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Journal of Cancer Research and Cellular Therapeutics
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Review Article

Nodular fasciitis: USP6-associated neoplasia through multiple pathways

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Received Date: October 09, 2021; **Accepted Date:** October 25, 2021; **Published Date:** October 29, 2021

Citation: Kazumi Fujioka. (2021). Nodular fasciitis: USP6-associated neoplasia through multiple pathways. *J Cancer Research and Cellular Therapeutics*. 5(5); Doi: 10.31579/2640-1053/100

Abstract

Even though nodular fasciitis (NF) is benign and self-limited nature, the presentations of clinical, ultrasonographic, and pathological features have been described as mimicking sarcoma. Erickson-Johnson et al. suggested that ubiquitin-specific protease 6 (USP6) transcriptional upregulation may be the driving force behind the high proliferative activity and growth of NF. When the lesion showed the proliferative findings of the margin on both ultrasonography (US) and pathology, accompanied by clinically rapid growth, self-limited and/or regress course, NF could be strongly suggested as previously described. In this article, the author reviews the current knowledge of NF as USP6-associated neoplasia and also describes the therapeutic strategy in NF. 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. It is putative that the inhibition of USP6-related genes might be the potential therapeutic strategies for the extremely rare malignant nodular fasciitis.

Keywords: nodular fasciitis; self-limited nature; USP6-associated neoplasia; high-resolution ultrasonography; USP6- related genes

Introduction

Erickson-Johnson et al. [1] suggested that USP6 transcriptional upregulation may be the driving force behind the high proliferative activity and growth and the consistent involutional nature of 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 behind the high proliferative activity and growth of NF from an established cytogenetic nature. In this article, the current knowledge of NF as USP6-related neoplasia will be reviewed. The author also describes the therapeutic strategy in USP6-associated neoplasia such as aneurysmal bone cyst (ABC) and NF.

Transient neoplastic nature in nodular fasciitis

NF is a benign soft tissue tumor of fibroblastic/myofibroblastic differentiation that was first described in 1955 by Konwaler et al. [2]. While, Goodlad et al. [3] documented the first case of dermal nodular fasciitis (DNF) in 1990. The author previously has reported a common subcutaneous NF [4] and a rare intradermal type [5]. Though this entity of the intradermal type have very rarely occurred, De Feraudy et al. [6] have studied intradermal nodular fasciitis as a rare lesion analyzed in a series of 24 cases, and recently the lesion involved both the dermis and subcutis as a superficial nodular fasciitis [7] and a dermally located lesion [8] have been reported in the dermatologic field. 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 [4]. The subcutaneous, fascial, intramuscular, and rarely intradermal type have been found [5]. NF shows a peculiar clinical behavior characterized by rapid, self-limited growth and spontaneous regression after a few weeks. Pathologically, NF typically featured 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. The background stroma ranged from myxoid to collagenous [4]. The characteristic tissue culture-like, feathery myxoid appearance was present at least focally [9]. Immunohistochemically, spindle cells in NF contain vimentin, muscle-specific action, and smooth muscle-specific actin [10], whereas it is known that NF is negative for several markers such as desmin, keratin, or S-100 protein in contrast to sarcoma [11]. Due to the aggressive clinical presentation, malignant ultrasonograpic appearances, and the histopathology with its high cellularity and high mitotic activity, NF can be misdiagnosed as a malignant soft tissue tumor, often leading to

unnecessarily aggressive therapy [12].

High-resolution ultrasonography appearances in nodular fasciitis

Recently, dermatologic ultrasound imaging has been growing because of the development of high-resolution multifrequency transducers and multichannel color Doppler machines [13]. In dermatology, a 15 MHz is the minimum frequency recommended for performing dermatologic examination by the international working group or DERMUS (Dermatologic Ultrasound) [13, 14]. The author has reported a subcutaneous NF representing compressed fascia using both high-resolution ultrasonography (US) and magnetic resonance imaging (MRI) appearances [4] and a rare case of intradermal type showing the primarily in the dermis accompanied by the dilatation and proliferation of the vessels using high-resolution color Doppler ultrasound [5], it is known that high- resolution US can clearly represent the location of the dermis and subcutaneous, association of the fascia, and the presence of dilation and proliferation of the vessels. The author usually performs US studies for dermatologic fields with a high-resolution, broad-band (5MHz-18MHz) linear transducer and described several studies [4, 5, 15-29].

