

## Presentations of Clinical, Ultrasonographic and Pathological Features of Nodular Fasciitis from an Established Cytogenetic Viewpoint: Review of the Case Series

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### Abstract

Even though nodular fasciitis (NF) is benign and self-limited, the clinical, ultrasonographic and pathological presentations have been described as mimicking sarcoma. We have reported that proliferative findings on both US and histology may be caused by the cytogenetic nature of NF. When the lesion showed the proliferative findings of the margin on both US and pathology, accompanied with clinical rapid growth and self-limited course, NF should be strongly suggested as one of the skin tumors as previously described. NF has been cytogenetically considered as a novel model of transient neoplasia induced by *MYH9-USP6* gene fusion. It has been suggested that strong overexpression of *USP6* under *MYH9* promoter appears to drive tumorigenesis. A clear association between NF and a recurrent genetic abnormality had been established in fluorescence in-situ hybridization (FISH) analysis.

In this article, we reviewed the clinical, ultrasonographic and pathological features of NF in the case series from an established cytogenetic viewpoint. Our study indicated that proliferative findings of the margin on US and pathology may be caused by the driving force of *USP6* transcriptional upregulation behind the high proliferative activity and growth of NF. All nodules clinically represented rapid growing, self-limited and/or regress course, suggesting the high proliferative growth and involutinal nature of NF.

We emphasize that the presentations of clinical, ultrasonographic and pathological features of NF are contributed to the cytogenetic nature, having the high proliferative growth and involutinal nature.

**Keywords:** Nodular fasciitis; *USP6*-induced neoplasia; High-resolution ultrasound; Proliferative growth; Involutinal nature

### Introduction

NF is a benign soft tissue tumor of fibroblastic/myofibroblastic differentiation that was first described in 1955 by Konwaler, et al. [1] and Goodlad JR, et al. [2] documented the first case of dermal nodular fasciitis (NF) in 1990. Ordinary NF and intradermal NF show a peculiar clinical behavior characterized by rapid, self-limited growth and spontaneous regression after a few weeks. The aggressive clinical presentation of NF will usually prompt a biopsy for definitive diagnosis [3]. Due to the histopathology with its high cellularity and high mitotic activity, NF can be misdiagnosed as a malignant soft tissue tumor, especially fibrosarcoma or low-grade myxofibrosarcoma, often leading to unnecessarily aggressive therapy [4].

To study the characteristic ultrasonographic features of NF will help to establish preoperative diagnostic criteria and to avoid unnecessary operation. On gray-scale US, a few reports [3] have described the lesion as irregular or lobulated margin and hypoechogenicity. There are also some reports [3,5-8] concerning the imaging features on color Doppler US. The high-resolution ultrasonography (US) is a valuable tool that the discrepancies of imaging feature between intradermal and subcutaneous cases [9]. We have recently reported characteristic power Doppler sonographic imaging of NF from a dermatological perspective [10]. Erickson-Johnson, et al. [11] first have reported that NF is as a

novel model of transient neoplasia induced by *MYH-USP6* gene fusion. It has been described that a strong overexpression of *USP6* under *MYH9* promoter appears to drive tumorigenesis [12]. A clear relation between NF and a recurrent genetic abnormality has been established in FISH analysis [11-16]. We think that proliferative findings on both US and histology may be caused by the cytogenetic nature of NF as previously reported [10]. In this article, we review the case series of NF and emphasize the presentations of clinical, ultrasonographic and pathological characteristics from an established cytogenetic perspective.

### Results

Summary of the pathologically confirmed case series of NF were shown (Table 1). The case series included 1 male patient and 3 female patients (mean age, 36.5 years; range, 21-47 years). Three of the 4 patients presented to their physicians with a history of an enlarging palpable mass. They noted pain at the site of the mass. One patient noted pain in the thigh and she incidentally found mass (case 2) [6]. The size of the incision-biopsied NF was found to greatly diminish to a mere shadow and no longer recognizable mass by follow-up US examination as previously described (case 2) [6]. The mean time to presentation of the 3 patients was 1 month. None of the patients reported a history of trauma. One lesion was located in the upper arm (case 1) [10]. 1 was located in the thigh (case 2) [6], and 1 was located in the forearm (case 3) [7] and 1 was located in the dorsum of the foot (case 4). One lesion was located in the subcutaneous tissues (case 1); 1

was located in the subcutaneous adjacent of the fascia (case 2); 1 was located in the primarily in the dermis (case 3) and 1 was located in the upper portion of the subcutaneous (case 4).

