Atypical Fibroxanthoma With Regional Lymph Node Metastasis

Report of a Case and Review of the Literature

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Background: Atypical fibroxanthoma (AFX) is a low-grade sarcoma usually occurring on sun-damaged skin of the head and neck in elderly patients. Metastatic disease has been reported very rarely. The potential aggressiveness of AFX is controversial.

Observations: We describe herein a patient who developed metastatic disease in cervical lymph nodes. Our patient was an 87-year-old man with a 7-week history of a rapidly growing AFX presenting as a 1.5-cm sessile nodule on his right mandible. Two months following excision, the patient developed cervical lymphadenopathy. Histopathologic analysis of the cervical lymph nodes revealed spindle-cell tumors with histologic characteristics identical to those of the primary AFX, and the tumors were immunonegative for cytokeratin MNF-116 and S-100. In addition, we review and analyze cases from the literature and articles related to immunohistochemical stains used to diagnose AFX.

Conclusions: Atypical fibroxanthoma is a diagnosis of exclusion, and only a small number of metastatic AFX cases have been reported. A review of the literature pertaining to immunohistochemical stains suggests the potential benefit of use of CD10, procollagen I, CD99, CD117, p63, and LN-2 in differentiating AFX from other spindle-cell tumors. The metastatic potential of AFX may not be fully appreciated, and clinicians should be reminded of its potential aggressive behavior.


Atypical fibroxanthoma (AFX) is considered a low-grade sarcoma and usually occurs on sun-damaged skin of the head and neck in elderly patients. The prognosis is generally excellent following adequate excision of the primary tumor. Recurrences occur in about 5% of cases and may be related to inadequate margins. Some cases are more aggressive and can involve metastatic disease. Currently, controversy exists over the classification and characteristic clinical behavior of AFX. Some authorities classify it as a superficial variant of a malignant fibrous histiocytoma (MFH); shallower depth of the tumor within the dermis and lack of involvement of the subcutaneous tissue favor a diagnosis of AFX. Others believe that an AFX is simply a variant of squamous cell carcinoma (SCC), although studies have refuted this claim.

Atypical fibroxanthoma is a diagnosis made histopathologically by ruling out other spindle-cell neoplasms, including spindle-cell SCC (SCSCC), spindle-cell melanoma (desmoplastic melanoma), MFH, leiomyosarcoma, and angiosarcoma. Immunohistochemical stains aid in establishing the diagnosis of AFX by differentiating it from other malignant neoplasms that commonly arise on sun-damaged skin, especially SCSCC and spindle-cell melanoma. Unfortunately, we do not have a sensitive or specific immunostain for AFX to rule out these other entities and establish the diagnosis. Stains that are currently used include cytokeratins, vimentin, smooth-muscle actin, CD68, desmin, and S-100. More recently, studies have demonstrated some utility of CD10, procollagen I (PC1), CD117, CD99, p63, and LN-2, as authors look for additional markers that will increase the sensitivity and specificity of traditional staining panels, especially in the setting of metastatic disease.

A recent article describes the current perception of AFX as a benign tumor with no risk of metastasis. However, we believe that the potential aggressive behav-
ior of an AFX should be given more consideration. Herein, we report a case of a metastatic AFX and review previously reported metastatic AFX cases and recent studies evaluating the use of immunohistochemical stains that may provide clarity when evaluating cutaneous spindle-cell neoplasms.

REPORT OF CASE

An 87-year-old white man with no history of skin cancer was seen with a 7-week history of a rapidly growing nodule on his right jawline (Figure 1). On physical examination, we found a 1.5-cm sessile, firm nodule with hemorrhagic crust. The patient did not have any other suspect cutaneous lesions or lymphadenopathy. Findings from a systems review were negative. He had no personal or family history of skin cancer.

Shave biopsy specimens revealed a completely excised spindle-cell tumor with atypical cells and a high mitotic index (Figure 2 and Figure 3). Tumor cells tested immunopositive with vimentin, CD68, and lysozyme and immunonegative for pancytokeratins, cytokeratin MNF-116, CD34, desmin, smooth-muscle actin, HMB-45, and S-100. A diagnosis of AFX was rendered based on clinicopathologic correlation.

