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Management of pediatric melanocytic lesions

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Abstract

Melanocytic lesions in children comprise a rare diagnosis and can be difficult to manage. We present a 5-year-old female with a suspicious melanocytic lesion in the setting of a congenital nevus on her back. Nevoid melanoma-like features of a polypoid lesion with nests of atypical melanocytes throughout the dermis were seen. Nuclei were enlarged with prominent nucleoli. Staining with markers of melanocyte differentiation and proliferation (Melan-A, HMB-45 and Ki-67) revealed atypical melanocytic proliferation. Findings were inconclusive for definitive diagnosis of nevoid melanoma. Due to the patient's young age and uncertain malignant potential of the lesion, aggressive management was undertaken with wide excision and sentinel lymph node biopsy.

Keywords

melanocytic proliferation; nevoid melanoma; atypical nevus

Abbreviations

MelTUMP: melanocytic tumor of uncertain malignant potential; WLE: wide local excision; SLNB: sentinel lymph node biopsy; CLND: completion lymph node dissection; NCCN: National Comprehensive Cancer Network; CGH: comparative genomic hybridization; FISH: fluorescence in situ hybridization; OS: overall survival; DSS: disease-specific survival

Introduction

Pediatric melanoma, often associated with congenital nevi, has a rare incidence of 300-400 cases per year. However, the rate of incidence in pediatric patients has been increasing 2.8% per year [1]. Some well-established risk factors include fair skin, xeroderma pigmentosa, multiple benign nevi, dysplastic nevi, and family history of melanoma [1]. While controversial, some authors proposed approaching melanocytic lesions as a spectrum of aggressive disease from melanoma to melanocytic tumor of uncertain malignant potential (MelTUMP) to atypical proliferative nevi to better direct appropriate treatment [2,3]. Suspicious atypical proliferative nevi may be observed or treated with narrow margin excision. Management of MelTUMP, however, is controversial because this entity is rare and differentiating aggressive from benign MelTUMP can be difficult [3].

Nevoid melanoma, also reported as minimal deviation melanoma or small-cell melanoma, is a rare subtype of melanoma with subtle histological findings that make it difficult to distinguish from benign lesions. Several authors have reported suggestive histological features of nevoid melanoma in an attempt

to improve the accuracy of diagnosis. Idriss et al reported architectural features of plaque-like lesion with raised center and polypoid growth pattern as the most common findings under scanning microscopy [4]. They also noted that 80% of their cases included junctional nests or non-nested melanocytes. Diwan et al identified a feature of immaturity, demonstrating irregular patchy HMB-45 and Ki-67 reactivity deeper into the dermis [5]. Yelamos et al reported differentiating features of melanoma from proliferative nodules in congenital nevi, listing expansive nodules with ulceration, high grade nuclear atypia, and high mitotic index as traits more predictive of melanoma [6]. Nevertheless, in a study of 43 cases of nevoid melanoma, as much as 40% missed melanoma as the initial diagnosis because of its obscure histologic traits [4]. Due to its indistinguishable features, it is not uncommon for pathologists to report nevoid melanoma as a benign lesion or vice versa. This is concerning because even though no large studies have analyzed the outcomes of nevoid melanoma, some have reported recurrence rates up to 50% and mortality of 25% [5]. The delay in diagnosis may contribute to its poor outcome. Due to its aggressive nature, treatment for nevoid melanoma is no different from conventional melanoma recommended by National Comprehensive Cancer Network (NCCN) guidelines. Cassarino et al reported a case of nevoid melanoma in a 4 and a half year old patient with no evidence of recurrence status post wide local excision (WLE) and completion lymph node dissection (CLND) following a positive sentinel lymph node biopsy (SLNB) [7].

Here, we discuss a rare pediatric case of a suspicious lesion diagnosed as atypical proliferative nevus, MelTUMP, and possible stage IIA nevoid melanoma that was managed aggressively as a melanoma. We review our own institutional experience with pediatric melanoma with regard to treatment and outcomes. We also present a review of the diagnosis and management specifically for nevoid melanoma.