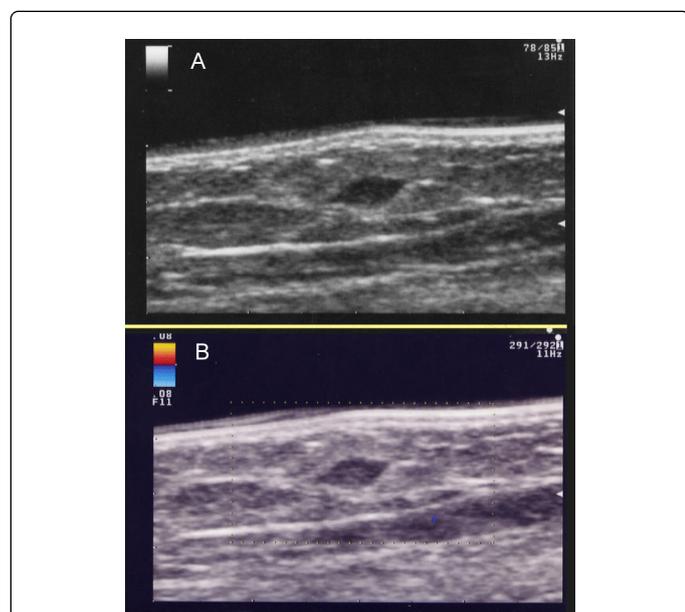
Clinical features				Ultrasonographic features			Immunohistochemical features			
Case	Age	Sex	Location	Size	Shape	Margin	SMA	Vimentin	Desmin	S-100 protein
1	21	F	Upper arm	7.8 mm	Oval	Irregular and lobular	+	ND	-	ND
2	41	F	Thigh	17 mm	Oval	Irregular and lobular	-	+	ND	-
3	37	M	Forearm	8.0 mm	Oval	Irregular and lobular	ND	ND	ND	ND
4	47	F	Dorsum of the foot	8.5 mm	Oval	Lobular	+	ND	-	ND

ND: Not determined

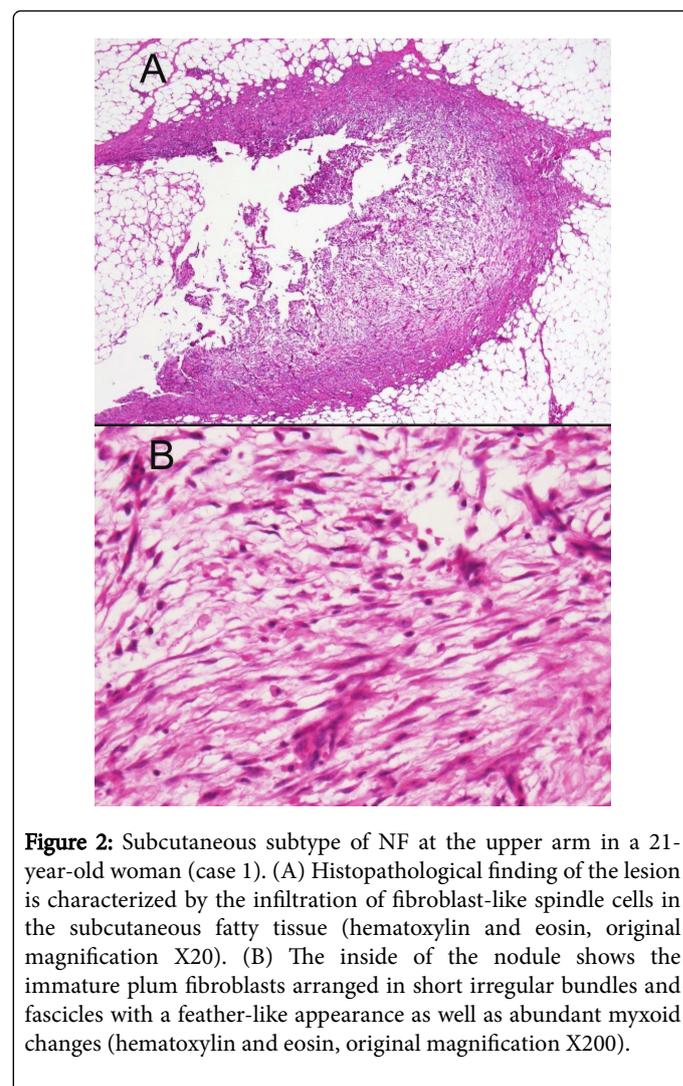
**Table 1:** Summary of the pathologically confirmed cases of NF.

