision with lamellar sclerectomy, and perilimbic lamellar keratectomy to achieve 2 mm circumferential margins. Adjuvant treatment with radiotherapy can be used if deep margins are involved, as well as topical chemotherapy in the case of multifocal

Table 1
Summary of existing case reports.

Case	Author	Year	Sex/ Age	Presentation	Location	Size	Morphology	IHQ	Tx	Outcome	Ethnicity	Initial presentation
1	Jensen[7]	1962	M/ 14	Xeroderma pigmentosum, pigmented lesion with progressive growth over 2 years.	RE, bulbar conjunctiva, limbus and cornea.	10x10 mm.	SEC, M+, I (sclera and cornea), LI.	NS	Enucleation	NS	Greenlandic	Melanoma
2	Croxatto[8]	1987	M/ 11	Pigmented lesion present since birth, progressive growth for few weeks, engorged feeder vessels, excision and recurrence.	RE, bulbar conjunctiva, limbus, and inferior fornix.	27 mm wide, 12 mm elevation.	EC, M+, LI.	NS	Exenteration	Died from extensive metastasis after 4 months.	NS	Nevus
3	McDonnell[9]	1989	M/ 12	Conjunctival mass present for 4 years.	RE, bulbar conjunctiva, limbus.	NS	LEC, LI.	NS	Excision	18 years DF	Caucasian	Nevus
4	McDonnell[9]	1989	M/ 12	Pigmented mass, present for 4 years, progressive growth for 7 months, parotid lymphadenopathy.	RE, bulbar conjunctiva, and limbus.	4 mm thickness.	NS	NS	Excision and chemotherapy.	20 months DF	Caucasian	Nevus
5	McDonnell[9]	1989	F/16	Conjunctival recurring mass with inflammatory reaction, present for months.	LE, bulbar conjunctiva, and limbus.	2.5 mm thickness.	EC, M.	NS	Excision	20 months DF	Hispanic	Nevus
6	Aoyagi[10]	1993	M/ 10	Xeroderma pigmentosum, fast growing pigmented recurring mass.	RE, limbus.	2x2 mm wide, 1 mm thickness.	SEC, M, LI.	S100 +	Excision and cryopexy.	9 months DF	NS	Melanoma
7	Mehta[11]	1996	F/8	Xeroderma pigmentosum, pigmented lesion, proptosis, conjunctival chemosis, restricted ocular movements, and astigmatism.	RE, bulbar conjunctiva, limbus, canthus, and fornix.	Raised 6 mm from surface.	SEC, LEC, I (extraocular muscles, lacrimal glands and sac)	NS	Orbital exenteration	Died from DIC during hospitalization	NS	Melanoma
8	Strempel[12]	1999	F/16	Past history of conjunctival nevus with focus of malignant change, new pigmented lesion in same eye.	RE, bulbar conjunctiva, canthus, and lacrimal sac.	NS	NS	NS	Excision	Died from extensive metastasis	NS	Melanoma
9	Strempel [12]	1999	M/3	Pigmented lesion present since birth with progressive growth in the past years.	LE, bulbar conjunctiva.	NS	NS	NS	Excision	NS	Turkish	Nevus
10	Strempel[12]	1999	M/4	Glassy lesion with progressive growth.	RE, bulbar conjunctiva.	NS	NS	NS	Excision	NS	Caucasian	Melanoma
11	Ohguro[13]	2003	M/ 14	Pigmented mass since 12 years of age, progressive growth, engorged feeder vessels.	RE, bulbar conjunctiva.	4 mm wide, height 0.8 mm.	Glomerular proliferation of SC, LI.	HMB-45 +, Melan A +	Excision and cryopexy.	NS	NS	Melanoma
12	Brownstein[14]	2006	F/9	Pigmented lesion, recurred two times.	RE, palpebral conjunctiva.	9 mm wide, 1.2 mm thickness.	LEC, PI, AM, LI.	NS	Excision	NS	Caucasian	Melanoma
13	Brownstein[14]	2006	M/4	Amenalotic nodule, stable for 5 years, progressive growth and ulceration.	LE, bulbar conjunctiva.	8 mm wide, 2.9 mm thickness.	Cords of SEC, AM, LI.	NS	Excision	NS	Mexican	Nevus
14	Polat[15]	2008	F/6	Pigmented lesion, engorged feeder vessels, present for 3 years, progressive growth in 6 months.	LE, bulbar conjunctiva, limbus.	3x4 mm wide.	SC, PI, AM.	HMB-45 +, S100 +	Excision and chemotherapy.	6 month DF	NS	Nevus
15	Rolón[16]	2011	M/8	Pigmented lesion, progressive growth, present since 3 years of age.	RE, bulbar conjunctiva, canthus, and lacrimal duct.	0.3 mm thickness.	EC, PI, M, LI.	HMB-45 +, Melan A +, BCL2 +, WT1 +	Excision	NS	NS	Nevus

