

An aggressive nodular fasciitis lesion protruding from the palm (USP6 gene fusion helps differentiate from sarcomas): A case report

CHIGUSA SAWAMURA¹, TABU GOKITA¹, AYATAKA ISHIKAWA², JUN MANABE¹ and HIROAKI KANDA²

Departments of ¹Orthopaedic Surgery and ²Pathology, Saitama Cancer Center, Saitama 362-0806, Japan

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Abstract. Nodular fasciitis is a mesenchymal lesion, which has been viewed as a reactive process. The MYH9-USP6 fusion gene was recently detected in nodular fasciitis, and nodular fasciitis is now considered to be a self-limiting neoplastic process. Recently, a case of nodular fasciitis that recurred a number of times and metastasized to soft tissues was reported, and the features of aggressive cases of nodular fasciitis are currently under investigation. Here, a case of locally aggressive nodular fasciitis is presented, in which the lesion grew rapidly and caused ulnar nerve palsy. The lesion was locally controlled via marginal excision, and no metastasis was identified at 24 months post-operation. Histologically, the lesion was consistent with nodular fasciitis, and the detection of the MYH9-USP6 fusion gene supported the diagnosis. Although most nodular fasciitis lesions are benign, some may be locally aggressive or even metastasize. In the case outlined in the present study, marginal excision was sufficient to locally control the lesion.

Introduction

Until recently, nodular fasciitis has been considered to be a reactive process of uncertain cause (1). The recent identification of genomic rearrangements indicates that nodular fasciitis is a self-limiting clonal neoplastic process (2). Nodular fasciitis is most commonly found in adults of 20 to 50 years of age and is rarely seen on the hands (3). Differentiating between nodular fasciitis and sarcomas is often clinically and pathologically challenging as nodular fasciitis exhibits rapid growth, high cellularity, and mitotic activity (3). In addition, a recent report suggested that nodular fasciitis displays malignant behavior such as multiple recurrent lesions and metastasis (4).

We report a case in which a locally aggressive nodular fasciitis lesion grew rapidly on the patient's palm, and discuss the surgical management of the lesion. Our case suggests that fusion gene analysis was useful for differentiating nodular fasciitis from sarcomas. In addition, marginal excision was sufficient even though the tumor was extremely aggressive and grew fast, since our patient did not develop local recurrence or metastasis in two years.

Case report

A 53-year-old female presented with a four-month history of a painful mass on her left palm. Her medical history included hyperthyroidism and uterine myomas, but she did not recall any trauma involving her left hand. On physical examination, a 2-cm mass was found around the hypothenar eminence. It was elastic, slightly mobile, and tender. The associated pain and numbness radiated towards the patient's ring and little fingers. On magnetic resonance imaging, a lesion measuring 20x15x30 mm was located between the palmar aponeurosis and flexor tendons (Fig. 1). It was well delineated and exhibited low intensity on T1-weighted imaging, whereas it was isointense on T2-weighted imaging and displayed inhomogeneous contrast enhancement. An open biopsy showed a lesion composed of spindle-shaped cells, which was consistent with nodular fasciitis. After the biopsy, the patient's pain and numbness were unchanged, and a marginal excision was planned.

Two weeks after the initial biopsy, the wound opened, and the tumor protruding from the palm had reached the size of a golf ball (Fig. 2). The numbness affecting the patient's left ring and little fingers disappeared after the wound dehiscence, possibly because the pressure on the ulnar nerve had been reduced. Another incisional biopsy was carried out to exclude malignancies, as the tumor had grown extremely fast, and we suspected that it was a sarcoma. The lesion outside the skin, which measured 47x35x40 mm, was excised for histological examination. The cut surface of the lesion was gelatinous and hemorrhagic. Histologically, it consisted of spindle-shaped cells proliferating in a myxoid stroma (Fig. 3). The lesion demonstrated low cellularity. There were some mitotic figures without atypical mitoses, and slight pleomorphism was seen among the proliferating spindle-shaped cells. Some of the cells exhibited slightly hyperchromatic nuclei, but no bizarre nuclei were seen. These are typical histological findings of nodular fasciitis. On