Case Presentation

The patient was a 5-year-old white female with a family history of melanoma presenting with a congenital nevus of her mid lower back with increasing central area of painful pinkish nodularity on the nevus. Initial excisional biopsy revealed a polypoid lesion showing nests of severely atypical melanocytes involving the superficial and deep dermis with positive margins (Figure 1A). These atypical melanocytes were epithelioid with enlarged nuclei and prominent nucleoli (Figure 1B). The usual maturation of dermal components in this area was not appreciated. There was an increased number of mitoses both in the superficial and deep dermis. The adjacent epidermis showed epidermal hyperplasia with interconnection of rete ridges. There was hyperkeratosis and parakeratosis. Some deep dermal melanocytes were noted surrounding cutaneous appendages and small dermal vessels. The Melan-A stain highlighted atypical melanocytic proliferation in a broad and asymmetrical distribution (Figure 1C). The Ki-67 stain identified basal keratinocytes and increased dermal cells (Figure 1D). At this point in the work-up of our patient, the histological and immunohistochemical findings were consistent with an irritated, severely atypical compound melanocytic neoplasm with Clark's level IV, maximal Breslow thickness approximately 2.42 mm, and mitotic index greater than $3/mm^2$. The atypical melanocytic proliferation extended to the inked margin of the specimen, and therefore re-excision was recommended.

Re-excision was performed with pathology revealing persistent atypical compound neoplasm with positive margins. However, now there was a concern for a possible nevoid melanoma arising within

a congenital nevus. A second opinion from an outside expert pathologist suggested the diagnosis of proliferative nodule of uncertain malignant potential. The nodule was situated in a background of a congenital nevus, and the overlying epidermis was intact without ulceration. There was evidence of blending between two cell types at periphery, consistent with feature seen in nodules within congenital nevi. HMB-45 showed top heavy, skin staining within the nodules.

Secondary to the uncertain malignant potential, including the possibility that the lesion was a clinical stage IIA melanoma arising from a congenital nevus, it was recommended that the patient undergo both 1cm margin wide local excision and sentinel lymph node biopsy for regional lymph node staging. The wide excision showed no residual melanocytic neoplasm. One left axillary sentinel lymph node was negative for metastatic disease. The patient had no post-operative complications. She has had no evidence of disease approximately 3 years later.

Discussion

We have presented a rare case of a 5-year-old female with, at times, varying diagnoses of atypical proliferative nevus to MelTUMP to possible nevoid melanoma for the same lesion. Due to the uncertain malignant potential of this lesion, we chose to aggressively manage the patient to avoid under treating malignant melanoma.

To better guide further treatment, in general, stage IB or stage II melanoma patients are offered SLNB. Within our institution's experience from 1950-2015 with a total of 63 pediatric melanoma patients (ages 18 and under), 12 patients with stage IB or higher disease underwent WLE and SLNB with a post-operative complication rate of 8.3%, resulting in wound infection and dehiscence. This was a rate similar to that reported in a large study [8]. Six of 12 patients had a positive SLNB, and 5 out of 6 underwent lymph node dissection. The mortality rate was 33% for patients with positive SLNB and 0% for negative SLNB status. This supports the notion that positive node status is associated with poor outcome providing support to the use of SLNB for further staging.

In our institutional analysis, certain clinical variables were associated with survival as shown in Table 1. Of 60 patients with available survival data, we found that age at diagnosis, thickness, ulceration, and node and metastasis status were associated with overall survival (OS). Similar variables were associated with disease-specific survival (DSS) and progression-free survival (PFS). OS at 5 and 10 years was 0.77 and 0.63 respectively; similar to other reports [1,9]. DSS at 5 and 10 years was 0.83 and 0.73.

