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Review Article

Intradermal Nodular Fasciitis: A Review of the Current Genetic Analysis

Kazumi Fujioka*

Department of Radiology, Nihon University School of Medicine, 30-1 Ohyaguchi-kamimachi, Itabashi-ku, Tokyo 173-8610, Japan

ABSTRACT

Erickson-Johnson et al. suggested that *USP6* transcriptional upregulation may be the driving force behind the high proliferative activity and growth and the consistent involution nature of Nodular Fasciitis (NF). The author previously reported the case series of NF and strongly suggested that proliferative findings of the margin of the nodule on US and pathological features are caused by the driving force of *USP6* transcriptional upregulation from an established cytogenetic nature. Recently molecular analysis of *USP6* gene rearrangements has been detected in the most of NF cases, while *MYH9* gene has been identified as the most common *USP6* partner. It is suggested that the identification of *USP6* fusion partners for NF may contribute to understand the biological effect. As intradermal NF is a rare lesion, few cases with molecular genetics have been shown until now. This review outlines the current knowledge and trends of the rare intradermal nodular fasciitis focusing on the genetic analysis. The result showed *USP6* rearrangement in all cases and two cases of *MYH9*, one case of *EIF5A*, and one case of *TPM4* as a fusion partner with *USP6* have been exhibited. The detection of *USP6* gene rearrangement using FISH may be the very useful and important genetic analysis for accurate diagnosis in even intradermal NF. Further study is needed to verify the pathogenesis and biological effect of fusion partner for this entity.

Keywords: Intradermal nodular fasciitis; *USP6*-associated neoplasia; *USP6* rearrangement; *MYH9* gene; Genetic analysis

INTRODUCTION

Erickson-Johnson et al. suggested that *USP6* transcriptional upregulation may be the driving force behind the high proliferative activity and growth and the consistent involutional nature of Nodular Fasciitis (NF) [1]. When the lesion showed the proliferative findings of the margin on both US and pathology, accompanied by clinically rapid growth, self-limited and/or regress course, NF could be strongly suggested as previously described [2]. Recently genetic analysis of *USP6* gene rearrangements have been detected in the most of NF cases. Though several fusion partners for ordinary NF have been identified, the most of NF cases commonly showed a *MYH9-USP6* gene fusion [3]. Because intradermal NF is a rare lesion, there are few reports of this entity with molecular analyses until now. In this review, the author outlined the current knowledge of the rare intradermal nodular fasciitis focusing on the recent molecular genetics.

Nodular fasciitis as *USP6*-related neoplasia through multiple pathways

Nodular fasciitis is a benign soft tissue tumor of fibroblastic/myofibroblastic differentiation that was first described in 1955 by Konwaler et al. and the first case of rare intradermal nodular fasciitis has been documented in 1990 [4,5]. The author previously has reported an ordinary type of NF and a rare intradermal NF [6,7]. Though this entity has rarely occurred, intradermal nodular fasciitis as a rare lesion analyzed in a series of 24 cases, seven cases of cutaneous NF with molecular analysis, and a few reports including dermatologic field have been studied [8-13]. Regarding clinical manifestations, NF presents most typically in the upper extremities, the trunk, and the head and neck between the ages of 20 and 40 years, often accompanying with tenderness. The subcutaneous, fascial, intramuscular, and

Correspondence to: Kazumi Fujioka, Department of Radiology, Nihon University School of Medicine, 30-1 Ohyaguchi-kamimachi, Itabashi-ku, Tokyo 173-8610, Japan, E-mail: spbk2xq9@ninus.ocn.ne.jp

