Atypical Spitz nevus versus Spitz melanoma: Is age a deceiving factor?

Charles Jian, Samih Salama, Gabriela Gohla, Sarab Mohamed, Brian H Cameron, Barbara Heller, Salem Alowami

ABSTRACT

Introduction: Spitz melanoma is very rare in the young pediatric (0–10) population, with clinical behavior differing from adult melanoma. It may be challenging to distinguish diagnostically from an atypical Spitz nevus, and patients' young age may cause hesitation despite histological support.

Case Report: We present a case report of pediatric-type Spitz melanoma in a 4-years-8-months-old girl which was reviewed by pathology groups from 1 tertiary and 2 quaternary centers. A diagnosis was made only after extensive genetic testing in conjunction with the supporting evidence from histology and immunohistochemistry. 19 previously published case reports of pediatric-type Spitz melanoma are also reviewed and summarized to give insight into its presentation and prognosis.

Conclusion: This case report and review of literature highlights that age can be a misleading factor in reporting atypical melanocytic lesions, and may deter pathologists from diagnosing a tumor as malignant. While clinical history is indispensable in pathology practice, the patient's age should not distract us from the histology. It also demonstrates the usefulness of molecular pathology as a future adjunct in the practice of pathology. Entities that overlap morphologically or that present with conflicting histological features may be more easily categorized based on the presence of genetic variants or deletions. In our case, p16 deletion and anaplastic lymphoma kinase (ALK) translocation were supporting features that in conjunction with histology clinched the diagnosis of melanoma.

Keywords: Age, Atypical Spitz nevus, Molecular pathology, Pediatric, Spitz melanoma

INTRODUCTION

Spitz melanoma is a very rare disease in the pediatric population, and differs from adult melanoma [1, 2], with variation even between infants (0–10 years of age) and adolescents (11–19 years of age) [3–5]. In the prepubescent population, the majority of melanomas are of the pediatric Spitz melanoma/atypical Spitz tumor type, as this patient was, with a second biologically separate category of melanomas arising in association with giant congenital nevi or de novo. Prognostically, the former tends to be more low-grade or borderline malignant in behavior, despite metastasis to lymph nodes [6, 7], while the latter is aggressive and invariably fatal. A note is made of recent changes in categorization by the WHO in 2018, which distinguishes spitzoid melanoma, a
purely morphological diagnosis, from Spitz melanoma, a subset of spitzoid melanoma with both the morphological features and the specific genetic signatures of mitogen-activated protein kinase (MAPK) activating alterations, which is present in this case [8]. This case report highlights age as a misleading characteristic in the diagnosis of Spitz melanoma, and a literature review is performed to examine trends, presentation, and prognosis in previous diagnoses of pediatric Spitz melanoma.

CASE REPORT

A 4-years-8-months-old Caucasian girl presented with an 18-month history of a 2.5 × 2.0 cm polypoid lesion with a 5 mm base on the right lateral lower chest wall, which clinically resembled a pyogenic granuloma (Figure 1). It had been enlarging since it was first discovered, frequently bled and wept, and was painful to the touch. There were no abnormal nodes palpable in the groin, axilla, or neck. The patient had no known past medical history or relevant family history. Specifically, there was no family history of melanoma or other genetic syndromes that predisposed this patient to developing malignancies.

The lesion was removed by a pediatric surgeon (BHC) approximately three weeks later with 3 mm clinical margins. She had a postoperative cellulitis wound infection that resolved with antibiotics. The pathology was initially reported as an atypical Spitz nevus with positive deep margins with concerns for melanoma. However, there was hesitation to diagnose the lesion as melanoma due to the patient’s age. Interdepartmental dermatopathology review agreed with the diagnosis of atypical Spitz nevus, with concerns for melanoma. An external dermatopathology review again diagnosed the lesion as an atypical Spitz tumor with high grade melanocytic atypia and features concerning for melanoma. A further quaternary care dermatopathology review made the diagnosis of a pediatric-type Spitz melanoma with ALK rearrangement.

