Original Research Article

Atypical Fibroxanthoma: Outcomes from a Large Single Institution Series

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Abstract

Background: Atypical fibroxanthomas (AFX) are rare malignant cutaneous neoplasms. Unfortunately, limited clinicopathologic and outcomes data on this cancer exists.

Objective: We report the clinical, pathologic, and treatment characteristics, as well as oncologic outcomes in this single-institution retrospective analysis.

Methods: This retrospective cohort study compiled clinical, pathologic, treatment, and outcome data for all patients with AFX on definitive excision diagnosed, evaluated, and treated primarily by surgical resection at a single institution between 2000-2020. Descriptive statistics evaluated clinical and pathologic characteristics. Kaplan-Meier method and Cox proportional-hazards models were used to evaluate overall survival and recurrence-free survival.

Results: 78 patients with AFX were identified. The majority were elderly, immunocompetent, Caucasian men. 85% of tumors were located on the head and neck. 63% of patients were correctly diagnosed only after complete resection of the index lesion. The median surgical margin was 1.0 cm. Overall, only 1.3% (1/78) of patients developed a local recurrence (RFS). No patients died of disease.

Conclusion: This study suggests that resection margins of 1 cm achieve excellent local control with close to 99% RFS and 100% disease-specific survival.

Keywords

cutaneous surgical oncology, skin cancer, atypical fibroxanthoma, pleomorphic dermal sarcoma, general dermatology, medical dermatology, oncology, clinical research, surgery

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Introduction

Atypical fibroxanthoma (AFX) is considered a rare cutaneous neoplasm, but of this group, it is the one most commonly encountered in clinical practice.[1,2] AFX falls into the category of nonmelanoma skin cancers (NMSC), which are most likely to develop on the sun-damaged skin of white elderly men.[3] AFX follows the same pattern, and radiation therapy is another major risk factor.[4-6] Due to the rarity of this disease, exact prevalence rates are unknown. However, a retrospective study of 42,000 NMSC treated by Mohs micrographic surgery (MMS) found .24% to be AFX.[2] In a New Zealand study analyzing surgically excised NMSC lesions, .002% (101/50,411) were diagnosed as AFX.[7]

Currently, limited patient data on the biological behavior of this cancer exists due to its rarity. This is compounded by the fact that this lesion is often confused diagnostically with a more aggressive sarcoma, pleomorphic dermal sarcoma (PDS). While some authors do not make a distinction between these 2 lesions, they are commonly considered to be distinguishable on re-excision. Specifically, AFX is found in the dermis and superficial subcutaneous tissue and lacks perineural or angiolymphatic invasion while PDS is infiltrative, involves deeper layers of subcutaneous fat, and may show perineural or vascular infiltration.[7] Currently, this cancer is classified as being of intermediate malignancy due to its limited capacity to metastasize. The primary goal of this research study is to identify the clinicopathologic characteristics of patients referred to a tertiary care cancer center and diagnosed with AFX upon definitive excision. The secondary goals are to describe outcomes, specifically, local recurrence-free survival, and distant recurrence-free survival.

Methods

A single-institution retrospective cohort review was conducted for patients diagnosed with atypical fibroxanthoma between January 2000 through December 2020. After obtaining institutional review board approval, patients diagnosed and treated at Moffitt Cancer Center were identified through the electronic medical record systems. Inclusion criteria for this study required patients to be 18 years of age or older and documented with a diagnosis of AFX confirmed on definitive excision by a board-certified dermatopathologist and treated primarily by surgical resection. Initial biopsy diagnoses made before referral to Moffitt were compared to final diagnoses based on re-excision and review by a Moffitt pathologist. Data on patient demographics, immune status, primary tumor characteristics, treatment, and recurrence were collected. Range and median values of margins were collected. Surgical margin is defined as the distance from the incision to the edge of visible or palpable tumor (or edge of biopsy scar if no clinical evidence of tumor). Margin size decisions were made with functional and cosmetic concerns in mind. All patient details were de-identified. Analysis was performed using descriptive statistics for demographic and disease characteristics and the Kaplan-Meier (KM) method and univariate and multivariate Cox proportional-hazards models were run to assess overall survival and recurrence-free survival. Missing clinicopathologic data were excluded from the analysis. The reporting of this study conforms to STROBE guidelines.[8]

