Atypical ALK-positive Spitz tumors with 9p21 homozygous deletion: Report of two cases and review of the literature

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ALK rearrangements occur in up to 10% of spitzoid melanocytic neoplasms. No reported cases have shown homozygous deletion of 9p21 (CDKN2A) or gains of 6p25 (RREB1) or 11q13 (CCND1), which have been associated with aggressive clinical behavior. Here we report 2 unique cases. Case 1 occurred in a 9-year-old male with a 14-mm nodule on the anterior left thigh. Biopsy revealed an ALK-positive Spitz tumor containing an irregular nodule of densely packed melanocytes with increased mitoses and loss of p16 immunoreactivity. FISH analysis showed homozygous deletion of 9p21 and gain of 6p25. Sentinel lymph node biopsy revealed small subcapsular foci of tumor. Case 2 occurred in a 7-year-old female with a 12-mm nodule on the anterior right ankle. Biopsy revealed an ALK-positive Spitz tumor containing an expansile nodule of pleomorphic epithelioid melanocytes with numerous mitoses and loss of p16 immunoreactivity. By FISH, the nodule showed homozygous deletion of 9p21 and gains of 6p25 and 11q13. Our cases show the transformation of tumors produced by an activating kinase fusion gene (ALK) through secondary genetic changes including loss of tumor suppressor activity (CDKN2A). Long-term follow up will be important to further define the behavior of these unique Spitz tumors.

KEYWORDS
9p21 homozygous deletion, ALK, Spitz tumor, spitzoid melanoma

INTRODUCTION

Like many tumors, melanocytic neoplasms begin with somatic mutations that activate oncogenes. Melanocytes proliferate into benign nevi but are restrained by mechanisms of tumor suppression and senescence. Subsequent genetic changes may override the restraints and transform nevi into borderline lesions or melanoma.

Spitz tumors arise from epithelium-associated melanocytes, typically on intermittently sun-exposed skin. They may be benign (Spitz nevus), borderline (atypical Spitz tumor) or (less commonly) overtly malignant (spitzoid melanoma). They show genetic aberrations that are rarely seen in other melanocytic lesions and that may be associated with distinct morphology. Approximately 15% have an activating HRAS mutation and often a desmoplastic phenotype. Approximately 5% have BAP1 inactivation and an epithelioid phenotype with loss of nuclear BAP1 expression by immunohistochemistry (IHC). BAPomas may occur within common nevi with oncogenic BRAF V600E mutations because of loss of BAP1 tumor suppressor activity. Many more Spitz tumors have activating rearrangements involving BRAF or the receptor tyrosine kinase loci ROS1, NTRK1, NTRK3, RET, MET and ALK.

ALK rearrangements occur in approximately 10% of spitzoid melanocytic neoplasms including Spitz nevi, atypical Spitz tumors and rare spitzoid melanomas. Common fusion partners are TPM3 and DCTN1. These tumors show strong ALK expression by IHC, a reliable surrogate for ALK rearrangement.

ALK-positive Spitz tumors have been reported in patients between 5 months and 64 years (median = 12 years) of age.