Results of margin analysis after surgical excision with 5-mm margins were negative for residual tumor. Two months following the excision, the patient developed a nontender 3 × 3-cm, deep-seated, skin-colored nodule 4 cm inferior to the surgical site on his right lateral neck. Analysis of fine-needle aspirate revealed atypical spindle cells. A modified radical neck dissection revealed 2 cervical lymph nodes containing metastatic tumor with features consistent with an AFX (Figure 4). The metastatic tumor showed diffusely positive staining for CD10 and CD99 and rare weak positivity for p63 while being immunonegative for S-100 protein and cytokeratin MNF-116. Following surgical excision of affected lymph nodes, the patient underwent 5 rounds of local radiation therapy and remained disease free 18 months following his initial presentation.

COMMENT

Since the first description of AFX by Helwig3 in 1963, the clinical behavior of this entity has been controver-
ranged from 0.6 cm to 4 cm (age range, 28-87 years). The size of the initial tumor was diagnosed at an average patient age of 69.5 years.

Men than women. In cases of metastasis, the primary tumor was confounded by the fact that AFX occurs more often in women (16 of 22 [73%] vs 6 of 22 [27%]); however, this has been reported. The average time interval between the diagnosis of the primary tumor and the metastatic disease was 19.7 months (range, 1-84 months). Metastatic disease has been more commonly reported in men than in women (16 of 22 [73%] vs 6 of 22 [27%]); however, this is confounded by the fact that AFX occurs more often in men than women. In cases of metastasis, the primary tumor was diagnosed at an average patient age of 69.5 years (age range, 28-87 years). The size of the initial tumor ranged from 0.6 cm to $4 \times 3$ cm.

Details concerning the depth of tumor invasion and results of immunohistochemical stainings were not consistently reported in all studies. It is difficult to draw absolute conclusions from these cases because potential subcutaneous involvement would favor the diagnosis of MFH rather than AFX. For example, case 20 involved the subcutis and was diagnosed as AFX. In the present study, we included all cases reported to be AFX for the sake of completeness. The case series reported by Helwig and May (cases 7-14, including the case also reported by Jacobs et al) excluded tumors if they involved the subcutis. Cases 15 and 18 and our case did not involve deep dermal structures. The other reports did not discuss the details of their histologic findings. Likewise, the use of immunohistochemical stains varied among studies.

Recurrences were noted in 36% of cases (8 of 22), with an average interval of 6.4 months. Recurrences occurred as soon as 3 months and as late as 23 months after initial treatment. Two cases had multiple recurrences (cases 11 and 14). Whether these were true recurrences due to aggressiveness of the tumor or inadequate treatment is a matter of debate. Of the 8 cases with recurrences, 100% showed distant metastatic disease. These findings underscore the importance of long-term, close clinical evaluation of patients who have a history of AFX, including a thorough skin examination and lymph node examination for recurrences and possible metastatic disease. They also highlight that local recurrence is an indicator that patients need to be monitored even more closely for metastatic disease.

Atypical fibroxanthoma is a diagnosis of exclusion and requires an experienced dermatopathologist and clinicopathologic correlation. Under routine processing with hematoxylin-eosin, AFX must be distinguished from the deeper and more aggressive MFH, which is associated with a higher rate of metastasis and was excluded as a diagnosis in our case, based on the superficial location of the tumor within the dermis. Some authors have suggested that AFX with certain histologic features such as necrosis, vascular invasion, and deep tissue invasion may portend more aggressive behavior. These features were not present in our case.

A thorough immunohistochemical evaluation is indicated to rule out other spindle-cell tumors including spindle-cell melanoma, SCSCC, angiosarcoma, and leiomyosarcoma. Our patient’s primary tumor stained immunopositive with CD68, vimentin, and lysozyme and was immunonegative for S-100, HMB-45, smooth-muscle actin, desmin, CD34, cytokeratin MNF-116, and pancytokeratin. His metastatic tumor had a staining pattern consistent with AFX, demonstrating immunonegative staining for S-100 and cytokeratin MNF-116 and immunopositive staining for CD10, CD99, and p63, further lowering the probability of metastatic disease representing a melanoma or SCSCC.

Ang et al describe a more than 20-year experience of treating 93 AFX tumors in 91 patients at the Mayo Clinic. Initially there were 96 total cases in 94 patients, but 3 initial diagnoses of AFX were changed to either SCSCC or MFH after metastatic disease occurred. The first patient whose diagnosis was changed was an 83-year-old man with a history of 5 surgical procedures and radiation treatment for SCSCC on the right upper eyebrow who subsequently was seen with a 3.9-cm lesion diagnosed as AFX. Six months after removal of this tumor, another growth, with characteristics more consistent with SCSCC, occurred at the same site. Four months after its resection, the patient developed massive infiltration of the frontal sinus. No tissue was taken from the metastasis because the patient died of the tumor within weeks. In this case, the authors believed that AFX was actually a misdiagnosed SCSCC.