Correspondence to: Dr Chigusa Sawamura, Department of Orthopaedic Surgery, Saitama Cancer Center, 780 Komuro, Ina-machi, Kitaadachi-gun, Saitama 362-0806, Japan
E-mail: chigusa-tmd@umin.ac.jp

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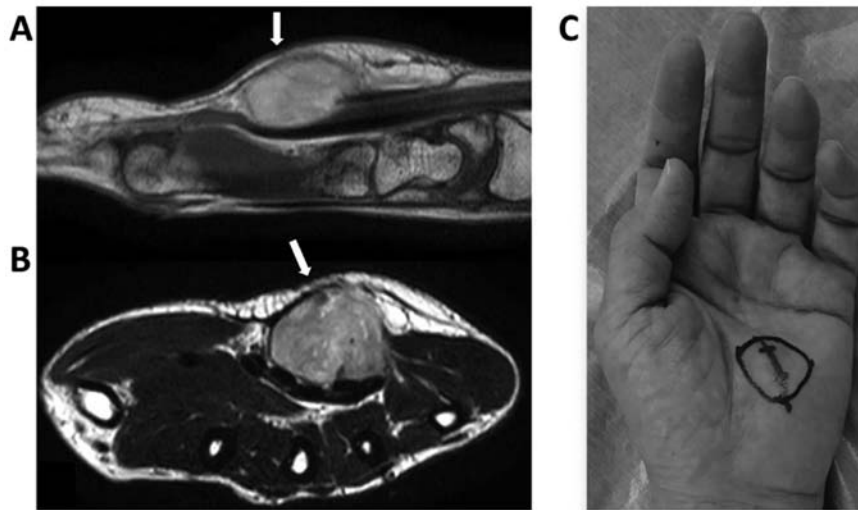


Figure 1. (A) T2-weighted sagittal and (B) axial images showed an isointense lesion between the palmar aponeurosis and flexor tendons (arrow). (C) A skin incision for an open biopsy was made over the mass at the hypothenar eminence.

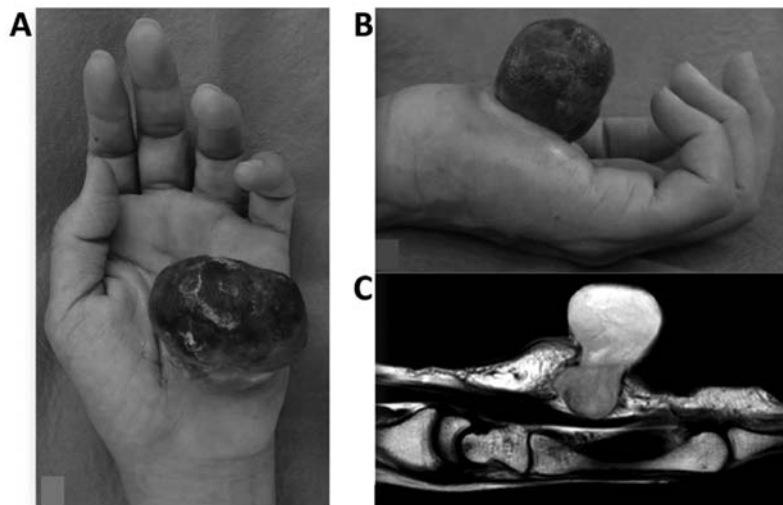


Figure 2. A 47x40 mm tumor protruded from the skin two weeks after the initial open biopsy. (A) frontal view and (B) side view. (C) T2-weighted sagittal imaging showed a gourd-shaped tumor on the flexor tendons. The lesion outside the skin was from the tumor inside the palm.

immunohistochemistry, the tumor was found to be positive for smooth muscle actin, vimentin, and p16, but negative for epithelial membrane antigen, bcl-2, CD34, CD56, cytokeratin AE1/AE3, desmin, mic2 (CD99), anaplastic lymphoma kinase, S-100, mucin 4, and signal transducer and activator of transcription 6. RNA was extracted from the frozen specimen and subjected to reverse transcription polymerase chain reaction (RT-PCR) using the primers myosin-9 (MYH9) 75F: 5'-AGG GCACGGAAGGCTAAGC-3' and ubiquitin carboxyl-terminal hydrolase 6 (USP6) 1630R: 5'-TGTGGATGTGAACTGCGG TC-3'. This revealed the presence of the MYH9-USP6 fusion gene, which supported a diagnosis of nodular fasciitis (Fig. 4). Fluorescence *in situ* hybridization (FISH) also confirmed the chromosomal translocation (Fig. 5).