Subsequently a local expert oncologic surgeon was consulted (BH), and there was discussion of management with other North American children’s hospitals. The patient also underwent further workup, including a complete staging with computed tomography (CT) of the chest, abdomen, and pelvis as well as a head magnetic resonance imaging (MRI) which showed no evidence of metastatic disease. A sentinel lymph node study showed focal activity in the right axilla in keeping with activity in sentinel nodes. This led to the decision to proceed with a scar re-excision with 2 cm clinical margins, flap reconstruction, and sentinel lymph node biopsy. Six nodes were excised from the right axilla, five of which were positive for metastatic melanoma.

The patient recovered well and has subsequently undergone close clinical follow-up with clinical exams and ultrasound imaging of the chest for recurrence. As of 16 months following the initial resection, the patient remains free of disease.

Investigations

Routine histology of the original lesion

Basic histology revealed a 2.5 cm polypoid tumor with neutrophilic crusts (see Figures 2 and 3). The dermal tumor contained both epithelioid and spindle cells arranged in solid nests and sheets with positive deep margins with concerns for melanoma. However, there was hesitation to diagnose the lesion as melanoma due to the patient’s age. Interdepartmental dermatopathology review agreed with the diagnosis of atypical Spitz nevus, with concerns for melanoma. An external dermatopathology review again diagnosed the lesion as an atypical Spitz tumor with high grade melanocytic atypia and features concerning for melanoma. A further quaternary care dermatopathology review made the diagnosis of a pediatric-type Spitz melanoma with ALK rearrangement.

Subsequently a local expert oncologic surgeon was consulted (BH), and there was discussion of management with other North American children’s hospitals. The patient also underwent further workup, including a complete staging with computed tomography (CT) of the chest, abdomen, and pelvis as well as a head magnetic resonance imaging (MRI) which showed no evidence of metastatic disease. A sentinel lymph node study showed focal activity in the right axilla in keeping with activity in sentinel nodes. This led to the decision to proceed with a scar re-excision with 2 cm clinical margins, flap reconstruction, and sentinel lymph node biopsy. Six nodes were excised from the right axilla, five of which were positive for metastatic melanoma.

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Figure 1: Clinical presentation preoperatively of patient’s polypoid lesion (2.5 × 2.0 cm) on the right lateral lower chest wall.

Figure 2: Excised primary lesion, 40× magnification, H&E stain. The lesion consists of an ulcerated hyperplastic epithelium with a neutrophilic crust. The dermal lesion consists of solid nests and sheets of both epithelioid and spindle cells. The box denotes the field of view in Figure 3.
Immunohistochemistry

The tumor cells were strongly positive for melan-A, WT-1, S100, and CyclinD1. It was focally positive for HMB45 in the upper dermis, a feature found more commonly in benign nevi. It was also patchy positive for p16 (CDKN2A), demonstrating partial loss of expression. This was later confirmed with fluorescence in situ hybridization (FISH) which showed homozygous deletion of this tumor suppressor gene. Anaplastic lymphoma kinase was diffusely positive in the tumor cells. Ki67 was diffusely positive, demonstrating a high proliferation index. Figures 6 and 7 show micrographs of selected stains.

The tumor cells were negative for AE1/AE3 (pankeratin), SMA, CD34, myogenin, and desmin.

Molecular pathology

Fluorescence in situ hybridization testing using a melanoma kit for RREB1, MYB, CEP6, and CyclinD1 (11q13) probes was positive. While this did not equate to a diagnosis of malignant melanoma, this kit was found to be positive in 80–90% of diagnosed melanomas, and
negative in 95–100% of benign nevi. However, benign Spitz nevi do have a higher incidence of positivity (10–35%), possibly due to polyploidy [9, 10].

Fluorescence in situ hybridization demonstrated homozygous loss of p16 (CDKN2A) tumor suppressor gene in the tumor. Break-apart FISH showed an ALK rearrangement.

Next-generation sequencing was performed on the tumor which detected no clinically relevant variants (i.e., class 1–3A) [11] in BAP1, BRAF, CDK4, CDK6, CDKN2A, GNA11, GNAQ, KIT, NRAS, EIF1AX, SP3, B1, or HRAS. Sanger sequencing did not reveal a telomerase reverse transcriptase (TERT) promoter mutation in this tumor, which was a favorable prognostic factor.