Results

Eighty-five charts with patients diagnosed with AFX were originally identified, after careful pathology re-review, 7 cases were determined to be either PDS, melanoma, or undifferentiated pleomorphic sarcoma based on histological features such as depth of tumor extension, perineural invasion, positive S-100 staining, etc. This left 78 patients with definitive diagnoses of AFX. The median age was 74 years (range: 38-89 years, standard deviation: 11 years). The majority were men (n = 63, 78%), immunocompetent (n = 71, 91%), and Caucasian (n = 76, 99%). Primary tumors typically developed within a single region, with 85% (66/78) of tumors located on the head and neck, 9% (7/78) on the upper extremity, and 5% (5/78) on the trunk. Of the 5 patients with truncal AFX tumors, all were located on the upper chest/sternum. Three patients had lesions on the sun-exposed/tanning bed-exposed skin of the chest. One patient was chronically immunosuppressed, and 1 patient developed AFX in an area of previous irradiation. (Figure 1; Table 1).

In 37% of cases (29/78 patients), the diagnosis on initial biopsy was AFX. In the remainder of the patients (63%, 49/78) the diagnosis of AFX was made only after evaluation of the complete resection of the sarcoma. In these indeterminate cases, the differential diagnosis on the initial biopsy included pleomorphic dermal sarcoma (PDS) in 53% (26/49), undetermined spindle cell malignancy in 27% (13/49), melanoma in 6% (3/49), malignant fibrous histiocytoma in 8% (4/49), poorly differentiated squamous cell carcinoma in 4% (2/49), and cutaneous leiomyosarcoma 2% (1/49).

Histologically, most AFX lesions were found to have mild nuclear pleomorphism (77%, 36/47). Immunohistochemical staining revealed all tested tumors to be CD10 positive, and most tumors tested for CD68 were also positive. In contrast, all tumors stained for desmin and S-100 were negative. AFX tumor invasion was typically confined to the dermis, with rare focal involvement of the superficial subcutaneous tissue in 9% (6/72). (Figure 2; Table 2).

Thirty-two percent (25/78) of patients received preoperative imaging, none of whom had findings suggestive of metastatic disease. The patients in this cohort were treated primarily with surgical resection and had a median surgical margin of 1.0 cm (range: 0.2-3 cm, standard deviation: .55 cm). Five percent (n = 4) patients underwent adjuvant

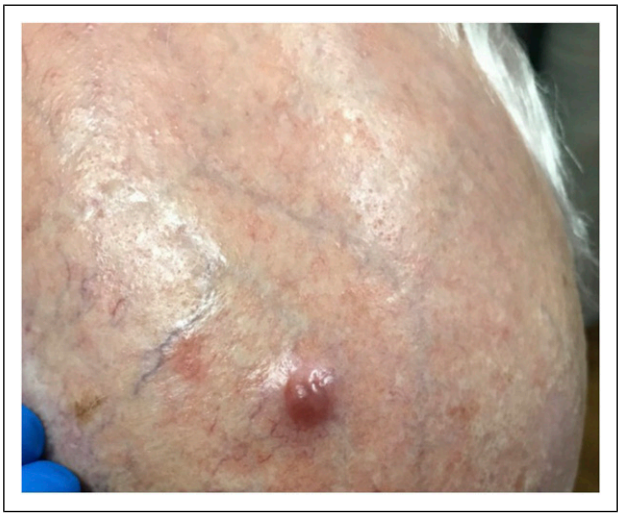

Figure 1. Atypical fibroxanthoma, typical clinical appearance of a tan/ redish-colored nodule on sun-damaged skin.