Since the histological examination did not suggest that the lesion was a sarcoma or other type of malignancy, the tumor was marginally excised. A spindle-shaped incision was employed, and the palmar aponeurosis was excised en bloc (Fig. 6). The palmaris brevis was partially resected together

with the tumor, as it was very close to the lesion. The ulnar nerve, which was located under the tumor, was released and kept intact. The median nerve was not exposed, as it was sufficiently far away from the tumor. The superficial palmar artery and venous arches had adhered to the tumor; therefore, they were ligated and sacrificed. After the excision of the tumor, the skin was closed directly without flaps or skin grafts. The patient had not suffered any local recurrence or metastasis at 24 months post-operation.

Discussion

We reported a rare case of aggressive nodular fasciitis of the hand. A strong point of this study is the confirmation of the MYH9-USP6 fusion gene by both RT-PCR and FISH. In addition, the tumor was biopsied twice to confirm the diagnosis. The patient was already followed up for two years without local recurrence or metastasis. A limitation of the study is that this is a case report and we do not have similar cases to compare

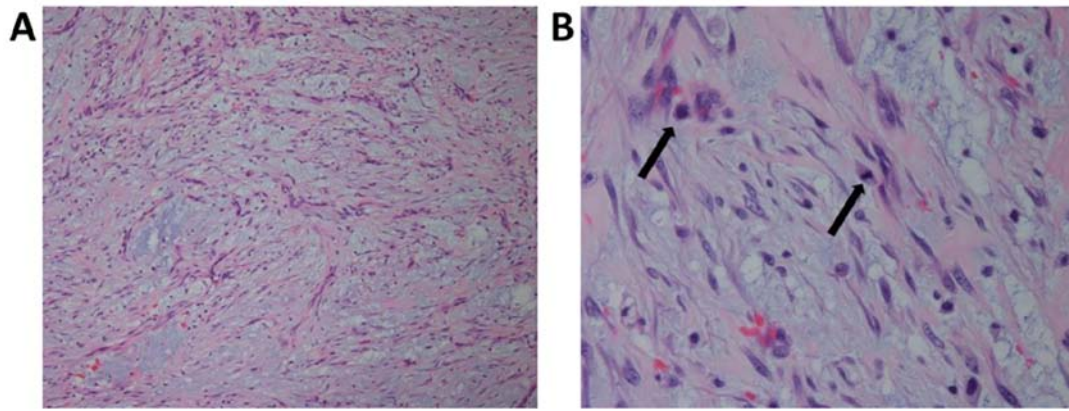


Figure 3. The histological features of the lesion detected during the excisional biopsy are shown (hematoxylin-eosin staining). (A) Spindle-shaped cells proliferated in a myxoid stroma. The lesion exhibited low cellularity. Magnification, x100. (B) Although there were several mitoses (arrows), no atypical mitoses were identified. Magnification, x400. Slight pleomorphism was seen among the proliferating spindle-shaped cells. Some cells had slightly hyperchromatic nuclei, although no bizarre nuclei were observed. These are typical features of nodular fasciitis.

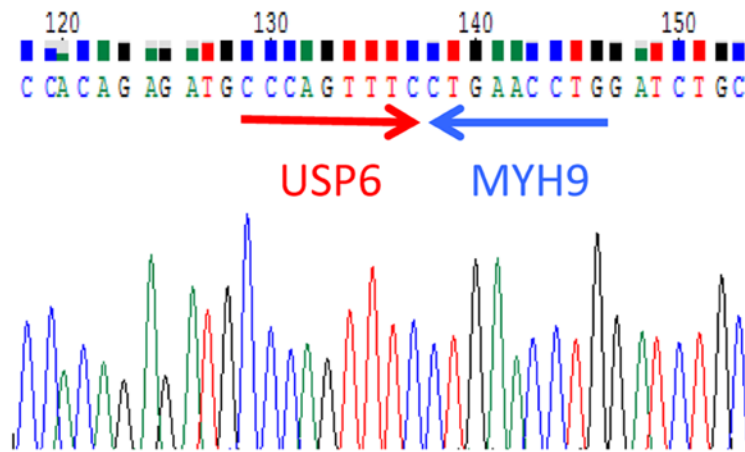


Figure 4. The sequencing chromatogram of type I MYH9-USP6 obtained using RT-PCR showed nodular fasciitis-specific gene rearrangement. MYH9, myosin-9; USP6, ubiquitin carboxyl-terminal hydrolase 6; RT, reverse transcription.