**DISCUSSION**

Diagnosis of melanoma in the pediatric population is challenging, as there are numerous benign histologic mimics, especially in the Spitz nevus/Spitz melanoma spectrum. Other possible differential diagnoses can include Reed nevi, cellular blue nevi, or pigmented epithelioid melanocytoma. An extensive literature search for cases of cutaneous pediatric melanoma (0–10 years of age) was performed and showed that since 1987, only 19 individual cases of cutaneous pediatric melanomas have been published, highlighting the rarity of the diagnosis in this age group. See Table 1 for details on these case reports. Pediatric-type Spitz melanomas rarely develop distant metastases despite nodal metastases [6, 12]. This is supported by our review; a large proportion (11/19) of the published cases appear to be clinically well on follow-up at around 12 months, 6 of these 11 cases reported a Breslow depth greater than 4 mm and had positive sentinel lymph nodes.

Another study [13] reported clinical findings similar to our own case, in which the presented lesion appeared to mimic a pyogenic granuloma. The lesion evolved into a rubbery, erythematous papule over one month, and began to ulcerate and bleed, similar to our presented case. While a pyogenic granuloma would be overwhelmingly more likely than melanoma in a 10-month-old child, our case demonstrates that melanoma should be considered in the differential, and that changes in the lesion’s appearance should be closely monitored.

Management of Spitz melanoma and atypical Spitz lesions in the pediatric population generally derives from guidelines for adult melanoma [12]. A sentinel lymph node biopsy (SLNB) is often performed to assess for the need for a complete lymph node dissection and adjuvant therapy. In children, while this is prognostically significant, it does not improve melanoma-specific survival [14].

Histologically our patient’s lesion met criteria for a malignant lesion. However, given the history and the patient’s young age, three separate groups of pathologists from two quaternary academic centers were able to diagnose it.

