SPITZOID SKIN LESIONS DIAGNOSIS ENGAGES HIGHT EXPERTISE - CLINICAL AND PATHOLOGIC INTERPRETATION OF TWO CASES

Abstract

Spitzoid skin lesions cause diagnosis difficulties due to their clinical, dermoscopic and histopathological similarities to melanomas. A correct diagnosis implies a high expertise and close collaboration between the dermatologist and the pathologist as there are no algorithms or methods of diagnosis with a 100% accuracy. This type of lesions continues to be of interest for scientists considering the fact that 30% of the malpraxis cases of misdiagnosed melanomas are caused by Spitzoid lesions. In most cases, Spitz nevi do not show any chromosomal aberrations and when present they are totally different from those seen in melanomas. In this paper we present two cases of Spitzoid lesions: desmoplastic Spitz nevus and atypical Spitz nevus. The paper underlines the clinical, dermoscopic, histopathological and immunohistochemical features and their impact on final diagnosis. Management of Spitzoid lesions is a challenge even for experts. Cytogenetic evaluation of atypical Spitzoid lesions, using comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) respectively, can be very useful when differentiating them from melanomas and establishing their most probable biological behaviour.
Rezumat
Leziunile cutanate spitzoide ridică dificultăți de diagnosticare, din cauza asemănărilor cu melanomul la nivel clinic, dermatoscopic și histopatologic. Stabilirea unui diagnostic corect implică un nivel înalt de expertiză și o colaborare strânsă între clinician și anatomopatolog, neexistând încă un algoritm sau o metodă de diagnosticare cu sensibilitate de 100%. Această categorie de leziuni continuă să suscite interesul comunității științifice, în contextul în care 30% din cazurile de malpraxis prin subdiagnosticarea melanomului sunt cauzate de leziunile spitzoide. Nevii Spitz în marea majoritate a cazurilor, nu prezintă aberații cromozomiale iar atunci când există sunt complete diferite de cele găsite în melanom. În această lucrare sunt prezentate două leziuni cutanate spitzoide : un nev Spitz desmoplazic și un nev Spitz atipic. În articol sunt discutate aspectele clinice, dermatoscopice, histopatologice și de imunohistochimie întâlnite și răsunetul lor asupra diagnosticului final. Managementul leziunilor spitzoide reprezintă o provocare chiar și pentru experți. Evaluarea citogenetică a leziunilor spitzoide atipice poate fi foarte utilă în diferențierea lor de melanom și în stabilirea comportamentului biologic cel mai probabil.

INTRODUCTION
Spitzoid skin lesions are a heterogeneous group of melanocytic proliferations with different biological potential varying from the benign nature of the classical Spitz nevus to the obvious malignancy of Spitzoid melanomas, between the two being the atypical Spitz nevus with unpredictable potential(1,2,3). Diagnosis of Spitzoid lesions is usually a real challenge because of clinical, dermoscopic and histopathological similarities with melanomas(4,5). Unlike melanomas, genetic aberrations are rarely found in classical Spitz nevi, in just about 25% of the cases being observed an increase in the number copies of the p-arm of chromosome 11(4,6-9). This genetic aberration has not been described in melanomas, which present multiple, frequent cromosomal aberrations which affect totally or just fragments of chromosomes(8,9). Although Spitz nevi represent a low percentage of the amount of excised nevi, medical reports reveal the fact that about one third of misdiagnosed melanoma cases are initially interpreted as Spitz nevi(4,10-12).
Over the past decades, current use of dermoscopy on evaluation of melanocytic lesions has increased the accuracy of diagnosis of Spitz nevus, these lesions being most often interpreted as suspicious for malignity(1,4,13,14,16,17).
Unfortunately, the accuracy of histopathological diagnosis for Spitzoid lesions is less than 100%, as there is a gray zone of uncertainty of atypical Spitz nevus also called Spitzoid tumour or atypical Spitzoid tumour, whose risk of metastasis is well known(2,4).
The diagnosis difficulties are even higher for the variants of Spitz nevus (SN) such as halo SN, pigmented SN, desmoplastic SN, recurrent SN, combined SN, angiomatoid SN, acral SN and the mucous membranes SN(1,4,6,16,19). Cytogenetic evaluation of Spitzoid lesions characterised by conflicting histopathological and immunohistochemical features hard to interpret in the diagnosis process, can provide valuable information which makes it
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Case Presentation

Figure 1C. Desmoplastic Spitz nevus. HE x 100.