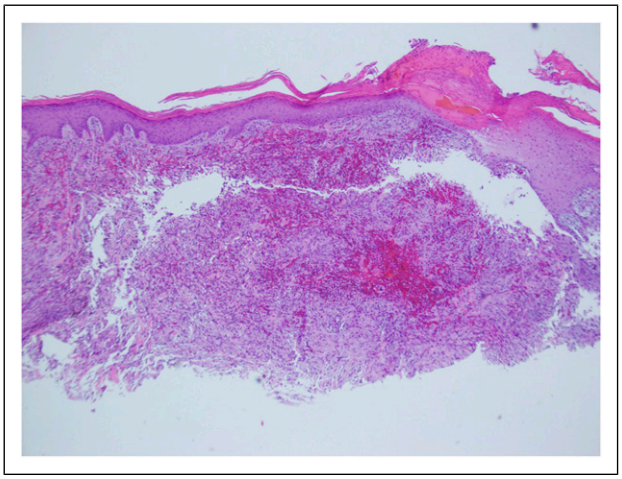

Figure 2. Atypical fibroxanthoma shave biopsy findings, showing malignant spindle cells filling the dermis growing in storiform fashion and extending to deep biopsy edge, so depth and invasion pattern cannot be evaluated (H and E, 5x).

Table 1. Patient Characteristics, Treatment, and Outcomes.

Clinical characteristics	
Median age at diagnosis	74 years (range 38-89)
Caucasian	76/77 (99%)
Gender	
Men	63/78 (81%)
Women	15/78 (19%)
Immunocompromised	7/78 (9%)
Tumor location	
Head/neck	66/78 (85%)
Trunk	5/78 (6%)
Upper extremity	7/78 (9%)
Pre-operative thoracic imaging	
Yes	25/78 (32%)
No	53/77 (68%)
Treatment and outcomes	
Operative margin (cm)	
<0.5	2/75 (3%)
0.5	8/75 (11%)
1	47/75 (63%)
>1	18/75 (24%)
Final margin	
Negative	74/77 (96%)
Positive	3/77 (4%)
Local recurrence	
Yes	1/78 (1%)
No	77/78 (99%)i

Table 2. Histologic Characteristics.

Nuclear Pleomorphism	
Mild	36/47 (77%)
Moderate	1/47 (2%)
Severe	10/47 (21%)
Immunohistochemistry staining	
S100 +	0/68 (0%)
Desmin +	0/37 (0%)
CD10 +	42/42 (100%)
CD68 +	37/41 (90%)
Depth of invasion	
Dermis	65/72 (91%)
Focal subcutaneous tissue	6/72 (9%)

radiation: 3 for positive margins, and 1 for a concurrent sebaceous carcinoma in the same region.

Over a median follow up of 12.5 months (range: 0 - 215 months), 1.3% (n = 1) of patients developed recurrence giving a 98.7% recurrence-free survival. Statistical analysis by cox-regression was not possible due to limited number of events (Figure 3).

The patient that recurred was initially treated with surgical excision (1.5 cm margins, positive margins) followed by re-excision and adjuvant radiation. This patient developed multiple local recurrences 99+ months post-operatively, these recurrences were treated with surgical resection and radiation therapy. None of the patients in this cohort developed evidence of distant metastatic disease. No patients in this cohort died of their disease.

Discussion

These data support that AFX is predominantly a lesion of the head and neck region of elderly white men. This study also suggests that patients experience excellent local control with a median resection margin of 1 cm resulting in 98.7% recurrence free survival and 100% disease-specific survival.