The second patient with changed diagnosis was a 94-year-old man with a 1.8-cm AFX lesion on the ear, which was treated with wide local excision (WLE). The lesion recurred twice despite WLE and led to hemi-amputation of the ear following the second recurrence. Thirty-seven months following the initial diagnosis, regional metastasis to the parotid gland occurred and was diagnosed as a grade 4 MFH.

The third patient whose diagnosis was changed was a 74-year-old man with a history of metastatic SCC to the tongue who developed an AFX on the ear and scalp treated with WLE. Recurrences occurred locally and were labeled as AFX and MFH. Brain metastasis occurred 3 years after initial diagnosis of AFX, and histologic examination of the metastasis was labeled MFH.

The decision to change the diagnosis in the first of these 3 cases seems reasonable. In regard to the other 2 cases, however, the histologic characteristics of metastatic MFH would be indistinguishable from those of metastatic AFX. Assuming that the primary lesion’s histologic characteristics were consistent with AFX, it seems reasonable to categorize these 2 cases as true metastatic AFX based on the information provided. If one were to include these 2 cases as metastatic AFX (and exclude the first), then metastatic disease occurred in 2 of 93 cases of AFX (2%). No details concerning the immunohistochemical analysis of these tumors were provided, and distinguishing metastatic MFH from AFX would have been impossible, since they share a similar immunophenotype.
<table>
<thead>
<tr>
<th>Source</th>
<th>Patient No./Sex/Age, y</th>
<th>Primary Tumor Site/Size, cm/Recurrence at Primary Site, Yes or No</th>
<th>Depth*/Immunohistochemical Stainings of Primary Tumor</th>
<th>Treatment</th>
<th>Site of Metastasis</th>
<th>Interval to Metastasis, mo</th>
<th>Immunohistochemical Stains of Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper et al4</td>
<td>1/M/77</td>
<td>Right antihelix/0.6/yes, with 12-mo interval, treated with Exc</td>
<td>ND/LN-2 (^{-})&lt;sup&gt;1&lt;/sup&gt; (CD74 (^{-}))</td>
<td>Exc with 1-cm margin through cartilage</td>
<td>Intraparotid lymph node</td>
<td>22</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>2/F/80</td>
<td>Left cheek/unknown/no</td>
<td>ND/ND</td>
<td>Mohs surgery with 1-cm margin to deep adipose tissue</td>
<td>Parotid and submandibular lymph nodes</td>
<td>3</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>3/M/85</td>
<td>Scalp/1/no</td>
<td>ND/ND</td>
<td>Mohs surgery with 1-cm margin</td>
<td>Liver</td>
<td>12</td>
<td>L2 (-)&lt;sup&gt;1&lt;/sup&gt; (CD74 (-))</td>
</tr>
<tr>
<td></td>
<td>4/M/66</td>
<td>Right upper extremity/unknown/no</td>
<td>ND/ND</td>
<td>Exc, UM</td>
<td>Local lymph nodes</td>
<td>12</td>
<td>L2 (-)&lt;sup&gt;1&lt;/sup&gt; (CD74 (-))</td>
</tr>
<tr>
<td></td>
<td>5/M/65</td>
<td>Right dorsal hand/1/no</td>
<td>ND/LN-2 (-)&lt;sup&gt;1&lt;/sup&gt; (CD74 (-))</td>
<td>Mohs surgery with 1-cm margins</td>
<td>Right wrist (cutaneous metastasis)</td>
<td>11</td>
<td>L2 (-)&lt;sup&gt;1&lt;/sup&gt; (CD74 (-))</td>
</tr>
<tr>
<td>Muenster and Hoang3</td>
<td>6/M/63</td>
<td>Left facial cheek over parotid gland/0.6/yes, with 12-mo interval, treated with Exc</td>
<td>ND/ND</td>
<td>Exc, UM</td>
<td>Intraparotid lymph nodes</td>
<td>30</td>
<td>CD68 (-); vimentin (-); Cytokeratins (AE1 (-)/AE3 (-)); smooth-muscle actin; CD45; S-100; HMB-45; CD31; glial fibrillary acidic protein</td>
