Pigmented Spindle Cell Nevus of Reed of the Eyelid

Melina I. Morkin Mitesh K. Kapadia Nora V. Laver

Department of Ophthalmology, New England Eye Center, Tufts Medical Center, Tufts University, Boston, MA, USA

Keywords

Nevus of Reed · Pigmented spindle cell nevus · Eyelid · Benign behavior

Abstract

Purpose: To report the clinical, pathological, and immunohistochemical features of the first pigmented spindle cell nevus (PSCN) of Reed documented to have appeared in the eyelid. **Methods:** The findings of clinical and histopathological examination are presented, along with differential diagnoses and a review of the pertinent literature. **Case:** A 3-year-old boy presented with a rapidly growing, heavily pigmented left lower lid papule raising the concern of malignancy, warranting excisional biopsy. Nests of predominantly junctional Mart-1-positive spindle cells were identified by histopathological examination. The cells were largely uniform in size, elongated, surrounded by granular and coarse melanin, with a Ki-67 proliferation index of 0–2%. Five-month follow-up did not evidence any recurrence or invasive behavior of this benign melanocytic tumor. **Conclusion:** This is the first documented case of PSCN of Reed, a distinct entity from Spitz nevus, presenting in the eyelid. The differential diagnoses include spindle cell and superficially spreading malignant melanoma as well as dysplastic nevus. Integration of clinical and histopathological findings with immunohistochemical and fluorescence in situ hybridization markers plays a central role in the diagnosis.

© 2017 S. Karger AG, Basel

Introduction

Acquired melanocytic eyelid lesions can pose a diagnostic challenge to the caring physician in the presence of features worrisome for melanoma, especially in the pediatric population [1]. The pigmented spindle cell nevus (PSCN) of Reed, first described in 1975 [2] and once considered a pigmented variant of a spindle cell type Spitz nevus, may simulate melanoma histologically and clinically [3]. It often presents silently as a small, relatively well-circumscribed and darkly pigmented lesion, with a history of recent-onset rapid growth followed by stability or rarely involution. Although PSCN may be found anywhere in the skin, the classic presentation is that of a symmetrical plaque-like black papule with smooth discrete borders on the thigh or leg of a young adult female [4]. We report the first documented case of an eyelid nevus of Reed and discuss the clinical, histological, and immunohistochemical findings that typically differentiate this lesion from its malignant counterparts, primarily spindle cell and superficially spreading melanoma.

Presented at the Joint Conference of the Verhoeff-Zimmerman and the European Ophthalmic Pathology Societies, Charleston, SC, 2016.

Fig. 1. Eyelid skin nevus of Reed. **a** Photograph of the left eye showing a darkly pigmented and minimally elevated lower eyelid papule with rather discrete margins. **b** The lesion displayed a dome-shaped configuration with increased pigmentation and hypercellularity (H&E, $\times 4$). **c** Ovoid intraepidermal and dermal nests oriented mostly perpendicular to the surface, containing spindle cells, and intracellular and dermal melanin clumps (H&E, $\times 10$).

d Large proliferations of elongated cells largely uniform in size, with few mitoses, as well as granular and coarse melanin (H&E, $\times 20$). **e** Stain with Mart-1 evidencing the presence of junctional melanocytic nests ($\times 10$). **f** Ki-67 labels the nuclei of actively proliferating cells found primarily in the lowest one-third of the epidermis ($\times 10$).

Case Report

A 3-year-old boy in good health presented to the New England Eye Center for evaluation of a pigmented left lower eyelid lesion having increased in size over a period of 9 weeks. Clinical examination showed a well-circumscribed heavily pigmented papular lesion measuring approximately 2.7 mm (Fig. 1a). There were no other associated symptoms or history of malignancies. A complete

excisional biopsy was performed for histopathological examination (Fig. 1b–f).

The paraffin-embedded formalin-fixed specimen was sectioned and stained with H&E, Mart-1, and Ki-67. At low power scanning magnification, the lesion appeared symmetrical and junctional (Fig. 1b). Elongated, heavily pigmented spindle cells whose borders seemed to partially blend with the surrounding keratinocytes were noted in the basal epidermis arranged in nests

Table 1. Salient features of pigmented spindle cell nevus in comparison with malignant melanoma

Pigmented spindle cell nevus	Spindle cell melanoma/superficially spreading melanoma
Usually >7 mm in diameter	Usually <7 mm in diameter
Young women, lower limbs	Trunk, upper limbs, head and neck
Symmetrical	Asymmetrical
Ovoid nests of cells oriented perpendicular to the epidermis	Nests variable in size, shape, and orientation
Little or no pagetoid spread into epidermis	Obvious pagetoid spread into epidermis
Abundant coarse melanin	Lesser pigment, finely divided
Cells in papillary dermis respect reticular dermis	Cells do not respect the interface if vertical growth is present
Maturation towards the dermis	Cells in dermis similar to cells in epidermis
Narrow elongated spindle cells	Large epithelioid cells predominate
Mitosis in epidermis, absent in dermis	Mitosis in epidermis and dermis
Cells uniform in size	Cellular variability

(Fig. 1c). The peripheral margins were well circumscribed, with few or no single cells present beyond the last melanocytic nest. Pagetoid spread into the epidermis was not present. At higher magnification, the lesional cells were more elongated and less round than those of Spitz nevi, with no prominent nucleoli (Fig. 1d). Scattered mitoses were present, measured as 1–2/mm². Mart-1 delineated the junctional epidermal location of the nests (Fig. 1e). Immunostaining with Ki-67 revealed a proliferation index ranging from 0 to 2%. The benign nature of this fully excised melanocytic tumor was confirmed. No further treatment was warranted. A 5-month follow-up has not suggested any recurrence or aggressive behavior.

