

Contralateral recurrence of aggressive fibromatosis in a young woman: A case report and review of the literature

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Abstract. Aggressive fibromatosis (AF) is a benign non-encapsulated tumor of mesenchymal origin, with a tendency for local spread along fascial planes. Local invasion can lead to extensive morbidity and even mortality due to destruction of the bones, organs and soft tissues. This rare lesion is observed 1,000 times more frequently in patients with familial adenomatous polyposis or Gardner's syndrome due to the inheritance of the adenomatous polyposis coli (*APC*) gene. While AF does not metastasize, local recurrence is common. Distant recurrence is extremely rare, but is observed in those with a germ line *APC* mutation. The present study details the case of a 20-year-old woman with a melanoma of the right shoulder, treated definitively with surgery. The patient then developed a painful mass at the surgical site; a surgical biopsy demonstrated that the mass was AF. The patient was treated with surgical resection, radiation therapy, and a course of tamoxifen. Five years later, the patient presented with left forearm pain and diminished range of motion due to an infiltrating mass. This was excised and a clinical diagnosis of recurrent AF was made, in this patient lacking familial predisposition to the disease.

Introduction

Aggressive fibromatosis (AF), first identified by Stout in 1954 (1), is a benign non-encapsulated lesion of mesenchymal origin, with a tendency for local spread along fascial planes. AF is locally invasive to bones, organs and other tissues, which can be fatal. The tumors are rare, observed in 2-4 cases per million individuals each year (2), and typically occur between puberty and the age of 40, with a slight female preponderance. AF can arise in the musculoaponeurotic tissue of any location, but is common in the abdominal wall, extremities, head and neck,

and shoulder girdle. Individuals with familial adenomatous polyposis (FAP) or Gardner's syndrome have a 1,000 times greater risk for developing the disease due to inheritance of the adenomatous polyposis coli (*APC*) gene (3). These patients may present with intra-abdominal lesions following colonic resection (4). While AF does not metastasize, local recurrence is common. Distant recurrence is extremely rare, but is typically observed in those with a new primary tumor associated with the *APC* mutation. The present study reports the case of a 20-year-old female with sporadic contralateral recurrence of clinically diagnosed AF and no familial predisposition.

Case report

A 20-year-old female first presented in April 1992 at Northeastern Pennsylvania Plastic Surgery Associates (Scranton, PA, USA) with a pigmented lesion on the right shoulder overlying the trapezius. The lesion had undergone a recent change in size and color. Upon physical examination, an irregularly contoured brown papule with portions of jet black speckling was noted. No cervical or axillary adenopathy was present. The past medical history was significant for a mitral valve prolapse and asthma. The patient's family history was free of any familial disease. A biopsy of the lesion was performed, which confirmed a 0.4-mm thick malignant melanoma, Clark's level III. The patient underwent a negative staging workup and the 1.7-cm tumor was excised with plastic reconstruction. The margins were negative.

One year later, in July 1993, the patient returned to Northeastern Pennsylvania Plastic Surgery Associates complaining of pain at the surgical site. The area was profoundly painful upon palpation and a discrete mass was identified deep to the incision (Fig. 1A). Two enlarged axillary lymph nodes were noted. Fearing a recurrent melanoma, magnetic resonance imaging (MRI) and biopsies of the lymph nodes and shoulder mass were obtained. MRI showed a 7x3x3-cm area of altered signal extending from the skin into the trapezius muscle. The lesion was isodense to muscle on T1-weighted imaging, with increased intensity on T2-weighted imaging (Fig. 1B). On biopsy, the nodes were benign and reactive in nature. The lesion itself showed a proliferation of spindle cells, with no evidence of increased mitotic rate or necrosis, in a collagenous matrix infiltrating into the adjacent muscle fibers (Fig. 1C). S-100 and HMB-45 stains were negative. A diagnosis of AF was made and confirmed by independent pathologists at the

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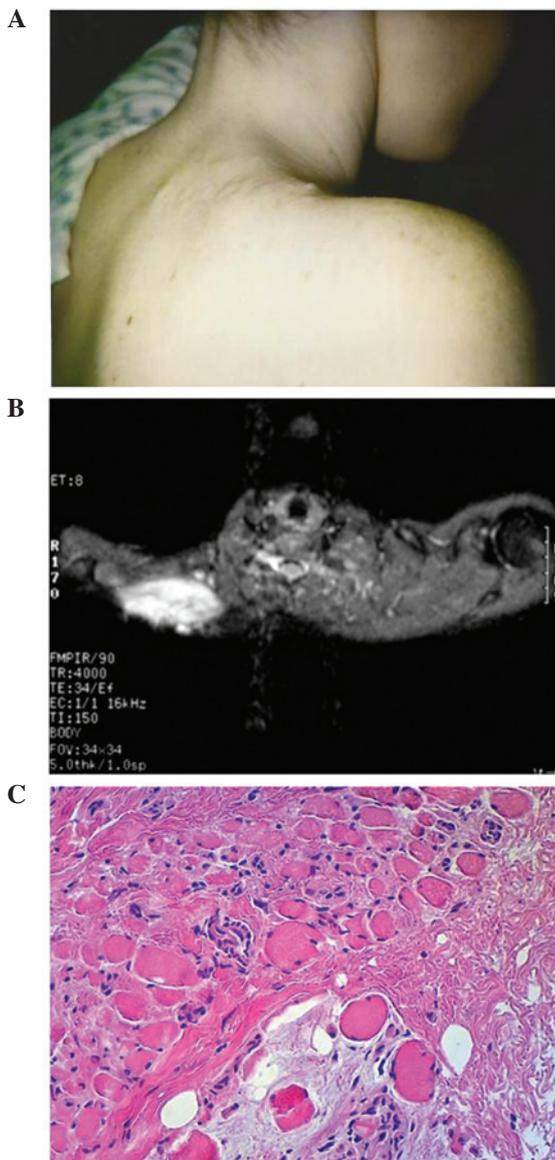