Presentations of clinical, ultrasonographic, and pathological features of nodular fasciitis from an established cytogenetic viewpoint

Even though NF is benign and self-limited, the clinical, ultrasonographic and pathological presentations have been described as mimicking sarcoma. Erickson-Johnson et al. [1] suggested that USP6 transcriptional upregulation may be the driving force behind the high proliferative activity and growth of NF. The author previously reported that irregular or lobular margin on US and poorly defined margin on histology is attributed to the cytogenetic nature of NF [15]. Furthermore, the research results strongly suggested 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 [17]. 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 as previously described [17].

Fusion patterns of USP6 in nodular fasciitis

A clear relationship between NF and a recurrent genetic abnormality had been established in FISH analysis [1, 9, 30-33]. Genomic rearrangements of the USP6 locus were found in 92% of NF. Rapid amplification of 5'-cDNA ends identified MYH9 as the transcription partner. The fusion of the MYH9 promoter region to the entire coding region of USP6 was shown using RT-PCR and direct sequencing [1]. The result indicated that the MYH9-USP6 fusion was demonstrated in 12 of 16 (75%) [1]. USP6 oncogenes was also detected in aneurysmal bone cyst (ABC) [34, 35], suggesting that these histological manifestations in ABC and NF may have a common pathogenic denominator mediated by USP6 transcription upregulation [1]. Regarding ABC, Ye et al. reported the USP6-induced expression of matrix metalloproteases through activation of NF-κB, a transcription factor with a key role in inflammation and proliferation [36]. Oliveira et al. suggested that ABC and NF reside in the same biologic spectrum, namely USP6-induced tumors [37]. Shin et al. reported that FISH analysis for USP6 had a sensitivity of 86% and specificity of 100% for a diagnosis of NF [9]. While, Erber et al. reported that the sensitivity and specificity of USP6 FISH for NF was 74.4% and 100%, respectively [31]. These studies indicate a clear association between NF and a recurrent genetic abnormalities in FISH analysis.

MYH9 is located on chromosome 22q12.3-q13 [1] and it is the most frequent fusion partner [1, 33]. RRBP1, CALU, CTNNB1, MIR22HG, SPARC, THBS2, and COL6A2 as less frequent gene partners has been detected [32]. These studies demonstrated the neoplastic nature of NF and USP6-associated neoplasia [32]. SEC31A, EIF5A, COL1A1, COL1A2, PAFAH1B1, SERP1NH1, COL3A1 have been also identified [38-45]. Regarding EIF5A, the USP6 gene rearrangement was shown by using FISH and a subsequent analysis demonstrated a novel EIF5A-USP6 gene fusion by means of the Archer fusionPlex Sarcoma kit [8]. They mentioned that the genesis of NF is also caused by Wnt signaling pathway which is the essential target of USP6 [8]. PPP6R3-USP6 fusion has been shown in two cases of NF accompanied with malignant manifestation [44, 45].Regarding the cutaneous NF, Kumar et al. [30] have described the presence of the USP6 rearrangement and MYH9-USP6 fusion, suggesting that the similar cytogenetic nature has been revealed both in subcutaneous NF and intradermal type.

Nodular fasciitis as USP6-associated neoplasia through pathway

Due to the identification of structural similar USP6 fusion gene in both ABC and NF, it is suggested that these diseases are clonal neoplasia that may have the same biological spectrum [37]. Myositis ossificans (MO) and fibro-osseous pseudotumor of digits (FOPD) also show the identification of USP6 gene fusion, indicating that these lesions may present the same entity. It is known that multiple fusion patterns of USP6 lead to transcriptional activation of USP6 [46, 47].

Regarding the signaling pathways, USP6 induces several signal pathways including NFκB, Wnt/β-catenin, and JAK-1-STAT3 during tumorigenesis [46, 48, 49]. The important role of Jak1-STAT3 signaling in USP-6-related tumorigenesis has been reported [48], whereas Madan et al. [49] described that USP6 oncogene promotes Wnt signaling by deubiquitylating Frizzleds. Recently, Li et al. [50] reported that c-Jun is a novel substrate of USP6 and might serves as an essential role of NF.