Discussion

In the ocular region, PSCN of Reed had only been reported to occur in the conjunctiva of a 9-year-old [5]. This is the first documented case of Reed nevus appearing in the eyelid. Although the prevalence of ocular Reed nevi has not been established given the small number of reports, underreporting may contribute to the rarity of this entity, which could be presumably more common than described.

PSCN of Reed, once considered a pigmented variant of spindle cell Spitz nevi, is now recognized by most authors as a distinct entity [6, 7]. Three cases of Spitz nevi located in the eyelid have been reported, but none with findings characteristic of PSCN [8]. Reed nevus is composed histologically of elongated spindle-shaped and nevoid cells with a benign biologic behavior. Histopathological features in common with Spitz nevi and in contrast with malignant melanoma include a relatively small size, lesion symmetry, uniformity of cell type, good circumscription, and maturation of cells from superficial to

deep. Eosinophilic Kamino bodies resembling those seen in Spitz nevi may be found. In contrast to classic Spitz nevi, the lesion is usually heavily pigmented, with abundant coarse melanin granules in the lesional cells and keratinocytes, and mostly confined to the papillary dermis or dermoepidermal junction. Spitz nevi usually involve the reticular dermis. Cases of hypopigmented Reed nevus have been described [9].

Dermatoscopy substantiates the distinction between nevi of Reed and Spitz. It has been proposed that a “starburst dermatoscopic pattern,” which demonstrates prominent diffuse dark pigmentation and peripheral radial streaks, is more typically seen with PSCN, while a “globular pattern” with central lighter brown-grey or blue pigmentation and a surrounding rim of large brown globules is largely associated with Spitz nevi [10]. These dermatoscopic features are thought to correlate with the location of the melanocytic nests, predominantly extending in the plane of the dermoepidermal junction for PSCN, and along the epidermis and deeper in the dermis for Spitz nevi. Naturally, the presence of atypical variants of PSCN and Spitz nevi can make this discernment more arduous [11].

The major differential diagnosis of PSCN of Reed includes spindle cell malignant melanoma, superficially spreading malignant melanoma, and dysplastic nevus. For a detailed comparison between PSCN and melanoma, see Table 1. A pigmented spindle cell melanocytic lesion involving the reticular dermis with pushing fascicles is worrisome for a melanoma diagnosis. A high mitotic rate in the dermis with abnormal mitosis is also suggestive of melanoma. Spontaneous ulceration, necrosis, or epithelioid cells are unusual in benign nevi. More cellular and thicker cases of PSCN also need to be distinguished from

spindle cell nodular melanomas, occurring in older populations and in sun-damaged skin.

PSCN usually does not exhibit the characteristic delicate elongation of rete ridges that characterizes dysplastic nevi. The spindle cell nevi are usually more cellular, and although dysplastic nevi may have some spindle-shaped melanocytes, this is not a uniform predominant population. The spindle cells in dysplastic nevi tend to be oriented horizontally, while the spindle cell nevus cells tend to “rain down” vertically.

Is there any immunohistochemical marker that can differentiate a benign PSCN from melanoma? Many immunohistochemical stains have been studied to serve as potential diagnostic tools. For instance, the Ki-67 protein, which is expressed during the proliferative cell cycle, has been logically found to have low expression in PSCN, ranging from 0 to 5%, while in contrast the mean Ki-67 expression in melanoma is 12.7% [12]. Unfortunately, despite the expression difference, these numbers lead to an unreliably low negative predictive value.

The tumor suppressor TP53 maintains cells in a resting stage after DNA damage and can also initiate apoptosis if DNA is not repaired. TP53 dysfunction is generally associated with p53 protein overexpression, which can be found in the vertical growth phase of malignant melanomas. p53 has been proposed as a useful concurrent marker with Ki-67 to identify the presence of vertical growth in nodular malignant melanoma with a sensitivity of 75% [13].

HMB-45 has been found to be highly expressed in the intraepidermal component of compound Spitz nevi, gradually decreasing with depth and being largely negative in the reticular dermis in comparison to malignant melanoma [14]. HMB-45 can prove a useful adjunct diagnostic method in the proper clinicopathological context, and may also delineate pagetoid and adnexal spread.