Figure 1. Right shoulder fibromatosis. (A) Palpable mass present at the previous surgical site. (B) Axial fluid-sensitive pulse sequence fat-suppressed T2-weighted magnetic resonance image. (C) Hematoxylin and eosin staining showing fibrotic tissue with bland spindle cells invading atrophic skeletal muscle fibers, with surrounding myxoid change, x200 magnification.

University of Pennsylvania (Philadelphia, PA, USA) and the Roswell Park Cancer Institute (Buffalo, NY, USA) (Fig. 1A). The patient initially refused surgery or radiation therapy and was treated with tamoxifen. Tamoxifen was started at 20 mg once daily beginning in June 1995 following recovery from surgery and radiation treatments. No improvement was noted and the patient eventually authorized surgical excision due to the rapid growth and infiltrative properties of the lesion. The mass was resected along with the right trapezius muscle due to tumor invasion and the shoulder girdle was resuspended with the levator scapulae muscle. Due to a positive margin, the patient was referred for radiation therapy and tamoxifen treatment was continued: Tamoxifen treatment continued at 20 mg once daily until January 1996, when the treatment was discontinued at the request of the patient. Radiotherapy consisted of 4,500 cGy in 180-cGy fractions, with 6 MeV photons to the

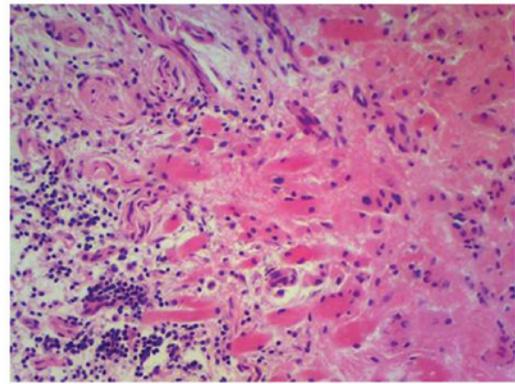


Figure 2. Hematoxylin and eosin staining of the left forearm lesion showing atrophic muscle fibers with interdigitating fibrosis and myxoid change, x200 magnification.



Figure 3. Depression of the scapula due to levator scapulae shoulder girdle resuspension, with post-radiation dermal changes.

right shoulder and scapula. A boost of 1,620 cGy in 180-cGy fractions, with 9 MeV electrons, was administered to the surrounding scar. The treatment was successful and follow up MRI scans showed no evidence of recurrent disease.

Nearly 5 years after the diagnosis of right shoulder AF, in March 1999, the patient presented at Northeastern Pennsylvania Plastic Surgery Associate with left forearm pain and failure to pronate or supinate the extremity $>10^\circ$. Flexion and extension were preserved. There was exquisite tenderness upon palpation between the radius and ulna proximally. Upper extremity sensation was intact and reflexes were 2+ bilaterally using the National Institute of Neurological Disorders and Stroke (NINDS) scale developed by Hallett in 1993 (5). An MRI scan was obtained showing a thin 5-cm area of enhancement located between the proximal radius and ulna, possibly involving the periosteum of each. The area was isodense to muscle on T1-weighted imaging, with increased intensity on T2-weighted imaging. A monophasic bone scan showed areas of increased intensity in the proximal radius and ulna. A computed tomography-guided needle biopsy demonstrated a collagenous fibrous stroma with plump spindle cells devoid of increased mitotic activity, consistent with AF. The patient underwent surgical resection of the forearm lesion, but declined further radiation or medical therapy. Although grossly and clinically the lesion behaved as AF, the final pathological report was equivocal, noting fibroadipose tissue with myxoid

change (Fig. 2). However, a clinical diagnosis of AF was made and the patient was treated accordingly.

The patient still attends follow-up examinations nearly 20 years after the initial diagnosis of melanoma. The patient is in a good condition and has experienced no further recurrence of either lesion. However, shoulder girdle suspension using the levator scapulae is a continual source of pain and weakness, and may require further stabilization in the future (Fig. 3).