</tr>
<tr>
<td>Helwig and May4</td>
<td>7/M/70</td>
<td>Left lower ear/1.5 \times 1/no</td>
<td>ND/ND</td>
<td>SubQ/ND</td>
<td>Left parotid area</td>
<td>6</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>8/M/78</td>
<td>Right facial cheek/1 \times 1/yes, after 5-mo interval</td>
<td>ND/ND</td>
<td>SubQ/ND</td>
<td>Intraparotid soft tissue and lymph nodes</td>
<td>5</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>9/M/82</td>
<td>Right forehead/1 \times 1/no</td>
<td>ND/ND</td>
<td>SubQ/ND</td>
<td>Right parotid area</td>
<td>60</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>10/8/86</td>
<td>Upper left ear/1.6 \times 1.2/no</td>
<td>ND/ND</td>
<td>SubQ/ND</td>
<td>Soft tissue near left mastoid</td>
<td>2</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>11/9/77</td>
<td>Right cheek/unknown/no, multiple recurrences, at 4, 7, and 9 mo</td>
<td>ND/ND</td>
<td>SubQ/ND</td>
<td>Right parotid area</td>
<td>12</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>12/8/74</td>
<td>Forehead/0.4 \times 0.4/yes, with 3-mo interval; second primary/0.7 \times 0.7/NR</td>
<td>ND/ND</td>
<td>SubQ/ND</td>
<td>Right parotid lymph node</td>
<td>4</td>
<td>ND</td>
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<tr>
<td></td>
<td>13/M/52</td>
<td>Right temple/2 \times 3/yes, with 7-mo interval</td>
<td>ND/ND</td>
<td>SubQ/ND</td>
<td>Ipsilateral parotid lymph node</td>
<td>7</td>
<td>ND</td>
</tr>
<tr>
<td>Jacobs et al5</td>
<td>14/9/28</td>
<td>Right side of nose/2 \times 7/yes, at 10 and 23 mo</td>
<td>ND/ND</td>
<td>SubQ/ND</td>
<td>Ipsilateral cervical lymph node</td>
<td>84</td>
<td>ND</td>
</tr>
<tr>
<td>Kargi et al6</td>
<td>15/M/68</td>
<td>Right thigh with intravascular invasion/3 \times 4/no</td>
<td>ND/ND</td>
<td>SubQ/ND</td>
<td>Tumor infiltrating papillary dermis/S-100; cytokeratin; myoglobin</td>
<td>6</td>
<td>ND (^{2})</td>
</tr>
<tr>
<td>Lum and King6</td>
<td>16/M/81</td>
<td>Scalp/1/NR</td>
<td>ND/ND</td>
<td>SubQ/ND</td>
<td>Merkel cell carcinoma, with CD10 (-); vimentin (-); CD8 (-); CD99 (-); focally; pan-cytokeratin; EMA; S-100; smooth-muscle actin; desmin; high-molecular-weight cytokeratin; Factor XIIIa; CD34; KX-6-31 in 20% of cells</td>
<td>36</td>
<td>ND</td>
</tr>
<tr>
<td>Giuffrida et al7</td>
<td>17/M/87</td>
<td>Scalp/3/no</td>
<td>ND/ND</td>
<td>Mohs surgery</td>
<td>Cutaneous metastasis to scalp</td>
<td>1</td>
<td>Vimentin (-); cytokeratin; S-100; MART-1 (-)</td>
</tr>
<tr>
<td>Grosso et al1</td>
<td>18/F/69</td>
<td>Left nostril/unknown/no</td>
<td>ND/ND</td>
<td>Nodular pattern did not affect deep structures, tumor cells invaded dermal blood vessels/Factor VIII (-); alpha-1-antitrypsin (-); lysozyme (-); ferritin</td>
<td>Unknown</td>
<td>15</td>
<td>Identical to primary tumor</td>
</tr>
<tr>
<td>Kamp et al12</td>
<td>19/M/79</td>
<td>Right facial cheek/2/yes, 3-mo interval</td>
<td>ND/ND</td>
<td>SubQ/ND</td>
<td>Ipsilateral parotid, buccal, and cervical lymph nodes</td>
<td>3</td>
<td>ND</td>
</tr>
</tbody>
</table>

(continued)
The use of staining with LN-2 (CD74) might have been useful in this situation. Lazova et al16 evaluated staining intensity of LN-2 in spindle-cell tumors, including 20 cases each of AFX and MFH. Their findings were promising in that strong staining was seen in 90% of MFH cases, and negative or weak staining was found in 90% of cases of AFX.