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rarely intradermal type have been reported with a peculiar clinical manifestation characterized by rapid, self-limited growth and spontaneous regression after a few weeks. With regards to pathological appearances, NF is typically characterized by uniform spindled cells arranged in irregularity intersecting short fascicles, and occasional storiform patterns. The cells contained plump, spindled to stellate nuclei with fine to open chromatin and small nucleoli accompanied with the background stroma ranged from myxoid to collagenous. It is well known that the characteristic tissue culture-like, feathery myxoid appearance is observed at least focally [14]. Immunohistochemical findings show that spindle cells in NF contain Muscle-Specific Actin (SMA), vimentin, and smooth muscle-specific actin [15], while NF is negative for several markers such as desmin, keratin, or S-100 protein in contrast with sarcoma [16]. Due to the aggressive clinical manifestation, malignant ultrasonograpic features, and its high cellularity and high mitotic activity in histopathology, NF can be misdiagnosed as a malignant soft tissue tumor such as fibrosarcoma and low-grade myxo-fibrosarcoma, often leading to unnecessary aggressive treatment [17].

LITERATURE REVIEW

USP6 fusion partners in nodular fasciitis

A clear association between NF and a recurrent genetic abnormality has been established by using FISH analysis [1,14,18,19]. *USP6* oncogenes was also detected in Aneurysmal Bone Cyst (ABC), suggesting that these histological manifestations in ABC and NF may have a common pathogenic denominator mediated by *USP6* transcription upregulation [1]. Shin et al. reported that FISH analysis for USP6 had a sensitivity of 86% and specificity of 100% for a diagnosis of NF [14], whereas another study reported that the sensitivity and specificity of *USP6* in FISH for NF was 74.4% and 100%, respectively [18]. These studies indicate a clear relationship between NF and a recurrent genetic abnormalities in FISH analysis. Previous study described that the level of *USP6* was associated with the cellularity and age of NF [20]. The author previously described a review of the literature on NF as *USP6*-associated neoplasia through multiple pathways [21]. In addition to the presentations of clinical, ulrtrasonographic, and pathological appearances of NF, the evaluation of percentage of *USP6* break-apart FISH signals reflecting lifetime and mitotic counts in NF may be a potential procedure for accurate diagnosis in particularly young NF (preoperative duration <1 month) [2,21]. Wang et al. described that *MYH9-USP6* gene fusion has been observed in most of NF cases [22]. Molecular analysis of *USP6* gene rearrangements has been detected in the most of NF cases, while *MYH9* gene has been identified as the most common *USP6* partner. Furthermore, the detection of the *USP6* gene rearrangement has also been recognized as a diagnostic procedure in cases with morphological uncertainty [3].

The detection of other fusion partners with *USP6* includes *TPM4*, *EIF5A*, *PPP6R3*, *CTNNB*, *SPARC*, *THBS2*, *COL6A2*, *TNC*, *SEC31A*, *COL1A1*, *COL1A2*, *COL3A1*, *CALU*, *NACA*, *SLFN11*, *LDHA*, *SERP1NH1*, *PDLIM7*, *MYL12A*, *PAFAH1B1* and *MIR22HG* as previously reported [3,23,24]. The recent study provided the new and rare fusion patterns with *USP6* in NF including one novel *KIF1A* and five rare types (*TMP4*, *SPARC*, *EIF5A*, *MIR22HG*, *COL1A2*) of fusion partners with *USP6*. A novel partner, *KIF1A* gene which is a member of 1A kinesin family has been identified in patient with superficial lesion of the arm [3].