Discussion

Sporadic AF arises from somatic mutations in the *APC* gene or in *CTNGB1*, which codes for β -catenin (6,7). Germline *APC* mutations found in individuals with FAP predispose the patient to AF. APC acts to downregulate the expression of β -catenin as part of the canonical Wnt pathway. In the absence of activation, a complex of APC, axin and glycogen synthase kinase 3 β phosphorylates β -catenin resulting in ubiquitin-mediated degradation (8). Mutation prevents this complex from forming, β -catenin accumulates in the cytoplasm and nucleus where it subsequently binds transcription factors of the T cell/lymphoid enhancer-binding factor family, inducing gene expression (9). Hedgehog signaling, which modulates the Wnt pathway and β -catenin expression, is also involved in the pathogenesis (10). The buildup of β -catenin within mesenchymal progenitor cells likely maintains an undifferentiated fibroblast-like state, producing uncontrolled proliferation and stromal expansion (11).

The tumor exhibits phases of progression, latency and occasional spontaneous regression. Extra-abdominal tumors produce symptoms, including pain, weakness and paresthesia. Intra-abdominal lesions can cause intestinal obstruction or ischemia (12). MRI is the most useful imaging technique for diagnosis, showing intermediate intensity on T1-weighted imaging and high signal intensity on T2-weighted imaging. Intravenous contrast agents produce moderate- to high-grade enhancement in highly cellular regions. Non-enhancing bands of low intensity dominate, representing densely packed fibrous tissue (13,14). Once AF is identified, a tissue biopsy should be performed. Fine-needle aspiration is acceptable if an open biopsy is contraindicated (15). Histological analysis shows a scattered proliferation of spindle cells with bland, occasionally bipolar, nuclei. Neoplastic cells are dispersed among a dense collagenous, keloid-like or myxoid matrix. Staining for nuclear β -catenin is positive, while staining for S-100, c-kit, cluster of differentiation 34, estrogen receptor α and desmin is negative (15). A cytogenetic association with trisomy 8 and 20 is occasionally noted (16).

For stable or slow growing masses, close monitoring is now advocated as the primary treatment strategy, as AF has a tendency to regress. Studies have shown no difference in survival between patients treated with surgery or radiation therapy compared with no treatment in this population (17,18). Surgical resection is indicated in those individuals with aggressive lesions. The 5-year risk of recurrence following resection is 17.6%, regardless of whether or not microscopic margins remain (19). Radiation therapy at a dose of 50-60 Gy is also an effective primary therapy (20). Neoadjuvant or adjuvant radiation is occasionally performed, but its use is controversial. Conflicting studies have shown either no

difference in recurrence rate following adjuvant therapy (21) or a delayed time to recurrence with no impact on overall survival (22). Patients with contraindications to surgery or radiotherapy can undergo medical treatment. Non-steroidal anti-inflammatory drug therapy with sulindac or indomethacin has proven effective due to tumor overexpression of cyclooxygenase-2 (23). A number of small trials and case reports indicate that anti-estrogen therapy, including tamoxifen or toremifene, appears to improve or stabilize AF lesions (24). A large randomized trial is required to corroborate these reports. Systemic chemotherapy also may be used, although specific guidelines are lacking. Tyrosine kinase inhibitors or anthracyclines are popular, but the use of a variety of other agents is possible (25).

The present study reports a case with a presumptive recurrence of AF at a site distant and contralateral to the initial lesion. Local recurrence of AF is common and is usually caused by residual tumor cells following treatment failure. There have also been reports of patients with local multicentric tumors present at diagnosis. These include a patient with masses on the right thigh and buttock (26), and another with masses in the left hip and popliteal fossa (27). In these cases, microscopic contiguous invasion of the initial lesion probably led to the formation of the second focus. Even rarer are reports of distant recurrence occurring on the same side of the body. A 2002 report by Watanabe *et al* reported the case of a patient with AF of the right dorsal foot. The tumor recurred on the right knee, followed later by the right thigh and right shoulder (28). To the best of our knowledge, there has been only one published case of AF present on contralateral sides of the body. Contralateral lesions were found in multiple members of a family with FAP secondary to an inherited *APC* gene mutation. The index case presented with multifocal AF of the paraspinal muscles, which later recurred intra-abdominally. Affected relatives include a woman with recurrent AF of the right occiput and bilateral breasts, as well as a male with cutaneous AF of each arm, the right occiput and multiple paraspinal masses (29). In this previous study, the germline *APC* gene mutation predisposed the family to form multiple AF lesions. The patient described in the present study, however, had no family history of AF or FAP. It is likely that the clinically diagnosed contralateral distant recurrence was the result of the development of a second primary tumor. Contiguous spread from the initial site on the right shoulder to the left forearm five years later is improbable.

Contralateral recurrence of AF is extremely rare. However, a low index of suspicion for recurrent AF should be maintained in patients presenting with symptoms of muscle weakness, pain, paresthesia and a palpable mass.

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