REVIEW ARTICLE

Clinical, Morphological and Molecular Features of Spitz tumors

Michele Donati[1,2], Boulos Mansour[3], Michael Hagstrom[4], Pedram Gerami[4], Dmitry V. Kazakov[5]

[1] Department of Pathology, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy
[2] University Campus Bio-Medico of Rome, Rome, Italy
[3] Department of Pathology, Ospedale Israelitico di Roma, Italy
[4] Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA.
[5] IDP Institut für Dermatohistopathologie, Pathologie Institut Enge, Zürich, Switzerland

SUMMARY

Spitz tumors represent a heterogeneous group of challenging melanocytic neoplasms, displaying a range of biological behaviors, spanning from benign lesions, Spitz nevi (SN) to Spitz melanomas (SM), with intermediate lesions in between known as atypical Spitz tumors (AST). They are histologically characterized by large epithelioid and/or spindled melanocytes arranged in fascicles or nests, often associated with characteristic epidermal hyperplasia and fibrovascular stromal changes. In the last decade, the detection of mutually exclusive structural rearrangements involving receptor tyrosine kinases *ROS1*, *ALK*, *NTRK1*, *NTRK2*, *NTRK3, RET*, *MET*, serine threonine kinases *BRAF* and *MAP3K8,* or *HRAS* mutation, led to a clinical, morphological and molecular based classification of Spitz tumors.
The recognition of some reproducible histological features can help dermatopathologist in assessing these lesions and can provide clues to predict the underlying molecular driver.
In this review, we will focus on clinical and morphological findings in molecular Spitz tumor subgroups.

Keywords: Spitz tumor – Atypical Spitz tumor – Spitz melanoma – molecular driver – molecular morphological correlation – *ROS1* – *ALK* – *NTRK1* – *NTRK2* – *NTRK3* – *RET* – *MET* – *BRAF* –*MAP3K8* fusion – *HRAS* mutation – *MAP2K1* mutation

Klinické, morfologické a molekulární vlastnosti Spitzoidních nádorů

SOUHRN

Spitzoidní nádory představují heterogenní skupinu melanocytárních neoplázií vykazujících široké spektrum biologického chování od zcela benigních afekcí typu névu Spitzové až po maligní léze v podobě spitzoidních melanomů. Mezi těmito dvěma skupinami se pak nacházejí léze s nejistým biologickým chováním v podobě atypických spitzoidních tumorů. Histologicky jsou charakterizované objemnými epiteloidními a/nebo vřetenitými melanocyty uspořádanými do fasciklů nebo hnízd a často s charakteristickou epidermální hyperplázií a fibrovaskulárními stromálními změnami v okolí.
Rozpoznání specifických strukturálních přestaveb v genech pro tyrozinkinázové receptory ROS1, ALK, NTRK1, NTRK2, NTRK3, RET, MET, serin threoninové kinázy BRAF a MAP3K8 či HRAS mutací v posledním desetiletí umožnilo přesnější klinickou, morfologickou a molekulární subklasifikaci spitzoidních tumorů. Rozpoznání specifických histologických rysů pak může dermatopatologům napomoct nejen v hodnocení těchto lézí, ale může i nepřímo poukazovat na konkrétní molekulární změny.
Tento doškolovací článek se zaměřuje na klinické a morfologické nálezy u molekulárně definovaných podskupin spitzoidních tumorů.

Klíčová slova: Spitzoidní tumor – atypický spitzoidní tumor – spitzoidní melanom – molekulární změna – molekulárně-morfologická korelace – ROS1 – ALK – NTRK1 – NTRK2 – NTRK3 – RET – MET – BRAF – MAP3K8 fúze – HRAS mutace – MAP2K1 mutace

Cesk Patol 2024; 60(1): 35–48

Spitz tumors encompass a heterogeneous group of melanocytic neoplasms displaying a range of biological behaviors, spanning from a benign lesion, Spitz nevus (SN) to Spitz melanoma (SM), as well as intermediate lesions, atypical Spitz tumors (AST) that manifest atypical histological features but do not suffice for the diagnosis of an overt malignancy (1,2).

Spitz tumors are histologically characterized by the presence of large epithelioid and/or spindled melanocytes arranged in fascicles or nests, often accompanied by characteristic epidermal hyperplasia and fibrovascular stromal changes. Kamino bodies, eosinophilic globules, are also frequently observed at the dermo-epidermal junction (3).

✉ ***Correspondence address:***
Michele Donati, MD
Department of Pathology
Fondazione Policlinico Universitario Campus Bio-Medico
Via Alvaro del Portillo, 200 -00128, Roma, Italy
Tel.: +393345033078
e-mail: micheledonati25@gmail.com

Since Sophie Spitz's initial description, the diagnosis of Spitz tumors has been challenging for pathologists owing to the lack of inter-observer consensus based on histological assessment alone (4-7). First of all, none of the morphological criteria commonly used in the diagnosis of malignant melanocytic neoplasms directly correlate with an aggressive clinical course in Spitz tumors, while, rarely, cases of a benign-looking lesion have metastasized and killed the patient (8-10).

Substantial progress has been made in the past decade regarding the identification of cytogenetic and/or molecular alterations in Spitz tumors, leading to a clinical, morphological and molecular based classification (11). These molecular events include mutually exclusive structural rearrangements, involving receptor tyrosine kinases *ROS1*, *ALK*, *NTRK1*, *NTRK2*, *NTRK3, RET*, *MET*, serine threonine kinases *BRAF* and *MAP3K8* or *HRAS* mutation (12,13).

These genomic data seem to be of clinical relevance, considering that malignant Spitz tumors seem to have a more indolent clinical course compared to melanomas with spitzoid features driven by mutations in *BRAF* or *NRAS* (14). Moreover, the detection of further specific molecular alterations involving