

Atypical Spitz Tumor of Uncertain Biologic Potential with Inopportune Localization in a 7-year-old Boy

The Spitz nevus was first described as the “melanoma of childhood” or “juvenile melanoma” by Sophie Spitz in 1948 (1). Most spitzoid melanocytic proliferations can be classified as benign Spitz nevi or spitzoid melanomas based on published criteria (2-3). However, a subset of spitzoid lesions have histological features that deviate from a typical Spitz nevus, yet are insufficient for a definitive diagnosis of spitzoid melanoma. The scope of spitzoid melanocytic proliferations includes the typical Spitz nevus, dysplastic Spitz nevus, Spitz nevus with atypia, melanoma evolving into a Spitz nevus, and spitzoid melanoma arising *de novo* (4). Lack of uniform criteria for discrimination between malignant and benign spitzoid melanocytic lesions makes it very difficult for pathologists and clinicians to interpret the histopathological findings and give an unequivocal diagnosis of melanoma. Using only histopathological criteria, it is often very difficult to differentiate melanoma arising in a Spitz nevus from a Spitz nevus with severe atypia. Thus, the term Spitz tumor

of uncertain malignant potential (STUMP) is often used (5). Molecular methods have been employed recently to evaluate a spectrum of melanocytic lesions, including Spitz nevi. Molecular methods used for discrimination between malignant and benign spitzoid tumors include fluorescence in situ hybridization (FISH) and sequencing. The FISH method employs hybridization of specific fluorescent probes to gene regions and/or chromosomes. If there are more or less chromosome/gene copies than two per cell, it is regarded as an abnormality. Sequencing methods compare the genetic code of bioptic samples to the reference gene sequence found online and discrepancies, mutations, insertions, or deletions of the analyzed gene are noted. While there have been some indications of a higher rate of chromosomal abnormalities and pathogenic mutations in spitzoid melanoma, no consensus has been reached (6,7). These new tools have provided further insight into these controversial lesions and can aid in their evaluation and further clinical approach.



Figure 1. A 7-year-old boy with a brown pigmented skin nodule at the ala of nose near the naso labial fold, before (A) and after (B) re-excision.

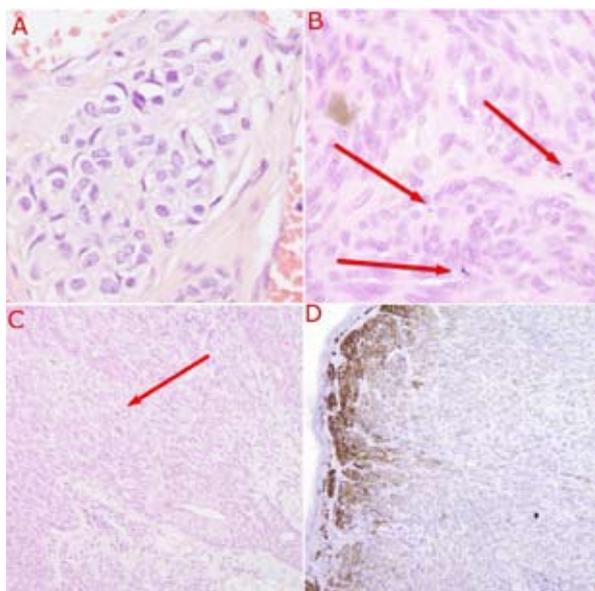


Figure 2. Atypical Spitz tumor stained with Hemalaun-eosin and immunohistochemically for human melanoma black-45 (HMB-45). (A) Nests near the base of the lesion harboring large, pleomorphic cells without signs of maturation and high nuclear-to-cytoplasmic ratios (H&E, magnification $\times 400$). (B) Three apparent mitoses are indicated with arrows (H&E, magnification $\times 200$). (C) Mitosis near the deep margin of the lesion is indicated with an arrow (H&E, magnification $\times 100$). (D) HMB-45 immunostaining in the upper part of the lesion (magnification $\times 100$).