Regarding Wnt signaling pathway [49], it has been noted that chromosomal translocations of NF cause USP6 overexpression, that in turn lead to transcriptional activation of the Wnt/β-catenin pathway. Inhibition of Wnt signaling pathway significantly attenuated the growth of USP6-driven xenograft tumors, suggesting that Wnt signaling is an essential target of USP6 in tumorigenesis of NF. The study by Madan et al. [49] revealed a new mechanism for pathological Wnt pathway activation in NF and ABC and suggested a novel treatment method to modulate Wnt signaling. With respect to the Jak1-STAT3 signal, Quick et al. [48] showed that the Jak1-STAT3 signals are potential effectors of the USP6-TRE17 oncogene in the tumorigenesis of ABC and NF. They showed that USP6 activates Jak1-STAT3 pathway by deubiquitinating Jak-1, resulting in the stabilization and STAT3 activation. It has been suggested that the tumorigenic activity of USP6 was decreased by a JAK family inhibitor, or by CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-mediated deletion of JAK1 or STAT3 [48]. It has been suggested that studies demonstrating the downstream effects of USP6 may contribute to the therapeutic strategy in patients with ABC and NF [50]. The novel genes, namely the Frizzled and JAK1 genes were recently demonstrated as USP6 substrates [48, 49]. While, Li et al. [50] described the transcription factor c-Jun as a novel substrate of USP6. It has been reported that USP6 stabilized the c-Jun protein and potentiated c-Jun-dependent downstream signaling and cell invasion. They suggested that the interaction between USP6 and c-Jun might be important in patients with NF. It is known that USP6 has been shown to have potential roles in ABC and NF. Therefore they also suggest that the inhibition of c-Jun and other USP6-associated genes including JAK1 and Frizzled genes would produce the benefit in the patients with ABC and NF. The author suggests that the inhibition of c-Jun and other USP-related genes may be the potential therapeutic strategies for recurrent and/or inoperable ABC. Whereas the most of NF is benign, self-limited process including high proliferative growth activity and regress nature. Extremely rare malignant

behavior of NF [44, 45] shown by USP6-PPP6R3 gene fusion has been reported. Based on the evidence, the author also suggests that the inhibition of USP6-related genes might be essential therapeutics in malignant behavior type of NF.

Self-limited nature of NF from USP6-FISH (%) viewpoint

The report [51] indicated that young NF defined as preoperative duration <1 month contains a high percentage of USP6 break-apart FISH signals than old NF defined as preoperative duration >3 months, suggesting that the result may demonstrate the connection with the self-limited nature of NF. The result indicated that in old NF, the percentage of USP6 break-apart FISH signals can be as low as 14-27%. It is putative that USP6 break-apart FISH signals reflect the growth activity and regress nature in NF. In addition to the presentations of clinical, ulrtrasonographic, and pathological appearances, the evaluation of percentage of USP6 break-apart FISH signals may be a potential procedure for diagnosis in young NF [17, 51]. In old NF, the author suggests that accurate diagnosis should be comprehensively made by the presentation of clinical, ultra sonographic, pathological, and cytogenetic features. The result showed a strong inverse relationship between the lifetime and percentage of USP6 break-apart signals and a strong positive association between USP6 break-apart signals and mitotic counts [51]. Based on the evidence, the author suggests that NF has the self-limited behavior so-called the proliferative activity and regression nature. It has been known that USP6 activation by promoter-swapping is characteristic feature accompanied with involvement of JAK-1/STAT1/STAT3 pathways leading to stabilization of the JUN protein [51]. In their research, the mRNA level of USP6, TRAIL, IFN-beta, JAK1, STAT1, STAT3, JUN, and CDKN2A as the pathways of the tumorigenesis of NF was evaluated using qRT-PCR, resulting in the significantly negative correlations between USP6-FISH and JAK1 and between USP6-FISH and STAT1. They also described that the role of the JAK-1/STAT1/STAT3 pathway is “active” during the whole lifetime of NF. While, it has been also suggested that cellular senescence through CDKN2A/p16 could be responsible for self-limited nature and a negative feedback mechanism that USP6 induces TRAIL-mediated apoptosis was revealed [52, 53]. They described that in young NF, the nuclear localization of TRAIL was shown and in old type, the dominant membraneous-cytoplasmic TRAIL positivity was represented [51].

Conclusion

In addition to the presentation of clinical, ulrtrasonographic, and pathological appearances, the evaluation of percentage of USP6 break-apart FISH signals reflecting lifetime and mitotic counts in nodular fasciitis may be a potential procedure for accurate diagnosis in particularly young nodular fasciitis.

It is putative that the inhibition of USP6-related genes might be the potential therapeutic strategies for recurrent and/or inoperable aneurysmal bone cyst and extremely rare malignant nodular fasciitis.

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DOI: 10.31579/2640-1053/100