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Molecular diagnostics complementing morphology in superficial mesenchymal tumors

Alison L. Cheah, MBBS, John R. Goldblum, MD, Steven D. Billings, MD

From the Department of Anatomic Pathology, Cleveland Clinic, Cleveland, OH.

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Molecular techniques are increasingly important in the practice of surgical pathology. In soft tissue tumors, there are a number of tumors with recurring cytogenetic abnormalities. Knowledge of these abnormalities has furthered our understanding of these tumors and has also allowed development of molecular techniques to aid in the diagnosis. This review will focus on mesenchymal tumors with specific cytogenetic abnormalities that may present as a superficial tumor of the dermis or subcutis.

The past 2 decades has seen the discovery of specific disease-defining genetic signatures in a number of mesenchymal neoplasms that involve the skin. Genetic aberrations may take the form of simple karyotypic abnormalities such as chromosomal translocations, amplifications, or deletions, or complex karyotypic abnormalities resulting from accumulated nonspecific gains and losses of uncertain significance. Chromosomal translocations causing specific gene fusions account for the majority of the genetic hallmarks identified in mesenchymal tumors. In addition to histologic examination and immunohistochemistry, molecular testing is gaining an increasingly important role as an adjunct to the diagnosis of cutaneous soft tissue tumors. Not only does molecular testing allow for more accurate diagnosis, but knowledge of the specific molecular aberrations has resulted in the development of targeted therapeutic approaches and will undoubtedly hold the key for the future development of therapies. Therefore, knowledge of these recurrent aberrations has increasing practical utility and is advancing our understanding of the underlying biology of mesenchymal tumors, with implications on better refined classification and prognostication. This review will focus on select superficial mesenchymal neoplasms with known specific genetic alterations that are useful diagnostically and/or represent significant developments in our understanding of the pathogenesis of these entities.

Address reprint requests and correspondence: Steven D. Billings, MD, Cleveland Clinic, Department of Anatomic Pathology, 9500 Euclid Ave, L25, Cleveland, OH 44195.
E-mail address: billins@ccf.org.

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Angiomatoid fibrous histiocytoma

Angiomatoid fibrous histiocytoma (AFH) is classified as a neoplasm of intermediate malignancy with a low rate of

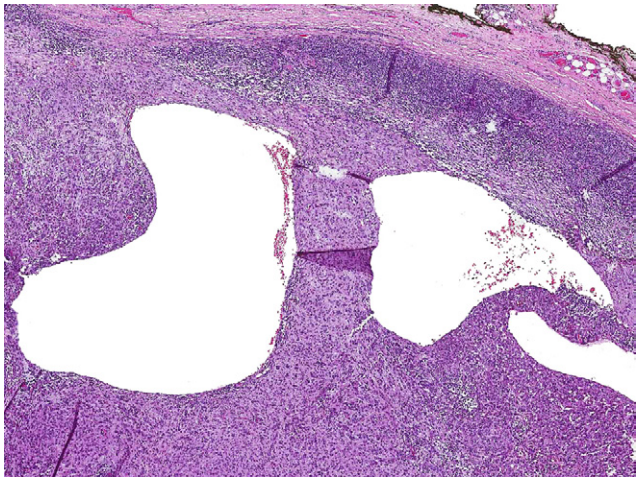

Figure 1 Angiomatoid fibrous histiocytoma. The classic low power appearance is of a nodular proliferation of histiocytoid tumor cells surrounded by a lymphoid infiltrate and dense fibrous capsule. Blood-filled cystic spaces are a characteristic, but not invariable, finding.

metastasis.[1] Originally regarded as a subtype of pleomorphic sarcoma/malignant fibrous histiocytoma, confusion has plagued this entity with regard to its behavior and nomenclature. In Enzinger's original study, 5 of 24 patients developed metastases and 3 died of disease.[2] Subsequent larger studies affirmed the mostly indolent nature of AFH in contrast with so-called malignant fibrous histiocytoma. Costa and Weiss reported 4 of 107 cases with regional lymph node metastases and 1 patient who died of disease.[3] Even lower rates of regional metastases, about 1%, have subsequently been reported.[4]

AFH is an unusual fibrohistiocytic tumor occurring in children and young adults. It most commonly involves the subcutis or deep dermis of the extremities, with the trunk and head and neck less commonly involved sites.[3] Rare involvement of the mediastinum, lung, retroperitoneum, gynecologic tract, and central nervous system has also been reported.[5,6] The mean age of patients is 20 years, with a wide reported age range (birth to 71 years).[1]