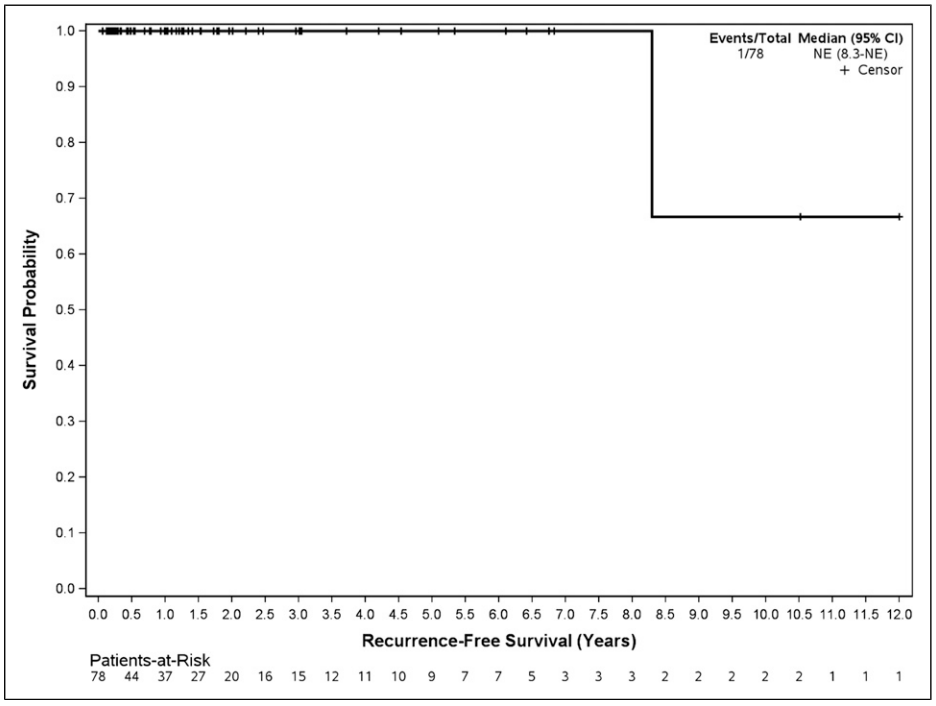

Figure 3. Kaplan-Meier curve of AFX recurrence-free survival measured in years. 1/78 patients experienced regional recurrence over a follow-up period of 8 years.

Additionally, the results demonstrate the challenge in making a definitive diagnosis of AFX on biopsy. For example, the distinction between AFX and PDS is difficult to make, specifically AFX is differentiated from PDS by involvement of the dermis, a non-infiltrative inferior border, and absence of necrosis, angiolymphatic or perineural invasion. Rarely AFX could involve the superficial subcutis but only the context of a smaller (<2 cm) tumor with a well-circumscribed inferior border. Therefore, making the distinction between these tumors requires complete excision, where these characteristics can be evaluated. Indeed, the majority of patients in this cohort diagnosed with AFX required a complete resection before this determination could be made (Figure 4). Our cohort also demonstrated that rarely, tumors histologically consistent with AFX on re-excision may show aggressive behavior: 1% of tumors diagnosed as AFX following a complete excision subsequently showed local recurrence, with multiple local recurrences.

The clinicopathological characteristics of patients that develop atypical fibroxanthoma tumors in this study match those reported in other studies. Specifically, the highest-risk individuals are elderly white men and lesions most often occur on the head and neck regions.[4-6,9] Zero cases of death by disease or distant recurrences in this cohort are consistent with existing data, a systematic review found that the rate of metastases for this cancer is relatively low, at less than 1%, and disease-specific deaths due to metastatic AFX tumors are also very uncommon, with only 15 cases reported.[1,5,10-16]

Histologically, the current literature supports this study's findings that AFX lesions are confined to the dermis,[9] and consistently stain positive for CD10, and CD68 while staining negative for desmin and S-100.[17] Since this immunoprofile is considered fairly non-specific, a diagnosis of AFX should be rendered after other superficial cutaneous spindle cell malignancies are excluded by a panel of immunohistochemical stains. These include Sox10 for melanoma, CK5/6 or p63 for spindle cell squamous cell carcinoma, desmin for muscle origin, and vascular markers such as CD34 or ERG if angiosarcoma is suspected.[18] Of note, immunohistochemical stains for both S-100 and MITF, considered predominantly melanocytic markers, can be focally positive in AFX because they can stain dendritic cells and histiocytes.[19] For example, 1 of this cohort's tumors showed focal S-100 positivity and was initially diagnosed as melanoma, but on re-excision the tumor was only focally positive for this marker in cells of dendritic morphology supportive of a diagnosis of AFX. Although it is important to note that there are documented cases where melanomas closely resemble AFX, and immunohistochemical staining was key to making final diagnoses. For example, a case report on a tumor with AFX-like morphology stained strongly positive for SOX-10, S100 and negative for CD68, which ultimately led to the diagnosis of melanoma.[20] Currently, AFX is considered to mostly represent a tumor of fibrohistiocytic/mesenchymal tissue origin. While histologically the initial biopsy is quite similar to PDS, the pattern of invasion in the re-excision can help distinguish these 2 tumors.[6,21-25] Adding to the challenge of differentiating AFX