Five rare partners including *TMP4*, *SPARC*, *EIF5A*, *MIR22HG*, and *COL1A2* of fusion partners with *USP6* have been reported [3]. *TPM4* gene which is an actin binding protein has been previously reported in a patient with cheek lesion and has been recently demonstrated in a patient with deep tibial lesion [3,13]. *MIR22HG* which is a gene connected closely to miRNA class has been previously reported in a patient with subscapular lesion and has been also identified in a man patient with superficial lesion of corner of the mouth [3,19]. *SPARC* gene that encodes cysteine-rich acidic matrix-associated protein has been shown in a patient with a mass of tendons and is recently demonstrated in a female patient with superficial lesion of temporal area [3,19]. *COL1A2* gene which encoded one chain of collagen type 1 has been reported in a patient with cervical lesion and is recently shown in a female patient with superficial lesion of the arm [3,22]. *EIF5A* gene that encodes transcription initiation factor 5A-1 involved in maintenance. In addition to the previous dermatologic report, the recent study described that *EIF5A* is identified in a female patient with subcutaneous region of forearm [3,11]. Regarding NF with malignant behavior, *PPP6R3-USP6* gene fusion has been shown in two cases of NF accompanied with malignant manifestation [25,26]. Guo et al. reported a case of NF with traditional histologic findings accompanying with multiple recurrences and metastatic manifestation showing the novel *PPP6R3-USP6* gene fusion by molecular analysis [25]. Recently, the detection of several fusion partners with *USP6* in NF has been popular, suggesting that the identification of *USP6* fusion partner of NF may contribute to understand the biological effects leading to accurate diagnosis and the prevention for the unnecessary aggressive therapy [3].

Intradermal nodular fasciitis as a rare lesion

Kumar et al. reported *USP6* rearrangement in all cases by FISH; in two of three cases, the characteristic *MYH9-USP6* fusion was shown by RT-PCR suggesting that the presence of the *USP6* rearrangement and *MYH9-USP6* gene fusion in cutaneous NF cases mirrors what has been reported in typical subcutaneous NF [9]. This review outlined the rare intradermal NF including clinical and pathologic presentations and molecular genetics (Tables 1 and 2). Pathological features revealed the involvement of the dermis location in all eleven cases (Table 1).

Table 1: Intradermal nodular fasciitis (clinical and pathologic manifestations).

Study	Case	Age/Sex	Location	Pathology
Kumar et al. [9]	1	15/m	Brow	Dermis and superficial subcutis
	2	34/m	Chin	Dermis and superficial subcutis
	3	19/m	Back	Dermis and superficial subcutis
	4	60/m	Back	Dermis and superficial subcutis
	5	46/m	Palm	Dermis and superficial subcutis
	6	34/w	Nasolabial fold	Dermis and superficial subcutis
	7	65/m	Tragus	Dermis and cartilage involvement
Maloney et al. [10]		39/f	Glabella	Dermis and subcutis
Lenz et al. [11]		41/f	Forearm	Predominantly dermal location
Sennett et al. [12]		9/f	Chin	Deep dermis and subcutis
Rodriguez et al. [13]		34/m	Cheek	Deep dermis and subcutis

Intradermal NF may tend to occur in the region with thin subcutaneous fat layer such as face, head, and neck as previously described [27]. Seven of eleven cases were shown in the face and head regions including brow, chin, nasolabial fold, tragus, glabella, and cheek suggesting the tendency of the occurrence of intradermal NF in the location of the thin subcutaneous fat layer (Table 1). Ten cases including dermatologic and pediatric cases revealed the *USP6* rearrangement by FISH (Table 2). Lenz et al. reported a novel *EIF5A-USP6* gene fusion of NF associated with predominantly dermal location and epidermal ulceration [11]. *USP6 gene rearrangement by FISH was shown and a novel EIF5A-USP6* gene fusion was identified using the Archer fusionPlex Sarcoma kit suggesting that the detection of *USP6* gene rearrangement is extremely useful molecular analysis for diagnosis of NF [11]. Recent study provided the cutaneous NF in the cheek region with rare *TPM4-USP6* gene fusion by using a comprehensive sarcoma fusion panel analysis [13]. The detection of *USP6* rearrangement was shown in all eleven cases and two cases of *MYH9*, one case of *EIF5A*, and one case of *TPM4* as a fusion partner with *USP6* were identified (Table 2).

Table 2: Intradermal nodular fasciitis (molecular analysis).