AFH usually presents as a slow growing nodular or cystic mass that may mimic a benign lesion clinically. A history of antecedent trauma is sometimes present. Constitutional symptoms including fever, anemia, weight loss, and polyclonal gammopathy have been reported in a minority of patients, which may reflect cytokine production by the neoplasm and resolve shortly after excision.[2-4] One reported case was associated with extensive lymphadenopathy simulating Castleman disease.[7]

The classic appearance of AFH is of a nodular proliferation of round to spindled histiocytoid tumor cells surrounded by a dense fibrous capsule (Figure 1). Typically, a dense lymphoplasmacytic infiltrate cuffs the tumor, some-

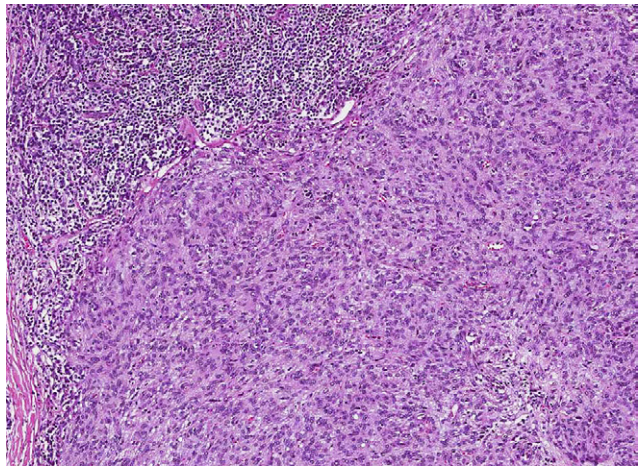

Figure 3 Angiomatoid fibrous histiocytoma. Bland cytology is typical of the histiocytoid tumor cells.

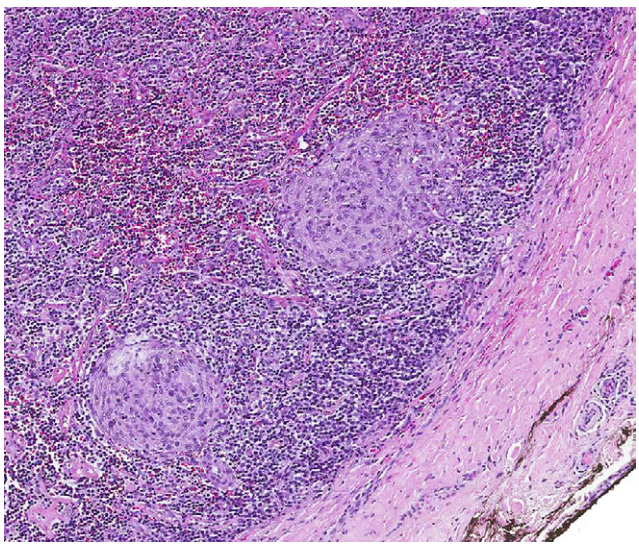

Figure 2 Angiomatoid fibrous histiocytoma. Occasional cases may simulate the appearance of a metastasis in a lymph node.

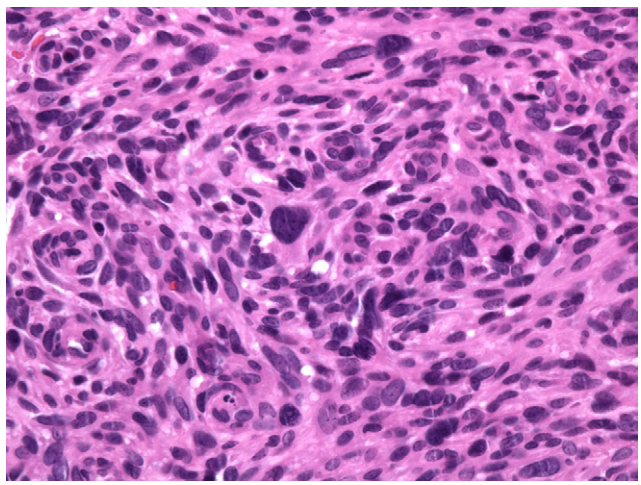

Figure 4 Angiomatoid fibrous histiocytoma. Occasional cases show striking pleomorphism, which may add to confusion with other atypical mesenchymal tumors.