On gray-scale US, all nodules were oval shape with irregular and/or lobular margin (Figure 1 A), averaging 10.3 mm (range, 7.8-17 mm). Two nodules were hypoechoic pattern and one was hyperechoic containing an irregular hypoechoic area in its center and one was hypoechoic pattern with hyperechoic streaks. A heterogeneous echotexture was observed in two cases and homogeneous echotexture in two cases. All cases did not represent posterior echo enhancement and one case represented the compressed fascia. Two cases showed clear blood flow within the nodule and two cases no substantial blood flow on color Doppler US (Figure 1B).

Proliferations of fibroblast-like spindle cells without obvious mitotic changes were seen in all cases (Figure 2B). All lesions showed myxoid change, collagen proliferations (Figure 3A). Capillary dilatations were seen in all lesions (Figure 3B).

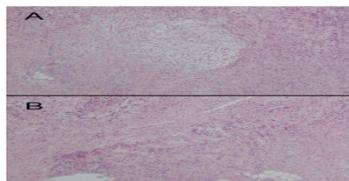


**Figure 1:** Subcutaneous subtype of NF at the upper arm in a 21-year-old woman (case 1). Sonography shows a subcutaneous hypoechoic lesion located in the upper arm. The shape of nodule is oval with irregular and lobular margin. (B) No substantial blood flow signals within the nodule on color Doppler sonography are observed.



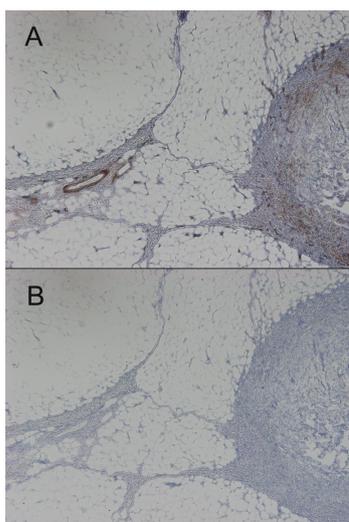
**Figure 2:** Subcutaneous subtype of NF at the upper arm in a 21-year-old woman (case 1). (A) Histopathological finding of the lesion is characterized by the infiltration of fibroblast-like spindle cells in the subcutaneous fatty tissue (hematoxylin and eosin, original magnification X20). (B) The inside of the nodule shows the immature plum fibroblasts arranged in short irregular bundles and fascicles with a feather-like appearance as well as abundant myxoid changes (hematoxylin and eosin, original magnification X200).

Pathologically, three nodules showed poorly defined margin (Figure 2A) and one represented relatively poorly defined margin.



**Figure 3:** Intradermal subtype of NF at the forearm in a 37-year-old man (case 3). (A) The pathologic examination showed spindle-shaped cells resembling fibroblasts and inflammatory cells primarily in the dermis. The inside of the nodule showed the deposition of the mucin in the stroma (hematoxylin and eosin, original magnification X100). (B) The dilatation of blood vessels filled with erythrocytes was observed (hematoxylin and eosin, original magnification X100).