**Table 1: Summary of case reports of cutaneous pediatric melanomas since 1987, by chronological order**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Presentation</th>
<th>Primary tumor size</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuen et al. (2019) [15]</td>
<td>5/M</td>
<td>Brown papule, mid upper back found at 2 years old, no ulceration</td>
<td>0.6 × 0.6 cm</td>
<td>Invasive melanoma 1.2 mm depth</td>
<td>Wide excision of primary</td>
<td>Disease free 20 months post-diagnosis</td>
</tr>
<tr>
<td>Yamaguchi et al. (2019) [16]</td>
<td>2/F</td>
<td>Scalp, arising from congenital melanocytic nevus. Rapid growth at 29-mo with ulceration pre-excision</td>
<td>13 × 11 cm (nevus pre-transformation)</td>
<td>Invasive melanoma 8.5 mm depth; metastasis to cervical lymph nodes by PET</td>
<td>Wide excision of primary, completion wide re-excision. Nivolumab initiated post-metastasis</td>
<td>N/A</td>
</tr>
<tr>
<td>Kumar et al. (2018) [17]</td>
<td>5/F</td>
<td>Right retroauricular swelling (metastatic nodule); pigmented nodule in right periorbital region (primary)</td>
<td>1.3 × 1.0 cm</td>
<td>Invasive melanoma, 6 mm. Metastatic to intraparotid lymph node</td>
<td>Parotidectomy, neck dissection, wide excision of primary</td>
<td>N/A, ongoing</td>
</tr>
<tr>
<td>Weyand et al. (2018) [18]</td>
<td>0/F (congenital)</td>
<td>Dark raised scalp lesion at birth</td>
<td>N/A; tumor present in liver, lungs, left tibia</td>
<td>Pigment synthesizing melanoma, 7.3 mm depth; widely metastatic</td>
<td>Nivolumab every 2 weeks</td>
<td>Stable disease 70 weeks post-diagnosis</td>
</tr>
<tr>
<td>Albino et al. (2015) [19]</td>
<td>3/F</td>
<td>Dark raised lesion, anterior right knee. No bleeding/ulceration</td>
<td>0.6 × 0.5 cm</td>
<td>Invasive melanoma, 4.95 mm (pT4a). SLN positive</td>
<td>Wide excision of primary, SLNB, CLND, medical adjuvant Tx</td>
<td>N/A</td>
</tr>
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<td>Case</td>
<td>Age/Sex</td>
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<tr>
<td>Batra (2015) [20]</td>
<td>6/F</td>
<td>Extremity</td>
<td>N/A</td>
<td>Spitz melanoma of childhood (depth not available), SLN positive, regional LND negative</td>
<td>Partial excision of primary with wide local re-excision, SLNB, CLND</td>
<td>Alive on follow-up at 17 months</td>
</tr>
<tr>
<td></td>
<td>10/M</td>
<td>Extremity</td>
<td>N/A</td>
<td>Spitz melanoma of childhood (depth not available), SLN positive, regional LND negative</td>
<td>Wide excision of primary, SLNB, CLND. Interferon × 1 year</td>
<td>Alive on follow-up at 34 months</td>
</tr>
<tr>
<td></td>
<td>2/F</td>
<td>Head/Neck</td>
<td>N/A</td>
<td>Spitz melanoma of childhood (depth not available), SLN positive, regional LND negative</td>
<td>Partial excision of primary with wide local re-excision, SLNB, CLND</td>
<td>Alive on follow-up at 50 months</td>
</tr>
<tr>
<td></td>
<td>4/F</td>
<td>Head/Neck</td>
<td>N/A</td>
<td>Spitz melanoma of childhood with Breslow depth &gt; 4 mm</td>
<td>Wide excision of primary</td>
<td>Alive on follow-up at 84 months</td>
</tr>
<tr>
<td>Kollipara et al. (2015) [21]</td>
<td>3/M, Li Fraumeni syndrome, congenital choroid plexus carcinoma</td>
<td>Pink nodule behind left ear</td>
<td>1.0 × 1.0 cm</td>
<td>Spitzoid melanoma of childhood, 6.5 mm depth</td>
<td>Excision of primary with 2 re-excisions, SLNB</td>
<td>Developed and died of myelodysplasia 14 months post-diagnosis with no recurrence</td>
</tr>
<tr>
<td>Tashiro et al. (2014) [13]</td>
<td>11 mo/F</td>
<td>Non-pigmented, rubbery erythematous papule, right face. Developed ulceration pre-excision</td>
<td>N/A</td>
<td>Spitz type melanoma 7.6 mm depth, SLN positive</td>
<td>Excision of primary with wide re-excision, SLNB</td>
<td>Disease free 12 months post-diagnosis</td>
</tr>
<tr>
<td>Katibi et al. (2014) [22]</td>
<td>3/F</td>
<td>6-mo history of multiple nodules on congenital melanocytic nevus in right axilla, with swelling in the axilla for 4 weeks. Extensive hyperpigmented patches on trunks and limb at birth</td>
<td>Multifocal 2 cm cutaneous nodules, with 10 × 7 cm axillary mass</td>
<td>Metastatic nodular melanoma on background of giant congenital melanocytic nevus, Clark stage 4; SLN positive by fine needle aspiration</td>
<td>Complete course of cisplatin, dacarbazine, vinblastine, interferon α-2B, granulocyte colony stimulating factor with minimal response. (Interleukin 2 was not available)</td>
<td>Died 1 month post-chemotherapy (4 months post-presentation, 12 months post initial discovery of lesion)</td>
</tr>
<tr>
<td>Sestini et al. (2012) [23]</td>
<td>4/M</td>
<td>Black nodule on scalp, with satellitosis; no ulceration</td>
<td>1.0 × 1.0 cm</td>
<td>Animal-type melanoma, 4.1 mm depth. SLN positive</td>
<td>Wide excision of primary, SLNB, LND of neck</td>
<td>Disease free 30 months post-diagnosis</td>
</tr>
<tr>
<td>Miranda et al. (2011) [24]</td>
<td>4/F</td>
<td>Red nodule, increased in sized over 3 months, bled easily. Anterior right shin</td>
<td>0.5 × 0.5 cm at biopsy</td>
<td>Spitzoid melanoma at least 3.0 mm depth</td>
<td>Wide excision of primary, SLNB, interferon α-2B 1 year</td>
<td>Disease free 12 months post-diagnosis</td>
</tr>
</tbody>
</table>
hesitant to label the tumor as malignant. Despite the use of immunohistochemistry, it was in fact only after exhaustive molecular analysis of the tumor at a third, subspecialized academic center in conjunction with the investigations performed prior that allowed the final diagnosis of pediatric-type Spitz melanoma to be made.

