Nodular fasciitis: A pseudomalignant clonal neoplasm characterized by USP gene rearrangements and spontaneous regression

Jennifer Hennebry, Douglas Mulholland, Nairi Tchrakian, Charles Martin Gillham, Peter Julian Beddy, Dearbhaile Mai O'Donnell, Máirín McMenamin

ABSTRACT

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Case Report: A 26-year-old female presented at surveillance computed tomography (CT) scan one year post-treatment for stage 1c ovarian dysgerminoma with a 4 cm axillary soft tissue mass, radiologically suspicious for metastasis with subclavian vein invasion. Histopathology of core biopsies favored NF, confirmed by detection of USP6 gene rearrangements by FISH analysis. This case describes an unusual relatively deep NF, suspicious for metastasis on CT scan with confirmed spontaneous regression over two years.

Conclusion: Nodular fasciitis should be considered in the differential diagnosis of rapidly growing enhancing soft tissue masses. Molecular cytogenetic testing of USP6 gene rearrangements allows definitive diagnosis on core biopsies in challenging cases, permitting a conservative approach and avoiding potentially radical and unnecessary surgery.

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CASE REPORT

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Keywords: Nodular fasciitis, Intravascular fasciitis, resolution, USP6, FISH

How to cite this article

Hennebry J, Mulholland D, Tchakian N, Gillham CM, Beddy PJ, O'Donnell DM, McMenamin M. Nodular fasciitis: A pseudomalignant clonal neoplasm characterized by USP gene rearrangements and spontaneous regression. Int J Case Rep Images 2017;8(1):80–85.

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Received: 14 September 2016
Accepted: 13 October 2016
Published: 01 January 2017

Article ID: Z01201701CR10752JH

doi:10.5348/ijcri-201713-CR-10752

INTRODUCTION

Nodular fasciitis (NF) is a self-limited mass-forming myofibroblastic proliferation, which typically presents with sudden appearance and rapid growth and is generally less than 3 cm in size [1, 2], first described as 'pseudosarcomatous fibromatosis' in 1955 [3]. Nodular

fasciitis usually presents between second and fourth decade of life with no gender predilection. Recurrence is rare, unless excision is subtotal in the active growing phase [2]. Spontaneous involution has been described [1, 2, 4, 5] and is probably the natural course in NF. However, the majority are excised due to clinical concern for malignancy and histological difficulty in making a definitive diagnosis on core biopsy. A minority of cases (10–15%) are associated with recent prior trauma [1].

Typical sites of presentation include the upper limb, trunk, and head and neck. Nodular fasciitis is usually subcutaneous, but can be intramuscular or fascial based, can rarely arise in an intradermal or intra-articular location and can be entirely or partly intravascular [2].

Radiologic and histologic features can be highly variable [2, 6], and in the clinical setting of a rapidly growing mass, distinction from sarcoma can be difficult. Diagnosis is usually confirmed on an excision specimen. Histologic appearances can vary depending on the area sampled and the duration/phase of the lesion. Early lesions comprise a haphazard or short fascicular arrangement of cellular spindle cell proliferations with brisk mitotic rate. Lesions can show a feathery or loose discohesive appearance mimicking granulation tissue with microcysts. Red cell extravasation and scattered lymphocytes, macrophages and osteoclast-like giant cells are often present. Older lesions are more paucicellular with hyalinized collagen, scattered apoptotic cells and macrophages and may show central cystic degeneration [2]. Immunohistochemical staining profile is not specific [7]. Smooth muscle actin is positive but this does not distinguish it from other myofibroblastic lesions such as cellular scars, fibrous histiocytomas, desmoid-type fibromatosis or desmin negative leiomyosarcomas. CD34, desmin and cytokeratin are negative. Detection of USP6 gene rearrangement by fluorescence in situ hybridization (FISH) has emerged as a very helpful tool in confirming the diagnosis of NF [5, 8, 9] and is of particular use in cases where there is limited tissue for diagnosis, or when histological, radiological, or clinical appearances are atypical.