The immunohistochemical staining profile showed smooth muscle actin (SMA) in two cases (Figure 4A) and did not stain for  $\alpha$ -SMA in one case. Lesion did not stain for desmin in two cases (Figure 4B). Case 2 showed positivity for vimentin and negative profile for S-100 protein as previously described [6].



**Figure 4:** Subcutaneous subtype of NF at the upper arm in a 21-year-old woman (case 1). (A) Immunohistochemical finding shows that lesion is positive for smooth muscle actin: original magnification X 100. (B) The lesion is negative for desmin: original magnification X100.

## Discussion

NF presents most typically in the upper extremities, the trunk, and the head and neck. It usually presents between the ages of 20 and 40 years, often with tenderness. Lesions can be found subcutaneous, fascial, intramuscular, and rarely intradermal type. Even though NF is benign and self-limited, the clinical, ultrasonographic and pathological presentations have been described as mimicking sarcoma. To study the characteristic ultrasonographic features of NF will help to establish preoperative diagnostic criteria and to avoid unnecessary operation.

The usefulness of high-resolution US has technically also enabled the discrepancies of imaging features between intradermal and subcutaneous NF [9,10]. Meanwhile, NF shows a peculiar clinical behavior characterized by rapid growing, self-limited, spontaneous regression after a few weeks; this peculiar clinical presentation has come to cytogenetic attention. Erickson-Johnson, et al. [10] first has reported that NF is as a novel model of transient neoplasia induced by *MYH9-USP6* gene fusion. A clear association between NF and a recurrent genetic abnormality has been established in FISH analysis [11-16]. Clinical presentation showed a few weeks history of a rapid growing mass, self-limited and/or tended to regress with pain in all cases. The size of the incision-biopsied NF (case 2) was found to greatly diminish to a mere shadow and no longer recognizable mass by follow-up US examination as previously described [6]. We will highlight that these features reflect high proliferative activity and growth and involution nature of NF.

On gray-scale US, there are a few reports [3] that the lesions were described as oval or lobulated and hypoechoic or mixed echogenicity with irregular or lobular margin. There are also a few reports [3,5-8] concerning the imaging features on color Doppler US. We have recently reported characteristic power Doppler sonographic imaging of NF from a dermatological perspective [10]. Present study indicated that all nodules showed irregular or lobular margin. No significant different findings between the intradermal and subcutaneous types on gray-scale US were detected. When the US and pathological findings in all cases were compared, irregular or lobular margin on US seemed to reflect histological proliferation of collagen and spindle-shaped fibroblasts. Mehregan [17] has reported that NF is usually composed of a central solid mass with many irregular projections extending outward into the surrounding fat tissue thus resembling a highly invasive growth. These histopathological findings were seen in most of all cases. We suggest that these aspects reflect high proliferative activity and growth of NF as previously described [10]. In this article, we will emphasize that proliferative findings of the margin on US and pathology are caused by the driving force of *USP6* transcriptional upregulation behind the high proliferative activity and growth of NF.

Histologically, accurate diagnosis, particularly on small biopsies, remains a challenge, as the morphology can be varied and immunophenotype is essentially nonspecific. Lesions that were considered to be definite diagnosis of NF typically featured uniform spindled cells arranged in irregularly intersecting short fascicles, and occasional storiform patterns. The cells contained plump, spindled to stellate nuclei with fine to open chromatin and small nucleoli, accompanied by lightly basophilic cytoplasm with ill-defined cytoplasmic borders. The background stroma ranged from myxoid to collagenous. The characteristic tissue culture-like, feathery myxoid appearance was present at least focally [13]. As NF closely mimics sarcoma, it is significant that NF differentiate from sarcoma. As sarcoma is composed of spindle cells which are believed to be of myofibroblastic/fibroblastic origin, these tumors have a diffuse inflammatory infiltrate and a variable myxoid stroma without tissue culture growth pattern seen in NF [12].

Immunohistochemically, it has been reported that NF is negative for several markers such as desmin, keratin, or S-100 protein in contrast to sarcoma [18,19]. NF spindle cells contain vimentin, muscle-specific actin and smooth muscle-specific actin [19]. On the basis of the stain profile, three cases were immunohistochemically consistent with as a NF.

