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

The Spitz nevus was first described as the “mela-
noma of childhood” or “juvenile melanoma” by So-
phie 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 his-
tological features that deviate from a typical Spitz
nevus, yet are insufficient for a definitive diagnosis
of spitzoid melanoma. The scope of spitzoid melano-
cytic proliferations includes the typical Spitz ne-
vus, dysplastic Spitz nevus, Spitz nevus with atypia,
melanoma evolving into a Spitz nevus, and spitzoid
melanoma arising de novo (4). Lack of uniform cri-
teria for discrimination between malignant and be-
ign spitzoid melanocytic lesions makes it very dif-
ficult for pathologists and clinicians to interpret the
histopathological findings and give an unequivocal
diagnosis of melanoma. Using only histopathologi-
cal criteria, it is often very difficult to differentiate
melanoma arising in a Spitz nevus from a Spitz ne-
vus 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 le-
sions, including Spitz nevi. Molecular methods used
for discrimination between malignant and benign
spitzoid tumors include fluorescence in situ hybrid-
ization (FISH) and sequencing. The FISH method em-

ploys 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 discrep-
ancies, mutations, insertions, or deletions of the ana-
alyzed gene are noted. While there have been some
indications of a higher rate of chromosomal abnor-
malities and pathogenic mutations in spitzoid mela-
noma, 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.
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. Maturity 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 ratio 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 mm² (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 children, 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 dermoscopy 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
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Received: January 2, 2015
Accepted: August 10, 2015