(*continued on next page*)

Table 1 (*continued*)

Case	Author	Year	Sex/ Age	Presentation	Location	Size	Morphology	IHQ	Tx	Outcome	Ethnicity	Initial presentation
16	Al Masaoudi[17]	2013	M/ 10	Pigmented lesion and parotid lymphadenopathy.	RE, bulbar conjunctiva.	8 mm wide, 3.5 mm thickness.	NS	HMB-45 +	Excision, parotidectomy, chemotherapy, and brachytherapy.	12 months DF	NS	Melanoma
17	Burgués-Ceballos[18]	2013	M/ 15	Pigmented mass, engorged feeder vessels, progressive growth, present since childhood.	LE, bulbar conjunctiva.	11x9 mm wide.	EC, LI.	Ki-67 +, HMB-45 +, Melan A +, S100 +	Excision	36 months DF	NS	Nevus
18	Walters[19]	2017	M/ 10	Amelanotic polypoid lesion, present since birth, progressive growth in previous months.	LE, caruncle.	6x6 mm wide, 2.5 mm thickness.	EC, M+.	Ki-67 +, Melan A +, Mart-1 +	Excision and cryotherapy.	NS	Caucasian and African American	Nevus
19	Liu[20]	2017	F/9	Pigmented raised lesion, engorged feeder vessels, burning sensation for 1 month.	LE, bulbar conjunctiva, limbus.	4x3 mm wide.	EC.	Ki-67 +, HMB-45 +	Excision and cryotherapy.	30 months DF	Caucasian	Nevus
20	Yangzes[21]	2018	M/ 16	Pigmented lesion, progressive growth in 2 years, present since childhood.	RE, bulbar conjunctiva.	20x12 mm wide.	SEC, AM.	Ki-67 +, HMB-45 +, Melan A +	Excision, cryotherapy, and chemotherapy.	9 months DF	Indian	Nevus
21	Ciuntu[22]	2018	M/7	Pigmented mass, engorged feeder vessels, progressive growth for 1.5 years.	RE, bulbar conjunctiva.	5.3x3 mm wide.	EC, PI.	HMB-45 +	Excision	36 months DF	Caucasian	Nevus
22	Vishnevskia-Dai[23]	2023	M/7	Amelanotic rapidly growing polypoid lesion.	RE, bulbar conjunctiva.	8 mm wide, 2.5 mm thickness.	SEC, M.	Ki-67 +, HMB-45 +	Excision and cryotherapy.	73 months DF	NS	Melanoma
23	Cantu et al.	2023	F/5	Pigmented lesion, two engorged FV, visual acuity 20/40, progressive growth for 2 years.	RE, bulbar conjunctiva, and limbus.	7x6 mm wide, 0.614 mm thickness.	EC, PI, M, LI.	Ki-67 +, HMB-45 +	Excision		Mexican	Nevus

FV: feeder vessels, XP: Xeroderma pigmentosum, SC: spindle cells, EC: epithelioid cells, SEC: spindle and epithelioid cells, LEC: large epithelioid cells, M: mitotic figures, M+: numerous mitotic figures, AM: atypical mitosis, I: invasion, PI: pagetoid invasion, LI: lymphocytic infiltration, DF: disease free, NS: not specified.