A clear association between NF and a recurrent genetic abnormality had been established in FISH analysis [11-16]. Genomic rearrangements of the *USP6* locus were found in 92% of NF. Rapid amplification of 5'-cDNA ends identified *MYH9* as the translocation partner. RT-PCR and direct sequencing revealed the fusion of the *MYH9* promoter region to the entire coding region of *USP6* [11]. The *MYH9-USP6* fusion was demonstrated in 12 of 16 (75%) [11]. *USP6* belongs to a large subfamily of de-ubiquitinating enzymes that act in diverse cellular processes such as intracellular trafficking protein turnover, inflammatory signaling and cell transformation. *USP6* was first identified as a possible oncogene located on chromosome 17p13 when it exhibited transforming properties upon overexpression in NIH-3T3 cell [20,21]. *USP6* oncogenes was also detected in aneurysmal bone cyst (ABC) [20,21]. It has been reported that ABC and NF have overlapping histological features and these histological manifestations may have a common pathogenic denominator mediated by *USP6* transcriptional upregulation [11]. Ye Y, et al. reported that *USP6*-induced expression of matrix metalloproteases through activation of NF- $\kappa$ B, a transcription factor with a key role in inflammation and proliferation in ABC [22]. Oliveira AM et al. suggested that ABC and NF reside in the same biologic spectrum of what they define as *USP6*-induced tumors [23]. It has been reported that the genomic rearrangements of the *USP6* locus were located in 92% of NF [11] and in 74% of NF [16]. It has been also reported that in the morphologically definitive cases of NF, FISH analysis for *USP6* had a sensitivity of 86% and specificity of 100% for a diagnosis of NF and the positive predictive value was 100%, and the negative predictive value 90% [13]. Erber R, et al. also reported that the sensitivity and specificity of *USP6* FISH for NF was 74.4% and 100%, respectively [14]. These studies indicate a clear relation between NF and recurrent genetic abnormality in FISH analysis.

*MYH9* is located on chromosome 22q12.3-q13 and is a member of the non-muscle myosin classfamily [11]. It has been described that *MYH9* is the most frequent fusion partner [11,16]. Less frequent gene partners include *RRBP1*, *CALU*, *CTNBN1*, *MIR22HG*, *SPARC*, *THBS2*, and *COL6A2* [15]. Their study detected the neoplastic nature of NF, defined additional pathogenic fusion partners and added to the growing body of literature on *USP6*-associated neoplasia [15].

In cutaneous NF, Kumar, et al. [12] reported *USP6* rearrangement by FISH; in two of three cases, the characteristic *MYH9-USP6* fusion was shown by RT-PCR. They concluded that the presence of the *USP6* rearrangement and *MYH9-USP6* fusion in cutaneous NF cases mirrors what has been reported in more typical subcutaneous presentation of NF. On the basis of these studies [11-16], the similar cytogenetic nature has been demonstrated both in subcutaneous NF and intradermal type.

Erickson-Johnson, et al. [11] suggested that *USP6* transcriptional upregulation may be the driving force behind the high proliferative activity and growth of NF. They also noted that the consistent involutonal nature of the lesion indicates that additional genetical or stromal factors are required for maintaining its long-term survival and viability. Previous report indicated that irregular or lobular margin on US and poorly defined margin on histology is contributed to the cytogenetic nature of NF [10]. This article strongly suggests that proliferative findings the margin of the nodule on US and pathological features are caused by the driving force of *USP6* transcriptional upregulation behind the high proliferative activity and growth of NF from an established cytogenetic nature. All nodules clinically represented rapid growing, self-limited and/or regress, suggesting high

proliferative activity and growth and involutonal nature of NF. When the lesion showed the proliferative findings of the margin on both US and pathology, accompanied with clinically rapid growth, self-limited and/or regress course, NF could be strongly suggested.

## Conclusion

We emphasize that clinical, ultrasonographic and pathological features of NF are contributed to the cytogenetic nature of the high proliferative growth and involutonal nature.

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