CASE REPORT

A 25-year-old female presented with a pelvic mass, which was surgically resected and diagnosed as a stage 1c ovarian dysgerminoma. The patient received adjuvant chemotherapy and a CT scan performed six months following treatment confirmed complete radiological remission. Four months post-chemotherapy, she developed bronchiolitis obliterans/organizing pneumonia as a complication of bleomycin chemotherapy. Following oral steroid therapy for several months, symptoms and radiological changes resolved and pulmonary function tests improved. Thirteen months post-chemotherapy, a CT scan showed a soft tissue mass, measuring 4x4x3 cm, deep to the pectoralis major muscle

and abutting the chest wall without rib invasion. This was detectable on clinical examination as a sub-clavicular anterior chest wall asymmetry. Radiological impression was of confluent pathologic adenopathy with central necrosis representing metastases from the patient's prior ovarian dysgerminoma. A soft tissue sarcoma was in the differential diagnosis. Contrast enhanced MRI scan showed central necrosis or degeneration within the mass with close proximity to the right subclavian artery and vein (Figure 1) and features suspicious for subclavian vein invasion and thrombosis. PET-CT scan demonstrated intense tracer uptake within the mass with an SUV of 9.6. (Figure 2).

Ultrasound confirmed that the mass was partly intravascular. Core needle biopsy yielded a cellular spindle-cell proliferation with some short fascicles (Figure 3). Elsewhere there was a haphazard arrangement of cells with a loose discohesive feathery appearance with scattered chronic inflammatory cells (Figure 4). Cytonuclear atypia was not conspicuous and there was no necrosis. Mitoses numbered up to 3 per 10 40x fields (Figure 5).

Immunohistochemical stains showed that lesional spindle cells were positive for smooth muscle actin (SMA) (Figure 6) and negative for desmin, cytokeratin and S100. CD68 stained lesional macrophages. The MIB1 proliferative index was <10%. Histological features favored NF but sampling of a bland area of a sarcoma could not be excluded. Due to the worrying clinical presentation and the lack of definitive tissue diagnosis, an MRI scan was performed with a view to planning surgical excision. Repeat core needle biopsy again favored NF. Given the histologic appearances and the proximity to major vessels, a 'watch and wait' approach was adopted with repeat MR scans scheduled at three-monthly intervals. However, over the next three-week period, the patient developed swelling of the right arm with skin mottling, worrisome for vascular compromise. The case was referred to the London sarcoma service for advice on further management. The FISH analysis using custom-made break-apart BAC probes detected USP6 gene rearrangement, confirming the diagnosis of NF (Figure 7). The FISH was performed by Dr. Fernanda Amary's group at the Royal National Orthopedic Hospital NHS Trust. This news coincided with spontaneous improvement in clinical symptoms. In the two years following detection of the mass, it has undergone spontaneous and complete resolution on MRI and the patient remains symptom-free.

DISCUSSION

Nodular fasciitis (NF) is a self-limited myofibroblastic proliferation, which is usually subcutaneous in location and rarely presents as multiple lesions [10]. Due to its typical clinical presentation as a rapidly growing mass and its variable radiological and histological features, NF

can be misdiagnosed as a sarcoma [1, 2, 6]. In this case, a female with a history of treated ovarian dysgerminoma, a relatively deep-seated axillary NF was identified on surveillance imaging. Nodular fasciitis was in the active growing phase and showed concerning clinical and radiological features simulating metastatic tumor or sarcoma, including enhancement, central degeneration and vascular involvement.

Figure 1: Axial post-contrast T1 fat suppressed MRI, demonstrating peripheral enhancement of a centrally necrotic mass in the right axilla in proximity to subclavian vessels.

Figure 2: Axial PET-CT showing intense radio tracer uptake (SUV 9.6) within the mass.

Figure 3: Core biopsy showing cellular spindle cell proliferation with short fascicular arrangement of cells (H&E stain, x100).

Figure 4: Bland spindle cells with haphazard discohesive feathery appearance (H&E stain, x100).

Figure 5: A mitotic figure is present in the center of the image (H&E stain, x200).

Figure 6: Lesional spindle cells are positive for smooth muscle actin immunostain [Cell Marque anti actin, smooth muscle (IA4)].

Figure 7: Rearrangements of USP6 gene (splitting of red and green signal) by fluorescence in situ hybridization using custom made break-apart probes. [Positive result: $\geq 15\%$ cells harbored break-apart signal]. Image courtesy of Dr. Fernanda Amary, Histopathology Department, Royal National Orthopedic Hospital NHS Trust, UK.