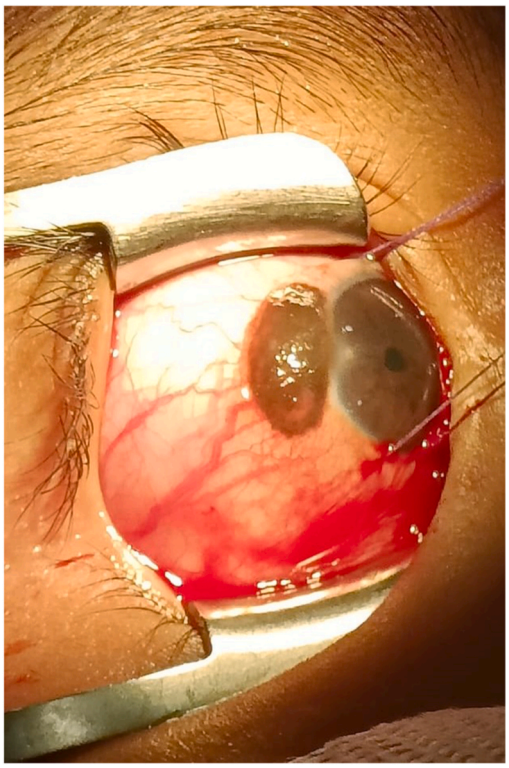

Fig. 1. Clinical presentation. Pigmented lesion on the temporal bulbar conjunctiva of the right eye.

primary acquired melanosis with atypia.[30] No adjuvant treatment was given to our patient. Exenteration is only used for primary or recurrent conjunctival tumors with orbital extension.[33]

The histopathologic diagnosis of conjunctival melanoma requires severe cytological and architectural atypia, exceeding those expected in a nevus. The subepithelial component shows nests or sheets of atypical melanocytes invading the stroma; the intraepithelial component can be nested, pagetoid, lentiginous, or absent.[24] Architectural patterns suggestive of conjunctival melanoma include pagetoid growth in the intraepithelial component, the radial extension of the intraepithelial component beyond the edge of the subepithelial component, inflammatory infiltrate at the base of the lesion, mitotic activity, lack of maturation or reverse maturation, and invasion of the sclera or cornea.[24,34] The cytomorphology of conjunctival melanoma shows the same spectrum of melanoma in other locations; melanoma cells can present as spindle or epithelioid cells.[24] Overall, the histopathological features described in the case report correlate well with the characteristic findings.

Immunohistochemical staining with HMB-45, Melan-A, S100, and Mart-1 can be used to support the diagnosis; recently BCL-2 has been implemented as a reliable marker; Ki-67 can also give us important data regarding aggressiveness.[5] HMB-45 and Ki-67 were performed in our case; HMB-45 was positive, and Ki-67 was positive in 20 % of nuclei.

Conjunctival melanoma has been reported to have a 5 and 10-year tumor-related mortality of 12–19 % and 23–39 %, respectively.[30] Local recurrences are common in conjunctival melanoma, ranging from 32 % to 62 %, and are associated with an increased risk of metastasis.[5] Metastatic disease develops in 20–30 % of patients, and tumors with BRAF mutations confer a higher risk for metastasis, thus genetic testing for BRAF mutations gives prognostic information.[5,30] Regional lymph nodes are the most common site of metastasis, predominantly parotid, preauricular, submandibular, and cervical. Systemic disease most commonly involves the lungs, brain, liver, skin, bones, and the gastrointestinal tract. Lesions located in the carunculae, lid margins, palpebral and forniceal conjunctiva, and plica semilunaris have a worse prognosis.[5] Our patient showed no evidence of lymphadenopathy or systemic disease and presented a temporal perilimbic location that does not confer a worse prognosis. Atypical melanocytes, mixed cells (spindle and epithelioid), absence of inflammatory response, lymphovascular invasion, tumor-associated lymphangiogenesis, nodular growth pattern, full thickness epithelial involvement, more than 2 mm tumor thickness, and positive margins on histopathology are associated with higher mortality.[5,35] None of these negative prognostic histopathological findings are present on our patient's excisional biopsy.