While positive node status has been associated with worse outcomes in adult melanoma patients, there is conflicting evidence in pediatrics. One of the largest long term outcome studies revealed no difference in 5-year OS in pediatric patients (ages 1-10) based on node status. Moreover, there was no survival benefit of surgical intervention including SLNB or CLND in these patients, suggesting that wide resection alone may be effective in this group. The 5-year OS of adolescents (ages 11-20), however, was significantly shorter in the positive node cohort, similar to the pattern seen in adults [9]. Interestingly, pediatric melanoma patients have been reported to have longer survival than the adult counterparts in early stages of disease [10]. These findings suggest that the biology of pediatric melanoma may be different from those found in adults and raise the question of whether management should also be different.

Appropriate treatment of MelTUMP is also controversial. Berk et al reported a retrospective review on management of pediatric melanoma, MelTUMP, and Spitz nevus with atypical features (SNAF), a type of atypical proliferative nevus. Melanoma was treated according to NCCN guidelines including WLE and possible SLNB [2]. MelTUMP cases underwent excision, and 71% underwent SLNB yielding 33% with positive microscopic nodes. Those with positive microscopic nodes were offered high dose interferon alpha for 1 year. SNAF was treated with narrow margin excisions. Overall survival of melanoma patients was 92% at 35 months while OS for MelTUMP or SNAF was 100% at 33 months. While SLNB may provide valuable prognostic information at a relatively low risk, some authors argue against performing SLNB for MelTUMP for the behavior of these lesions is not fully understood to clearly proceed with biopsy based management [11]. However, some authors report cases of metastatic atypical nevi and support the use of SLNB as tool to manage these aggressive lesions [12]. While SLNB is considered relatively safe, there is significant morbidity associated with CLND, which is the typical next step in patients with positive nodes [13].

Due to the unreliable histologic distinction of nevoid melanoma from its mimics like MelTUMP or atypical proliferative nevi, other methods to assess the malignant potential may be helpful. Moreover, further research to understand the biological behavior of melanocytic tumors is necessary to provide a more definitive classification and appropriate treatment for these patients. Recent advances in cytogenetic studies have been shown to help determine the malignant potential of lesions suspicious for nevoid melanoma. In a study of 58 cases of nevoid melanoma, FISH was positive in 74% of cases with 6p25 gains being the most common feature [14]. Comparative genomic hybridization (CGH) was positive in 88% of 8 cases of nevoid melanoma with most common losses of 9p or 2q and most common gains of 22q or 6p. In differentiating nevoid melanoma from proliferative nodules, FISH showed isolated gains in 6p25 for melanoma, and either FISH and CGH revealed multiple whole chromosome aberrations in proliferative nodules [14]. While cytogenetic studies may help add ancillary information, the methods are still experimental and thus require more refinement to be used as a reliable tool in the clinical setting.

There is limited evidence on managing pediatric melanoma partly due to the rarity of the disease in this population. Additional large studies are needed to elucidate the effectiveness of surgical and adjuvant treatments in pediatric melanoma patients. This may be done by referring pediatric patients with melanocytic tumors to high volume centers for treatment and follow up to build a multicenter database. Referral to these centers may also improve outcomes as comprehensive care from specialized centers has been shown increase survival [15].

Conclusion

In conclusion, there is conflicting evidence on the management of pediatric melanocytic lesions. What seems to be clear is that advanced melanoma in children is just as lethal as in adults. Until there exists a better understanding about the behavior of melanoma in children, it is reasonable to follow the guidelines set for adults to prevent advancement of early disease. For MelTUMP, a personalized approach to management discussing the width of excision and the risks and benefits of SLNB should be taken with each patient, as there is no strong evidence to support extensive management. This may equate to undergoing wide excision and close observation, delaying node sampling until clinically evident disease presents itself. An individualized approach, with expert pathology, is recommended for pediatric

patients with this atypical and challenging lesion.

Table

Table 1: Variables associated with overall survival analyzed by Cox regression model.