A 7-year-old boy presented with a brown nodule on the nose (Figure 1, A). The mother noticed that the lesion had been traumatized a few days prior to examination, with minor bleeding. Family history was negative for skin cancer. Examination showed a smooth brown papule 5 mm in diameter. On dermatoscopy, the pigment was uniform and symmetric with a sign of the trauma in the center of the lesion. Findings for the remainder of the physical examination were normal. Photoprotection and possible preventive excision was suggested. However, on second examination the mother noted a recurring trauma to the area of the nose, after which excision was suggested. A full excision was performed, and histological examination demonstrated a well demarcated, symmetrical, compound proliferation of large Spitzoid melanocytes (Figure 2). Cells were predominantly arranged in nests, while the intradermal component displayed peri- and inter-adnexal growth patterns. Maturation with descent was apparent in a larger part of the lesion. Centrally, however, in the deep levels of the tumor, several large nests of strikingly enlarged melanocytes with a high nuclear-to-cytoplasmic ra-

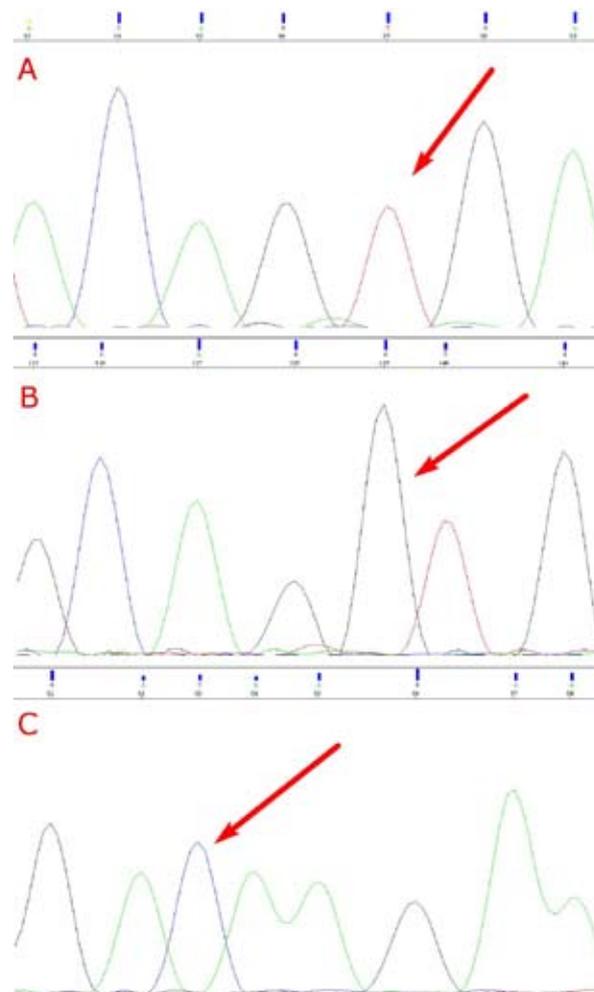


Figure 3. Sequencing electropherograms, with positions of possible mutations indicated with arrows: (A) BRAF exon 15 V600E wild-type; (B) NRAS exon 2 G12V wild-type; (C) NRAS exon 3 Q61K wild-type.

tio were found, with a lack of maturation (Figure 2, A). Kamino bodies could not be seen. Mitotic figures were noted in both the superficial and deep levels of the tumor, and there were 2 mitosis per mm^2 (Figure 2, B and C). Human melanoma black-45 (HMB-45) expression was strongly positive at the junctional component and decreasing toward the base of the lesions (Figure 2, D). Taken together, these findings were concerning but not diagnostically decisive with regard to malignancy, as determined by two dermatopathologists. The diagnosis of an atypical Spitz tumor was made and upon consultation updated to a high-risk atypical Spitz tumor (Spitz nevus of uncertain malignant potential). A thoracic X-ray and ultrasound of the neck and abdomen were performed, revealing reactive lymph nodes of hypoechoic structure and a

slightly enlarged liver with a normal echogenic structure. No focal lesions were observed.

A consulting dermatopathologist thought that although some features were reminiscent of a Spitz nevus, other characteristics were worrisome and indicated melanoma, so molecular analysis was recommended. Sequencing of NRAS and BRAF genes on DNA isolated from cells suspected to have malignant potential was performed. A pathologist selected the area which contained 70% of atypical cells, which were sampled by manual microdissection. The polymerase chain reactions (PCR) and sequencing reactions were performed using primers and annealing temperatures according to van Dijk *et al.* (7). Both NRAS (exon 2 and 3) and BRAF genes were wild-types (Figure 3). A reduced re-excision using a Thiersch free skin graft was performed (Figure 1, B).

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The study was approved by the institutional ethics committee clearance.