The differential diagnosis of nodular fasciitis on MRI scan is broad, spanning benign and malignant lesions, including neurofibroma, extra-abdominal desmoid fibromatosis, fibrous histiocytoma, early myositis ossificans and sarcoma [6]. MRI scan imaging is helpful for defining the intrinsic signal characteristics, size and compartmental extensions of these lesions. Depending on the distribution of the myxoid or fibrous components, nodular fasciitis is usually isointense to skeletal muscle on T1 sequence and hyperintense to fat on T2 sequence. Lesions with predominantly cellular content or myxoid degeneration appear hyperintense on T2-weighted sequence and those with mostly collagenous contents appear hypointense [4, 6]. Contrast enhancement pattern is most commonly diffuse but it may also be peripheral in lesions with cystic degeneration, as in this case. Histological examination is essential for the diagnosis of NF as radiological appearances are not specific.

Nodular fasciitis is typically circumscribed, but may display an infiltrative growth pattern, especially those that are fascial based [2]. The cut surface of a macroscopic lesion varies from myxoid to fibrous, sometimes with central cystic change [1]. The lesion is typically composed of spindled fibroblast-like cells with a haphazard, ‘tissue culture’-type architecture resembling granulation tissue with cellular areas and looser areas and scattered inflammatory cells [2]. Cellular areas can show a fascicular arrangement of cells. The looser areas have a discohesive arrangement of cells with a feathery

appearance and can show microcystic change. Mitotic figures are usually readily identified, but atypical forms are not generally present. Other microscopic features of NF include extravasated red blood cells and osteoclast-like giant cells [2] but they were not seen in this case. Older lesions show more hyalinized collagen. It is easier to make a histological diagnosis on an excision specimen as the architectural pattern is evident. It can be difficult to make a definitive diagnosis on core biopsy, when limited features are available. Immunohistochemistry is not specific— smooth muscle actin and muscle-specific actin are typically positive, supporting a myofibroblastic phenotype [2, 7]. CD68 stains lesional macrophages, osteoclast-like giant cells and occasionally weakly stains the spindle cells [1].

Until recently, no specific or consistent cytogenetic abnormality was observed in NF and diagnosis was based on histological features. Furthermore, due to its rapid growth, low risk of recurrence, spontaneous resolution and the fact that it has not been associated with malignant transformation, NF has traditionally been considered reactive in nature. In 2011, Erickson-Johnson et al. reported genomic rearrangements of the USP6 locus on chromosome 17 in 92% of NF, the majority of which resulted in the formation of the fusion gene MYH9-USP6 [8] and have proposed that the identification of a recurrent somatic fusion gene event in NF is supportive of a clonal transient neoplasm. This suggestion challenges the traditional paradigm that nonrandom fusion gene formation is associated solely with sustained autonomous neoplasms. This molecular diagnostic approach is a tremendous advance in the diagnosis of NF [5, 8, 9]. Spontaneous resolution is likely by cellular apoptosis but to date the mechanism has not been elucidated.

Opinions have varied on the optimal treatment of NF. Most have advocated for simple excision [2]. Following a confirmed biopsy diagnosis, a conservative ‘watch and wait’ approach with repeat imaging and anticipated spontaneous involution is preferable particularly in surgically challenging sites [4, 5]. The FISH is cost effective, especially if challenging surgery can be avoided. The price of USP FISH can be obtained from referral centers. Current price is approximately 300 GBP.

CONCLUSION

We present an unusual nodular fasciitis (NF) in a young woman that was discovered on follow-up for previous ovarian dysgerminoma. As the NF was in the active growing phase, clinical and radiological features were suspicious for malignancy with progressive subclavian vein involvement and compromise. The suspected histopathological diagnosis of NF was confirmed by detection of USP6 gene rearrangements and permitted a conservative approach, sparing this patient unnecessary surgery and potential morbidity. There was spontaneous resolution over two years, confirmed radiologically.

Acknowledgements

We gratefully acknowledge the assistance of Dr. Fernanda Amary and colleagues at the Histopathology Department, Royal National Orthopedic Hospital NHS Trust for performing USP FISH analysis and also acknowledge the assistance of the London Sarcoma Service for their clinical advice.

Author Contributions

Jennifer Hennebry – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Final approval of version to be published

Douglas Mulholland – Acquisition of data, interpretation of data, Drafting the article, Final approval of version to be published

Nairi Tchakian – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Charles Martin Gillham – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of version to be published

Peter Julian Beddy – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of version to be published

Dearbhaile Mai O'Donnell – Substantial contribution to conception and design, acquisition of data, Revising it critically for important intellectual content, Final approval of version to be published

Máirín Eibhlín McMenamin – Substantial contribution to conception and design, acquisition of data, Revising it critically for important intellectual content, Final approval of version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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