**CONCLUSION**

This case demonstrates two major lessons. The first is that age can be a misleading factor in reporting atypical melanocytic lesions, and may deter pathologists from diagnosing a tumor as malignant. While clinical history is indispensable in pathology practice, the patient’s age should not distract us from the histology. Children can get melanoma, although the clinical behavior generally differs from melanoma in adults. The second lesson highlights the usefulness of molecular pathology as a future adjunct in the practice of pathology. Entities that overlap morphologically or that present with conflicting histological features may be more easily categorized based on the presence of genetic variants or deletions. In our case, p16 deletion and ALK translocation were supporting features that in conjunction with histology clinched the diagnosis of melanoma.

**REFERENCES**


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<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>Fox et al.</td>
<td>8/M</td>
<td>Fast-growing pink papule posterior right shoulder</td>
<td>N/A</td>
<td>Invasive melanoma &gt;4 mm depth. SLN positive</td>
<td>Completion wide re-excision, SLNB, CLND, Interferon α-2B for 7 months; stopped from elevated liver enzymes</td>
<td>Disease free 36 months post-diagnosis</td>
</tr>
<tr>
<td>Bernhardt et al. (2009)</td>
<td>2/F (20 mo)</td>
<td>Superficial nodule, arising in 14 × 8 cm melanocytic nevus across mid lower back</td>
<td>1.5 × 1.2 cm</td>
<td>Invasive nodular melanoma, small cell type, 5 mm depth. SLN positive</td>
<td>Wide excision of primary with SLNB, CLND of bilateral axilla. Initially treated with interferon α-2B. Recurrent on therapy. Subsequently with high-dose IL-2, with recurrence</td>
<td>Died 90 days post-completion of high-dose IL-2</td>
</tr>
<tr>
<td>Stănescu et al. (2009)</td>
<td>10/F</td>
<td>Lesion arising in flat tan congenital lesion, cutaneous superior lip, 4 mm diameter</td>
<td>0.6 × 0.6 cm</td>
<td>Invasive melanoma 1.5 mm depth</td>
<td>Wide completion re-excision</td>
<td>Disease free 36 months post-diagnosis</td>
</tr>
<tr>
<td>Adedoyin et al. (2004)</td>
<td>2.5/F</td>
<td>5-mo history multiple swellings in upper back, left axilla, on background of congenital giant hairy nevus</td>
<td>Multifocal 3–10 cm lesions on back, 10 cm axillary mass</td>
<td>Malignant melanoma with axillary lymph node metastasis; depth not available</td>
<td>Initial two doses vincristine and cyclophosphamide</td>
<td>Lost to follow-up secondary to treatment costs</td>
</tr>
<tr>
<td>Prose et al. (1987)</td>
<td>0/F (congenital)</td>
<td>Mid-gastric nodular skin lesion, 6 wk history increasing in size vertically. Jet-black, irregular shiny surface with focal ulceration</td>
<td>2.5 × 2.0 cm</td>
<td>Malignant melanoma 9 mm depth</td>
<td>Excision of primary</td>
<td>Disease free 12 months post-diagnosis</td>
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CLND: completion lymph node dissection; PET: positron emission tomography; SLNB: sentinel lymph node biopsy.


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Author Contributions

Charles Jian – Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Samih Salama – Conception of the work, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Gabriela Gohla – Conception of the work, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Sarab Mohamed – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Brian H Cameron – Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Barbara Heller – Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Salem Alowami – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission
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Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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