ORIGINAL ARTICLE

DNA copy number changes in tumors within the spectrum of cellular, atypical, and metastasizing fibrous histiocytoma

Yann Charli-Joseph, MD,[a,b] Andrea Saggini, MD,[a,b] Leona A. Doyle, MD,[d] Christopher D. Fletcher, MBBS,[d] Jingly Weier, PhD,[a] Sonia Mirza, MBBS,[a] Swapna Vemula, MS,[a] and Philip E. LeBoit, MD[a,b,c]
San Francisco, California, and Boston, Massachusetts

Background: Cutaneous fibrous histiocytoma (FH) is a common mesenchymal neoplasm. Metastasis is rare, disproportionately occurring among the aneurysmal, cellular, atypical, and deep variants.

Objective: We determined whether DNA copy number changes occurred in atypical FH (AFH), and whether they were similar to those in metastasizing FH (MetFH) and benign cellular FH (CFH).

Methods: Five primary tumors of MetFH were evaluated by array-based comparative genomic hybridization analysis, with tissue from local recurrences and lung metastases in 2 and 2 patients, respectively. Seven indolent AFH and 5 CFH were identified for comparison.

Results: Substantial differences between the groups were found both in the frequency of chromosomal aberrations (higher among MetFH and absent or solitary in CFH) and array-based comparative genomic hybridization profiles (frequent gains of 7 and 8q and losses of Xq in MetFH; recurrent losses of chromosomes 9 and 22 in AFH; isolated loss of 5q and gain in chromosome 20 in 2 CFH). Fatal MetFH cases (2 of 5 cases) exhibited the highest rate of chromosomal aberrations.

Limitations: This study included a small sample size with a short-term follow-up.

Conclusions: Benign CFH, indolent AFH, and MetFH represent distinct biological entities within the spectrum of FH; array-based comparative genomic hybridization may be a tool in recognizing FH cases with metastatic potential and increasingly aggressive behavior. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2014.03.015.)

Key words: array-based comparative genomic hybridization; atypical fibrous histiocytoma; cellular fibrous histiocytoma; fibrous histiocytoma; genomic instability; metastasizing fibrous histiocytoma.

Cutaneous fibrous histiocytoma (FH) or dermatofibroma is one of the most common cutaneous mesenchymal neoplasms. Numerous histopathological variants exist, and a few portend the possibility of an intermediate or aggressive clinical course. Ordinary FH and most of its variants convey a low risk of recurrence even when incompletely excised (<1%-2%) and null

Abbreviations used:

aCGH:	array-based comparative genomic hybridization
AFH:	atypical fibrous histiocytoma
CFH:	cellular fibrous histiocytoma
FFPE:	formalin-fixed paraffin-embedded
FH:	fibrous histiocytoma
MetFH:	metastasizing fibrous histiocytoma

From the Pathology[a] and Dermatology[b] Departments, and the Helen A. Diller Family Comprehensive Cancer Center,[c] University of California, San Francisco; and Pathology Department, Brigham and Women's Hospital, Boston.[d]
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Correspondence to: Philip E. LeBoit, MD, Dermatopathology Service, University of California, San Francisco, 1701 Divisadero St, Suite 280, San Francisco, CA 94115. E-mail: philip.leboit@ucsf.edu.
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metastatic potential in contrast to the cellular, atypical, aneurysmal, and deep variants, which have an approximate recurrence rate of 20%.[1]

Cellular FH (CFH) is characterized by a large size, high cellularity, minimum intercellular collagen, abundant mitotic figures, common extension into the subcutis, and a lack of cellular atypia or nuclear pleomorphism. In the largest case series studied to date, a local recurrence rate of 26% but no evidence of metastases was reported.[1] However, it soon became evident that CFH rarely metastasized to regional lymph nodes, lung, and soft tissues. Because these patients usually have a protracted clinical course, authorities concluded that despite the presence of metastases, these tumors behave in an indolent but rarely fatal manner.[2,3]

Atypical FH (AFH) is characterized by foci of strikingly pleomorphic cells with large, irregular, and hyperchromatic nuclei with prominent nucleoli against a background of ordinary FH or, more commonly, CFH.[4] Enzinger and Weiss[5] distinguish AFH from the so-called "dermatofibroma with monster cells" and argue that AFH displays areas of more generalized atypia and some mitotic figures in contrast to the occasional pleomorphic cells encountered in the latter. However, a precise dichotomy is not always straightforward. A large clinicopathologic analysis revealed a wider range of morphologic features in AFH than previously recognized, with some lesions of small size and scant cellular pleomorphism and others large, markedly pleomorphic, and with frequent or atypical mitotic figures; local recurrence rate was 14%, 2 patients developed distant metastases, and 1 of them died of disease. No histopathologic features were found to predict aggressive clinical behavior.[6]

At least 35 cases of cutaneous metastasizing FH (MetFH) have been reported.[7-9] A recent description of 16 cases by 2 of the authors of the current study (L. A. D., C. D. F.) confirmed that although certain findings oblige a complete excision and close follow-up (ie, large size, cellular and atypical subtypes, and early or frequent local recurrences), aggressive behavior cannot be predicted on morphologic grounds alone. Furthermore, they showed that contrary to previous reports, some patients with MetFH have rapidly progressive and fatal disease.[7]

CAPSULE SUMMARY

- Cutaneous fibrous histiocytoma displays a low but nonzero metastatic potential among the cellular and atypical variants.
- The number of chromosomal aberrations increases along a spectrum in fibrous histiocytoma, correlating with biological behavior.
- Array-based comparative genomic hybridization analysis is a potential tool for recognizing which fibrous histiocytomas portend an intermediate, aggressive, or fatal course.

Array-based comparative genomic hybridization (aCGH) evaluates changes in DNA copy number across the entire genome of tumors, signaling gains and losses of parts of, or of whole, chromosomes. Because genomic instability and chromosomal aberrations are a sine qua non of human cancers,[10] aCGH is of practical use in several clinical scenarios.[11] Chromosomal copy number changes often affect regions important in cancer progression, with gains pointing to areas containing oncogenes, and losses pointing to those of tumor suppressor genes.[12] Hence, aCGH could unveil the acquisition of genetic hits in certain FH. These alterations could enable their progression to a transitional state of intermediate aggressive potential and enable their eventual metastasis. Morphologic analysis alone would reliably predict such behavior. Recently, Mentzel et al[8] showed chromosomal aberrations by aCGH in 5 of 7 MetFH and a lack of them in 10 non-MetFH. In this study we explored the cytogenetic profile in a wide spectrum of FH by comparing indolent cases of CFH with cases of morphologic abnormalities albeit a benign clinical course (AFH) and with MetFH. Moreover, we analyzed if the aCGH profile among primary, recurrent, and metastatic tumors was similar or if additional aberrations were obtained longitudinally during progression.

METHODS

Case selection

Five cases of MetFH, included in a recent study,[7] were identified in the consultation files of 1 of the authors (C. D. F.) and tested for genomic aberrations. All of these cases were classified morphologically as CFH. Primary neoplasms were available for aCGH analysis for all 5 cases, with tissue from recurrences and lung metastases available in 2 and 2 patients, respectively. Seven indolent AFH and 5 nonmetastasizing CFH were selected for genomic comparison. We included only cases with primary lesions on the dermis in which there were unambiguous cytologic and architectural features of FH. Cases classified as CFH had pronounced cellularity with no atypical features; AFH cases were characterized by the presence of foci containing numerous cells with markedly enlarged nuclei, some of which were