Variable		5-Year OS Rate (95% CI)	Hazard Ratio (95% CI)	P-value
Age (years)	Unit Inc. (1 year)		1.234 (1.010, 1.506)	0.039
Thickness (mm)	Unit Inc. (1 mm)		1.426 (1.168, 1.740)	<.001
Ulceration	No	95.2% (70.7%, 99.3%)	1.000	0.012
	Yes	57.1% (17.2%, 83.7%)	5.630 (1.470, 21.561)	
N status	N0	93.5% (76.1%, 98.3%)	1.000	0.003
	N1+	61.9% (38.1%, 78.8%)	4.084 (1.639, 10.179)	
M status	M0	91.5% (75.8%, 97.2%)	1.000	<.001
	M1+	91.5% (75.8%, 97.2%)	7.749 (2.871, 20.914)	

Figures

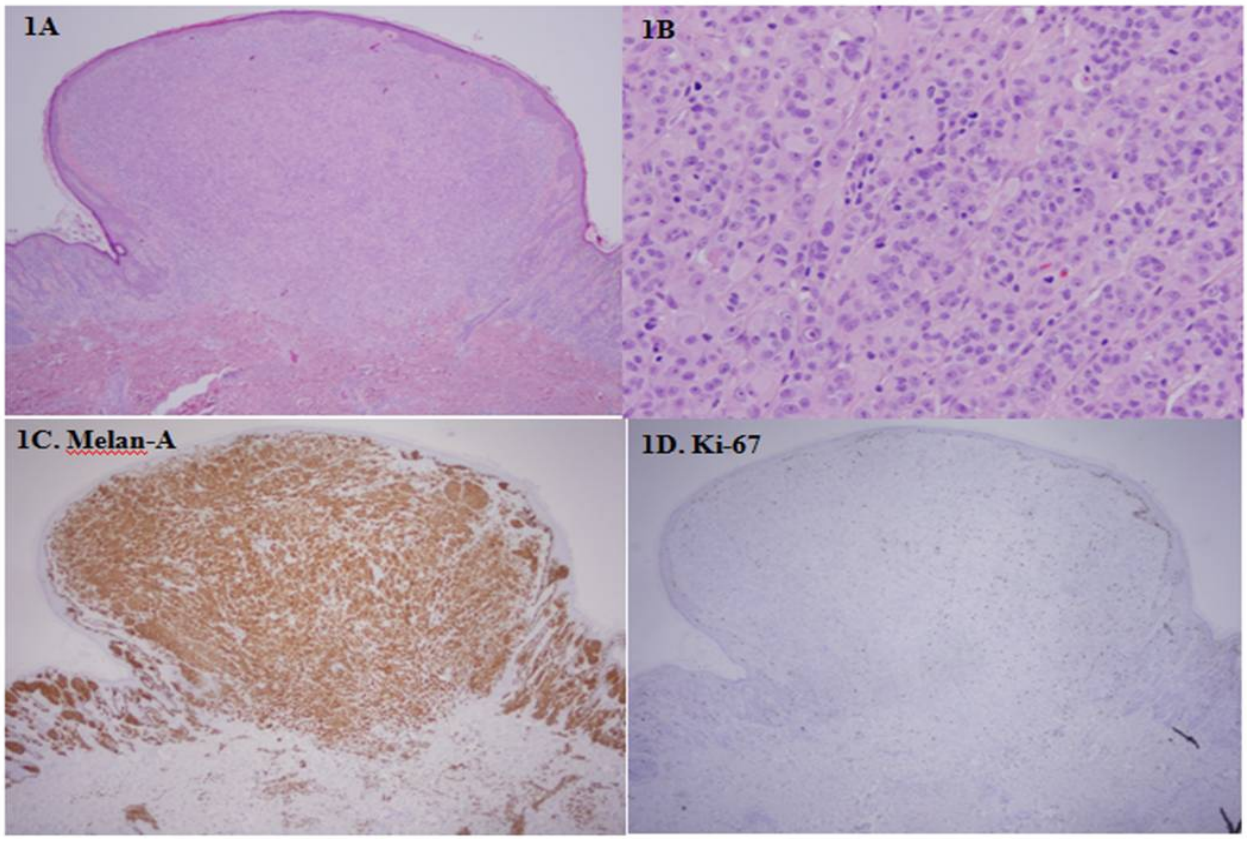

Figure 1: Histology of Patient Biopsy

1A) Polypoid lesion showing nests of atypical melanocytes involving the superficial and deep dermis.

1B) The atypical melanocytes in the polypoid area are epithelioid with enlarged nuclei and prominent nucleoli. The usual maturation of dermal components is not appreciated. There is an increased number of mitosis both in the superficial and deep dermis.

1C) The Melan-A stain highlights atypical melanocytic proliferation in a broad and asymmetrical distribution.

1D) The Ki-67 stain labels basal keratinocytes and is increased in dividing dermal cells.

References

1. Strouse, J.J., et al., Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. J Clin Oncol, 2005. 23(21): p. 4735-41.

2. Berk, D.R., et al., Melanoma and melanocytic tumors of uncertain malignant potential in children, adolescents and young adults--the Stanford experience 1995-2008. Pediatr Dermatol, 2010. 27(3): p. 244-54.

3. Cerroni, L., et al., Melanocytic tumors of uncertain malignant potential: results of a tutorial held at the XXIX Symposium of the International Society of Dermatopathology in Graz, October 2008. Am J Surg Pathol, 2010. 34(3): p. 314-26.

4. Idriss, M.H., et al., Nevoid melanoma: A study of 43 cases with emphasis on growth pattern. J Am Acad Dermatol, 2015. 73(5): p. 836-42.