Figure 1D. Desmoplastic Spitz nevus. HE x 200.

Figure 1E. Desmoplastic Spitz nevus. HE x 400. Dermal melanocytic proliferation with overall symmetric architecture; moderate cellular pleomorphism; epidermal hyperplasia.

Figure 1F. Desmoplastic Spitz nevus. HE x 200.

Figure 1G. Desmoplastic Spitz nevus. HE x 200.

Figure 1H. Desmoplastic Spitz nevus. HE x 400. Transition to a sclerotic dermis with sparse pigmentation with plump spindle melanocytes interspersed between collagen bundles.
possible to obtain a clear-cut differentiation from melanomas in some cases\textsuperscript{4,8}. Below we report two cases of Spitz nevus resembling melanoma in varying degrees.

**CASE PRESENTATION 1**

Case 1. A 35 year old male came to our clinic for a 3/5 mm diameter light-brown nodule with a dark brown halo around (Fig. 1A), that had appeared 2 years before on the right side of the abdomen. Dermoscopic exam established the melanocytic nature of the lesion and revealed a fine typical pigmented network in the halo area and an unspecific global pattern with a structural gray-brownish areas on the nodular part of the lesion (Fig. 1B). The history along with the clinical and dermoscopic features raised the suspicion for melanoma, the diagnosis of Spitz nevus being considered only because of the patient’s age. The lesion was surgically excised with a 5 mm safe margin and the histopathological exam followed by immunohistochemical tests, confirmed the diagnosis of intradermic Spitz nevus with desmoplastic component (Fig. 1C-H).

**CASE PRESENTATION 2**

Case 2. A 53 year old female came to our clinic for a round pale-pink plaque, 8/8mm in diameter, slightly raised, surrounded by an incomplete pale-brown halo, that had appeared on the right shoulder three years before (Fig. 1A). Considering the clinical appearance of the lesion, we took into account a dermatofibroma, amelanotic melanoma and less likely Spitz nevus because of the patient’s age. Dermoscopic examination showed an unspecific global pattern with homogenous pale-brown colour at the periphery, associated with a pale-pink hue in the central part (Fig. 2B). The lesion was surgically excised and the histopathological exam confirmed the diagnosis of atypical Spitzoid tumour with 0.5 mm thickness having a desmoplastic dermal component and a pagetoid epidermal component (Fig. 2C-F). The immunohistochemical tests revealed the Ki67 index <1% in the superficial tumour component and absent in the dermis. Considering the patient’s age and the metastatic potential of the lesion, routine blood tests and imaging exams (chest X-ray, abdominal ecography) were performed with negative results. The patient will be followed up every 6 months for 2 years and then annually.

**DISCUSSION**

Diagnosis difficulty of Spitzoid lesions is well known and requires a close collaboration between the dermatologist and the pathologist\textsuperscript{6}. The final diagnosis can be established based on the close correlation between the clinical and his-
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topathological criteria\textsuperscript{2,13}. Molecular tests CGH and FISH have been recently added to the diagnosis methods for Spitzoid lesions, being applied in difficult cases since their high costs limit a wide scale use\textsuperscript{4,6-8,13}.

Typical Spitz nevus is usually a symmetrical, monochromatic nodule, with a diameter under 6 mm and affects children and young people and has a worrisome rapid growth\textsuperscript{4,20,21}.