Evaluating the malignant potential and assessing the risk of aggressive behavior of atypical Spitz tumors is one of the biggest challenges in modern skin pathology. Only a few studies with sufficient numbers of cases and long-term follow-up are available, and there are still many uncertainties regarding the nature of the disease. Recent finding by Hung *et al.* that the sentinel node metastasis is not predictive for poor outcome in patient with spitzoid melanocytic tumors only narrows down the possibilities of risk assessment and survival prediction using classical pathohistological methods (8).

Tom *et al.* suggested an algorithm for the evaluation of pediatric STUMP lesions (5). It includes comparative genomic hybridization (CGH) and several specific fluorescence in situ (FISH) probes to check for genetic instability (5). However, CHG is time consuming, expensive, and less reliable for lesions with only a subset of atypical cells, i.e. spitzoid melanomas evolving from a Spitz nevus. Furthermore, FISH probes failed to detect several malignant spitzoid lesions according to Raskin *et al.* (6). The study by van Dijk *et al.* (7) concluded that NRAS and BRAF sequencing in STUMP lesions is the most promising tool for evaluation of Spitz nevi with low percentage of cells suspected to have malignant potential. For that reason, we decided to perform NRAS and BRAF gene sequencing on DNA of isolated tumor cells.

The excision of sentinel lymph nodes could have a negative impact on the immunological system of chil-

dren, so there is a need for development and further consideration of less invasive methods for evaluation of STUMP lesions. The other widely accepted evaluation method for high-risk atypical Spitz nevi is wide re-excision. In our case, a 5 mm lesion on the nose and additional 1 cm wide re-excision would leave a scar which could have serious psychological implications for the child. Considering that, and due to negative molecular analysis along with other characteristics of the tumor, we decided to perform reduced re-excision of the lesion. Close clinical follow-up was done every 6 months for the next 28 months, finding no recurrent Spitz's nevi or detectable focal lesions. Follow-up included ultrasound of the axillary region, neck, abdomen and the inguinal region as well as dermatoscopy of the nasal region. We believe that newer techniques may provide information that can be helpful in evaluating the possible malignant potential of the lesion and in deciding further therapeutic approach. However, there is no easy way for managing such an ambiguous disease; every case needs to be carefully analyzed and all the decisions need to be made carefully, weighing possible advantages and disadvantages for the patient, including the fact that children are not simply "small adults" and that each localization requires distinct access.

References

1. Spitz S. Melanomas of childhood. *Am J Pathol* 1948;24:591-609.
2. Barnhill RL, Flotte TJ, Fleischli M, Perez-Atayde A. Cutaneous melanoma and atypical Spitz tumors in childhood. *Cancer* 1995;76:1833-45.
3. Walsh N, Crotty K, Palmer A, McCarthy S. Spitz nevi vs spitzoid malignant melanoma: an evaluation of the current distinguishing histopathologic criteria. *Hum Pathol* 1998;29:1105-12.
4. Kamino H. Spitzoid melanoma. *Clin Dermatol* 2009;27:545-55.
5. Tom WL, Hsu JW, Eichenfield LF, Friedlander SF. Pediatric "STUMP" lesions: evaluation and management of difficult atypical Spitzoid lesions in children. *J Am Acad Dermatol* 2011;64:559-72.
6. Raskin L, Ludgate M, Iyer RK, Ackley TE, Bradford CR, Johnson TM, *et al.* Copy number variations and clinical outcome in atypical spitz tumors. *Am J Surg Pathol* 2011;35:243-52.
7. van Dijk MC, Bernsen MR, Ruiters DJ. Analysis of mutations in B-RAF, N-RAS, and H-RAS genes in

the differential diagnosis of Spitz nevus and spitzoid melanoma. *Am J Surg Pathol* 2005;29:1145-51.

8. Hung T, Piris A, Lobo A, Mihm MC Jr, Sober AJ, Tsao H, *et al.* Sentinel lymph node metastasis is not predictive of poor outcome in patients with problematic spitzoid melanocytic tumors. *Hum Pathol* 2013;44:87-94.

**Nedeljka Glavan¹, Gordana Zamolo²,
Miljenko Katunarić², Nives Jonjić²**

¹*Clinical Department of Pediatric Surgery, Rijeka
Clinical Hospital Centre, Rijeka, Croatia*

²*Department of Pathology, School of Medicine,
University of Rijeka, Rijeka, Croatia*

Corresponding author:

Nedeljka Glavan, MD
Clinical Department of Pediatric Surgery
Rijeka Clinical Hospital Centre
Istarska 43
51000 Rijeka
Croatia
neda.glavan@ri.t-com.hr

Received: January 2, 2015

Accepted: August 10, 2015