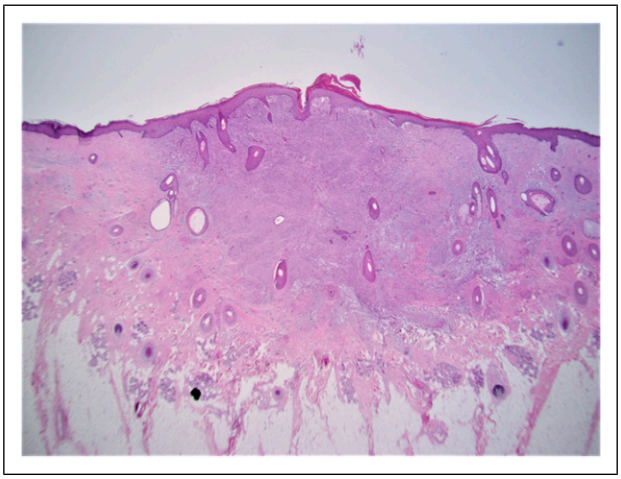

Figure 4. Atypical fibroxanthoma re-excision specimen, showing lesion confined to dermis with wellcircumscribed inferior border (H&E, 1.25x).

from PDS is that there are no immunohistochemical markers that signify 1 from the other. While the standard method for diagnosing an AFX tumor remains histological examination of a skin biopsy and excision,[26] IHC staining is primarily useful for ruling out cutaneous cancers such a melanoma, squamous cell carcinoma, and leiomyosarcoma.[22]

The primary limitation of this study is its retrospective design. The ability to report on risk factors is constrained to what is clinically documented, so risk factors such as a history of irradiation, tanning bed use, level of sun exposure, sunscreen use, etc. could not be addressed. Additionally, as this study is focused on reporting patient and tumor characteristics and their associations with recurrence-free survival without the use of a control group, we cannot assess causations, only correlations. Many patients had pathology reports missing histological characteristics, therefore the data collected for Table 2 is less robust. Additionally, the median follow up time of this study was relatively short, and may have contributed towards the low recurrence free survival in this cohort. A recent meta-analysis of 598 patients noted a 1-year recurrence risk of 3.2%, which is lower than our cohort, but the 5 year recurrence rate was much higher at 7.3%.[27] The final limitation is the inability to run statistical analysis via the cox-regression.

Conclusion

The high level of congruence between this cohort's demographical data and existing AFX literature increases the generalizability of the study results. Given the 100% disease-specific survival and the excellent 98.7% recurrence-free survival of patients with AFX treated with median 1 cm margins as well as the essential nature of complete excision for final diagnosis, this study supports the use of a 1 cm margin wide excision as a surgical standard for the treatment of localized AFX. There is no data to support the proposition that wider margins would be beneficial and the narrower margin (1 cm) would also likely limit the use of of larger grafts and flaps, or hopefully elimate the need for graft and flap closure, especially in the head and neck where most AFXs will occur. Distinguishing AFX from other histologically similar cancer types using immunohistochemical staining is essential to exclude other higher-risk tumor types, and thus is an integral component of the workup and diagnosis.

Appendix

Abbreviations

AFX: atypical fibroxanthoma; KM: Kaplan-Meier; NMSC: nonmelanoma skin cancer; MMS: Mohs micrographic surgery; PDS: pleomorphic dermal sarcoma.

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Declaration of Conflicting Interests

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Ethics Statement

Written consent was obtained from the Institutional Reviewer Board via expedited review, IRB#00000971.

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