Study	Case	Age/sex	FISH	RT-PCR	*USP6* fusion partner
Kumar et al. [9]	1	15/m	*USP6* rearrangement	NA	NA
	2	34/m	*USP6* rearrangement	NA	NA
	3	19/m	*USP6* rearrangement	NA	NA
	4	60/m	*USP6* rearrangement	NA	NA
	5	46/m	*USP6* rearrangement	Positive	*MYH9*
	6	34/f	*USP6* rearrangement	Positive	*MYH9*
	7	65/m	*USP6* rearrangement	Negative	NA

Maloney et al. [10]	39/f	*USP6* rearrangement	NA	NA
Lenz et al. [11]	41/f	*USP6* rearrangement	Negative	*EIF5A*
Sennett et al. [12]	9/f	*USP6* rearrangement	NA	NA
Podriguez et al. [13]	34/m	NA	Positive	*TPM4*

Note: NA-Not Applicable; ND-Not Done.

Based on the evidence, the author will suggest that the identification of *USP6* gene rearrangement using FISH is very useful and important tool of accurate diagnosis for even rare intradermal NF with the reduced risk of misdiagnosis such as sarcoma and overtreatment. Though several fusion partners have been identified for typical NF, it is well known that most of NF cases commonly exhibits a *MYH9-USP6* gene fusion. While, as intradermal NF is a rare lesion, therefore few cases with genetic analyses have been investigated until now. The differential diagnosis of intradermal nodular fasciitis includes malignant cutaneous entities such as low-grade fibromyxoid sarcoma and low-grade myofibroblastic sarcoma [9]. Previous report suggested that the detection of *MYH9-USP6* rearrangement by FISH may assist the differential diagnosis of cutaneous spindle cell tumors [9]. Further investigation is significant to elucidate the pathogenesis and biological effect of fusion partner for intradermal NF.

DISCUSSION

In this article, the author described a review of the literature on the rare intradermal NF including clinical and pathologic manifestations and molecular genetics (Tables 1 and 2). Seven of eleven cases were shown in the face and head region suggesting the tendency of the development of this entity in the location of the thin subcutaneous fat layer (Table 1). It is well known that *USP6* gene rearrangement by FISH is a very useful procedure for the accurate diagnosis of typical NF [3]. As several fusion partners for ordinary NF have been identified, the most of NF cases commonly showed a *MYH9-USP6* gene fusion. The recent study investigated the new and rare fusion partners with *USP6* in NF including one novel *KIF1A* and five rare types (*TMP4, SPARC, EIF5A, MIR22HG, COL1A2*) of fusion partners with *USP6* [3]. It is suggested that the identification of *USP6* fusion partners for NF may contribute to understand the biological effect [3]. While few cases with molecular analyses have been shown until now, because intradermal NF is a rare lesion [27]. The result showed *USP6* rearrangement in all cases and two cases of *MYH9*, one case of *EIF5A*, and one case of *TPM4* as a fusion partner with *USP6* have been exhibited (Table 2). Based on the evidence, the author will suggest that the detection of *USP6* gene rearrangement using FISH may be the very useful and significant molecular genetics for accurate diagnosis in even intradermal NF to avoid the misdiagnosis such as fibrosarcoma and low-grade myxofibrosarcoma and unnecessary aggressive therapy. Further investigation is significant to elucidate the pathogenesis of development and biological effect of fusion partner for rare intradermal NF.

CONCLUSION

The result provided that intradermal nodular fasciitis tended to occur in the face and head regions of the thin subcutaneous fat layer. The detection of *USP6* gene rearrangement using FISH may be the very useful and important molecular findings for even intradermal nodular fasciitis. lt has been suggested that the identification of *USP6* fusion partners for ordinary NF may contribute to understand the biological effect. *MYH9*, EIF5A, and *TPM4* genes as a fusion partner with *USP6* gene have been identified in rare intradermal nodular fasciitis. Further study is needed to verify the pathogenesis and biobgical spectrum of fusion partner for even this entity.

CONFLICT OF INTEREST

Author declares that there are no conflicts of interest.

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