Other immunohistochemical markers that have been shown to differ significantly in PSCN compared to melanoma unfortunately pose some challenges in interpretation, given the highly variable expression levels of the proliferation regulator cyclin D1 in melanocytic nevi, and the poorly perceptible nuclear uptake of the apoptosis inhibitor survivin in melanoma [12].

Clonal chromosomal aberrations discriminating melanoma from nevi can be analyzed with a fluorescence in situ hybridization panel targeting 4 known sites in chromosomes 6 and 11 [15], which aid in the identification of malignant melanoma with a 93% specificity and 83–90% sensitivity [12]. However, the sensitivity is lower for in situ malignant melanoma and PSCN at approximately 70–73% [12].

In summary, a review of the literature reveals that there is no single marker that can reliably differentiate benign melanocytic tumors – and PSCN in particular – from malignant melanoma. Therefore, combination of the clinical and histopathological features with immunohistochemical and fluorescence in situ hybridization markers whenever possible remains central to achieve the correct diagnosis.

Statement of Ethics

This article does not meet the Federal Policy for the Protection of Human Subjects definition of Research and therefore does not need to be approved by Tufts Medical Center’s Institutional Review Board. The appropriate consents for treatment was obtained. There is no identifiable personal information to be disclosed or divulged, which protects the patient’s health information and nullifies any HIPAA violations.

Disclosure Statement

The authors have no conflicts of interest.

References

- 1 Ferrari A, Bono A, Baldi M, Collini P, Casanova M, Pennacchioli E, Terenziani M, Marcon I, Santinami M, Bartoli C: Does melanoma behave differently in younger children than in adults? A retrospective study of 33 cases of childhood melanoma from a single institution. *Pediatrics* 2005;115:649–654.
- 2 Reed RJ, Ichinose H, Clark WH Jr, Mihm MC Jr: Common and uncommon melanocytic nevi and borderline melanomas. *Semin Oncol* 1975;2:119–147.
- 3 Pedrosa AF, Lopes JM, Azevedo F, Mota A: Spitz/Reed nevi: a review of clinical-dermatoscopic and histological correlation. *Dermatol Pract Concept* 2016;6:37–41.
- 4 Schmoekel C, Wildi G, Schafer T: Spitz nevus versus malignant melanoma: Spitz nevi predominate on the thighs in patients younger than 40 years of age, melanomas on the trunk in patients 40 years of age or older. *J Am Acad Dermatol* 2007;56:753–758.
- 5 Seregard S: Pigmented spindle cell naevus of Reed presenting in the conjunctiva. *Acta Ophthalmol Scand* 2000;78:104–106.
- 6 Webber SA, Siller G, Soyer HP: Pigmented spindle cell naevus of Reed: a controversial diagnostic entity in Australia. *Australas J Dermatol* 2011;52:104–108.
- 7 Ferrara G, Argenziano G, Soyer HP, Chimenti S, Di Blasi A, Pellacani G, Peris K, Piccolo D, Rubegni P, Seidenari S, Staibano S, Zalaudek I, De Rosa G: The spectrum of Spitz nevi: a clinicopathologic study of 83 cases. *Arch Dermatol* 2005;141:1381–1387.

- 8 Shields PW, Jakobiec FA, Stagner AM, Yoon MK: Spitz nevus arising in the eyelid of a teenager. *Surv Ophthalmol* 2016;61:228–235.
- 9 Requena C, Requena L, Sánchez-Yus E, Kutzner H, Llombart B, Sanmartín O, Botella-Estrada R, Nagore E, Serra C, Guillén C: Hypopigmented Reed nevus. *J Cutan Pathol* 2008;35(suppl 1):87–89.
- 10 Argenziano G, Scalvenzi M, Staibano S, Brunetti B, Piccolo D, Delfino M, De Rosa G, Soyer HP: Dermatoscopic pitfalls in differentiating pigmented Spitz naevi from cutaneous melanoma. *Br J Dermatol* 1999;141:788–793.
- 11 Cook MG: Benign melanocytic lesions mimicking melanomas. *Pathology* 2004;36:414–418.
- 12 Diaz A, Valera A, Carrera C, Hakim S, Aguilera P, Garcia A, Palou J, Puig S, Malvey J, Alos L: Pigmented spindle cell nevus: clues for differentiating it from spindle cell malignant melanoma. A comprehensive survey including clinicopathologic, immunohistochemical, and FISH studies. *Am J Surg Pathol* 2011;35:1733–1742.
- 13 Kaleem Z, Lind AC, Humphrey PA, Sueper RH, Swanson PE, Ritter JH, Wick MR: Concurrent Ki-67 and p53 immunolabeling in cutaneous melanocytic neoplasms: an adjunct for recognition of the vertical growth phase in malignant melanomas? *Mod Pathol* 2000;13:217–222.
- 14 Bergman R, Dromi R, Trau H, Cohen I, Lichtig C: The pattern of HMB-45 antibody staining in compound Spitz nevi. *Am J Dermatopathol* 1995;17:542–546.
- 15 Gerami P, Zembowic A: Update on fluorescence in situ hybridization in melanoma: state of the art. *Arch Pathol Lab Med* 2011;135:830–837.