4. Conclusions

Conjunctival melanoma in pediatric patients is an exceedingly rare malignancy with a poorly understood etiology. While cumulative solar damage is a well-known risk factor in adults, its significance in pediatric cases is uncertain. Further research is needed to elucidate the underlying factors and molecular mechanisms contributing to the occurrence of conjunctival melanoma in this unique population. By expanding our knowledge through systematic case reporting, we can gain valuable insights into clinical presentation, management approaches, and long-term outcomes.

Despite the favorable clinical and histological characteristics observed in our case, the scarcity of evidence regarding this rare disease prevents us from providing definitive reassurance. Consequently, close monitoring is imperative.

Patient consent

To publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of

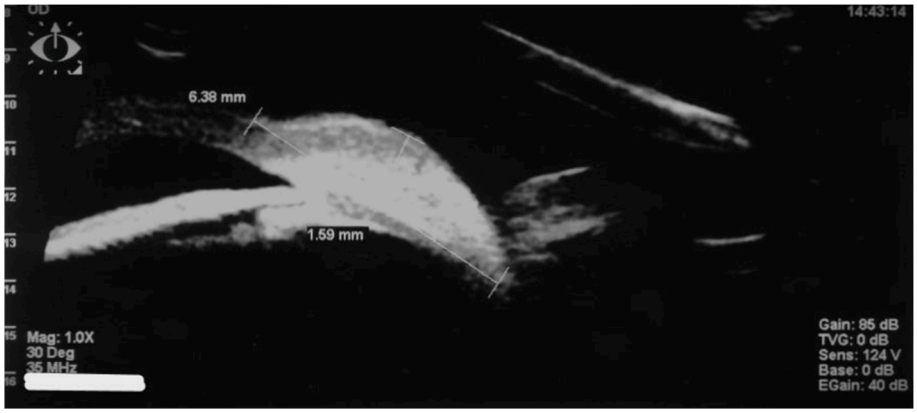

Fig. 2. Imaging. Ultrasound bio-microscopy shows the dimensions of the lesion and absence of invasion.

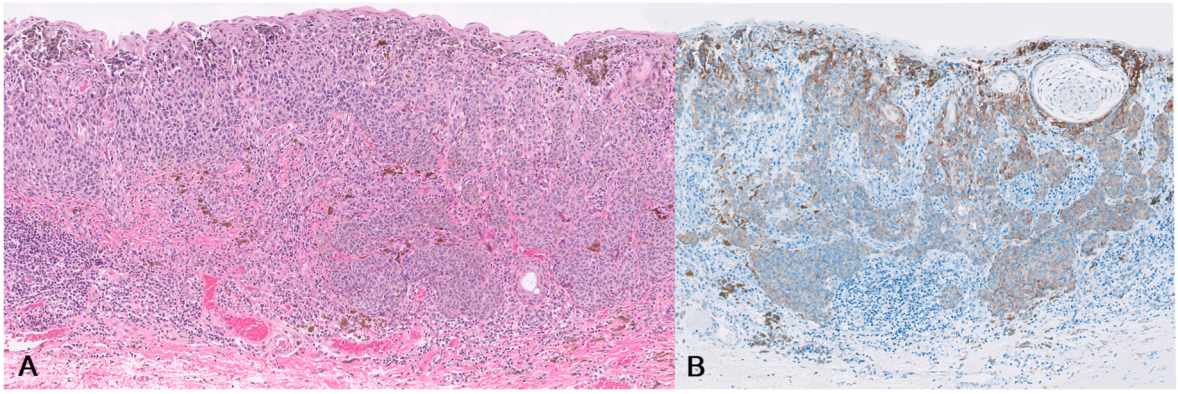

Fig. 3. H&E stain, magnification ×10. A. Excision biopsy shows nests of epithelioid melanocytic cells. HMB-45 stain B, magnification ×10. B. Immunohistochemistry with HMB-45 stained the cytoplasm and membrane of the neoplastic cells.

the patient.

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Authorship

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

CRediT authorship contribution statement

G.N. Cantu-Soriano: Validation, Visualization, Writing – original draft, Writing – review & editing. **N.G. Sanchez:** Methodology, Supervision. **L. Suarez-Reynoso:** Data curation, Supervision. **A.L. Padilla-Rodriguez:** Conceptualization, Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – review & editing.

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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