Differentiating AFX from SCSCC is also challenging. Cytokeratin stains (both low-molecular-weight and high-molecular-weight keratins) are useful in the vast majority of cases. While a minority of cells from SCSCC may stain weakly positive or even negative, typically they stain intensely positive. Given the propensity of SCSCC to metastasize to regional lymph nodes and the occurrence of these tumors on sun-damaged skin of older individuals, it is reasonable to be concerned that unidentified cases of SCSCC are mislabeled as AFX, especially in the setting of aggressive disease. Some authors believe that AFX is simply a dedifferentiated variant of SCSCC, while others refute this claim based on the lack of cytokeratin staining in cases of AFX. Vimentin staining can be used to help differentiate these 2 entities because SCSCC cells typically stain negative, while most cases of AFX stain positive.

Monteagudo et al17 have proposed that CD99, in addition to the traditional battery of immunostains, might aid in the differentiation of SCC and AFX. They evaluated 26 cases of AFX and 10 cases of SCC and found that 73% of the AFX cases showed immunoreactivity for CD99 vs none of the SCC cases, suggesting that CD99 is a helpful positive marker for AFX. Mathew et al18 evaluated CD117 (c-kit) expression in AFX and found positive staining in 94% of the cases (15 of 16), suggesting that CD117 may prove to be a sensitive marker. In 2007, Hultgren and DiMaio19 reported the possible benefit of CD10 immunostaining, in combination with a panel of stains, to help differentiate AFX from SCC and melanoma. They looked at 16 cases of AFX, 10 cases of SCC, and 9 cases of spindle-cell and/or desmoplastic melanoma and demonstrated strong diffuse CD10 staining in 94% of AFX cases, weak to moderate staining in 50% of SCC cases, and weak expression in 33% of desmoplastic melanomas cases.

de Feraudy et al20 performed an evaluation of CD10 and PC1 expression in AFX and support the use of both as positive stains for AFX lesions within the context of an immunoperoxidase panel. Specifically, they demonstrated PC1 positivity in 96% of cases of AFX (45 of 47) (and 78% of these were strongly positive) compared with only weak staining in 15% of cases of carcinoma (2 of 13). Group 2 of their study demonstrated that CD10 staining was positive in 100% of cases of AFX (11 of 11) and in 100% of cases of dermatofibroma (11 of 11). Group 3 showed that CD10 staining was positive in 97% of cases of AFX (37 of 38), and PC1 staining in this group was positive in 79% of cases of AFX (27 of 34). More recently, p63 was reported to be a helpful marker to differentiate SCSCC from AFX. Gleason et al21 evaluated 20 AFX and 10 SCSCC lesions and found strong expression of p63 in 100% of SCSCC cases and negative staining in 100% of cases of AFX, suggesting that p63 has utility as part of a standard immunohistochemical panel for differentiating spindle-cell tumors.

One legitimate concern about metastatic AFX reports is that the tumor is in fact not an AFX but another entity. Supporting the diagnosis of metastatic AFX in our
patient, the metastatic tumor showed morphologic characteristics on hematoxylin-eosin staining identical to the original skin lesion; S-100 and cytokeratin MNF-116 stainings were negative; and CD10, CD99, and p63 stainings were positive. These results are consistent with AFX, and although no truly confirmatory stain exists at this time, these findings decrease the probability that the evaluated lesion is metastatic SCC or melanoma.

The use of p63, CD10, PC1, CD117, and CD99 staining may prove beneficial in delineating AFX from SCC, especially in cases of metastasis. Likewise, the use of LN-2 may prove beneficial in distinguishing AFX from MFH. Clinicians should be aware of the rare but real possibility of AFX behaving aggressively and should monitor patients closely for recurrence and metastatic disease, especially to regional lymph nodes. We stress the importance of immunohistochemical evaluation by an experienced dermatopathologist to rule out other spindle-cell tumors, especially in the setting of metastasis. Future studies will be needed (1) to determine if histologic features or tumor markers may help predict tumor outcome and (2) to evaluate the most efficient and thorough immunohistochemical panel to distinguish genuine cases of primary and metastatic AFX from other entities.

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REFERENCES