5. Diwan, A.H. and A.J. Lazar, Nevoid melanoma. Clin Lab Med, 2011. 31(2): p. 243-53.

6. Yelamos, O., et al., A comparative study of proliferative nodules and lethal melanomas in congenital nevi from children. Am J Surg Pathol, 2015. 39(3): p. 405-15.

7. Cassarino, D.S., et al., Metastatic nevoid melanoma in a 4 1/2-year-old child. J Cutan Pathol, 2003. 30(10): p. 647-51.

8. Moody, J.A., et al., Complications of sentinel lymph node biopsy for melanoma - A systematic review of the literature. Eur J Surg Oncol, 2016.

9. Lorimer, P.D., et al., Pediatric and Adolescent Melanoma: A National Cancer Data Base Update. Ann Surg Oncol, 2016. 23(12): p. 4058-4066.

10. Richards, M.K., et al., Survival and Surgical Outcomes for Pediatric Head and Neck Melanoma. JAMA Otolaryngol Head Neck Surg, 2016.

11. Kwon, E.J., H.L. Winfield, and A.S. Rosenberg, The controversy and dilemma of using sentinel lymph node biopsy for diagnostically difficult melanocytic proliferations. J Cutan Pathol, 2008. 35(11): p. 1075-7.

12. Mones, J.M. and A.B. Ackerman, "Atypical" blue nevus, "malignant" blue nevus, and "metastasizing" blue nevus: a critique in historical perspective of three concepts flawed fatally. Am J Dermatopathol, 2004. 26(5): p. 407-30.

13. Roaten, J.B., et al., Sentinel lymph node biopsy for melanoma and other melanocytic tumors in adolescents. J Pediatr Surg, 2005. 40(1): p. 232-5.

14. Yelamos, O., et al., Morphologic clues and utility of fluorescence in situ hybridization for the diagnosis of nevoid melanoma. J Cutan Pathol, 2015. 42(11): p. 796-806.

15. Freemyer, B., et al., Treatment outcomes in pediatric melanoma-Are there benefits to specialized care? J Pediatr Surg, 2016.