Histopathological Spitz nevus is in most cases a compound nevus, but it can also be junctional or intradermal, with a symmetrical architecture, an absent or low mitotic activity in the superficial nevus cells with cell maturation in depth and central pagetoid spreading\textsuperscript{4,6,13,20,21}. The genetic aberrations are infrequent, the increase in the number of chromosomal copies 11p present in 25 % of the cases and they are commonly associated with H-RAS oncogenic mutation\textsuperscript{4,6,7,20}. Neither of the above mentioned genetic aberrations have been described in melanomas\textsuperscript{4,22}. Recently, Spitz nevus has been considered to be similar to other melanocytic nevi, showing a growth period, faster than that of other melanocytic nevi, followed by a stagnation period and with a spontaneous involution occurring in the final\textsuperscript{13,19,21}. Because of its similarity to melanomas and the possibility of acquiring atypical features over its evolution, difficult to interpret, the surgical excision with a 3-5mm safe margin is recommended in the patients older than 11 years\textsuperscript{4,13}. In younger children, the decision to follow up or to excise will be taken according to

**Case Presentation**
The immunohistochemical and molecular tests can contribute to establishing the diagnosis; however, they are not always able to make a sharp differentiation of Spitz nevi from melanomas. A subset of atypical Spitzoid nevi may show chromosomal aberrations that may indicate an aggressive biological behaviour. Unfortunately, such clinical and histopathological borderline Spitzoid lesions can often reveal borderline cytogenetic features.

The lesion presented in case 2 showed symmetrical proliferation of epithelioid and fusiform cells, rare mitosis, with pagetoid spreading in epidermis and desmoplastic aspect in papillary and reticular dermis (Fig. 2C-F). The immunohistochemical tests revealed the following: Ki 67 proliferation index under 1%, p21 negative, HMB 45 positive in the upper part of the tumour, S100 highly positive in the entire tumour. However, the diagnosis of atypical Spitz nevus on the upper thorax in a 53 year old patient, a common site also for desmoplastic melanomas, requires a careful follow-up of the patient. The low tumour thickness and rare mitotic activity are good prognosis factors for our patient.

The histopathological diagnosis of Spitzoid melanomas is not yet a standard procedure, the importance of each parameter found is established according to all existing parameters which causes considerable subjectivism and disagreement among experts. The conflicting clinical, dermoscopic and histopathological data should compel physicians to make a cautious categorising of such lesions considering the medico-legal and therapeutic impact. The molecular tests CGH and FISH are valuable tools to acquire a higher accuracy of the diagnosis. Melanoma chromosomal aberrations - present in 95% of the cases - are multiple and result from telomeric crisis; they are structural and numerical. The most frequent chromosomal aberrations found in melanomas are by losses of 9p, 10q, 6q, 8p and by gains of 7, 8, 6p, (1q). Most melanomas have BRAF or NRAS mutations. The type and number of mutations depend on the evolution span of lesions, on the patient’s age and melanoma type.

CONCLUSIONS

The Spitzoid term for pigmented melanocytic lesions needs a very careful evaluation of clinical, dermoscopic, histopathological, immunohistochemical and molecular features by expert teams. Both dermatologist and pathologist are responsible for the medico-legal impact. All participants in the diagnosis process should be aware of discrepancies between clinical, dermoscopic and histopathological features of such lesions and must evaluate the promalignant potential, avoiding misdiagnosis of melanomas.

For atypical Spitz nevus the therapeutical approach should be similar to that for melanomas, according to tumour thickness. Molecular tests CGH and FISH represent valuable tools for categorizing Spitzoid lesions with confidence. Atypical Spitz
nevi compel a cautious post-surgical attitude, the management of such lesions depending on the thickness of the tumor, on the genetic aberration pattern and on the patient’s age\(^{11,24}\). Where the molecular tests do not reveal any chromosomal aberrations or show only an increased of the copy number of 11p, the lesions should be approached like a Spitz nevus\(^{2,4,9}\). The future directions of Spitz nevus management remain its proper identification and the avoidance of needless therapies\(^{19}\).

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Bibliography