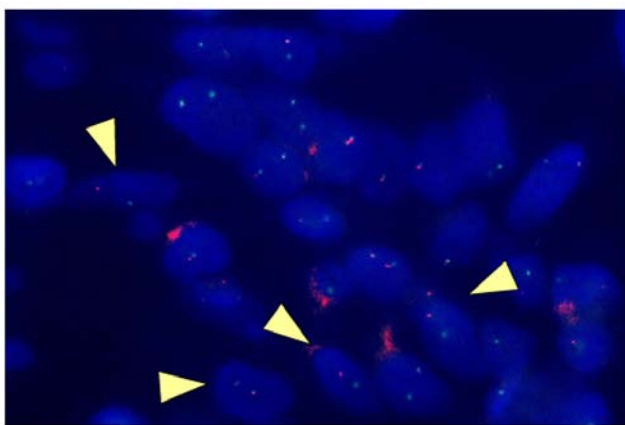


Figure 5. Break-apart FISH probe was used to identify gene fusion. Break-apart signal seen in tumor nuclei indicates *USP6* gene rearrangement (arrows). Magnification, x1,000. USP6, ubiquitin carboxyl-terminal hydrolase 6.

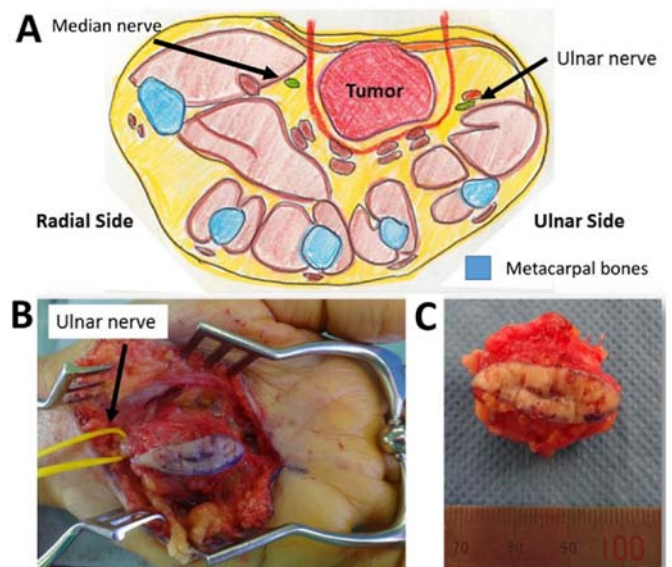


Figure 6. (A) The image presents the surgical plan. The tumor was marginally excised, whereas the ulnar nerve and flexor tendons were not excised. (B) Intraoperative examination indicated that the ulnar nerve had adhered to the tumor. (C) The excised specimen measured ~3 cm in diameter.

the outcomes. Some nodular fasciitis may behave differently and require different treatment strategies. Although we believe that our case is sufficiently informative because the size and

speed of tumor growth were aggressive, the tumor was locally controlled by surgical excision only.

Nodular fasciitis of the palm is rare and may exhibit very rapid growth, mimicking that of sarcomas. Such aggressive growth can cause nerve palsy, especially when the tumor is located in the hand, as it is rich in nerves. Kanaya *et al* reported a case in which intraneural nodular fasciitis caused median nerve palsy and eventually required the resection of the median nerve (5). Sevilla *et al* reported a case in which a large nodular fasciitis lesion on the palm grew to 9 cm in five months (6). According to the latter report, the patient stated that the lesion had grown faster in the few weeks before their initial visit. The location and size of the tumor were similar to those of our case; thus, nodular fasciitis of the palm may have the potential to grow rapidly and to be of considerable size.

The relationship between the malignant potential of nodular fasciitis and its oncogenic mechanism is currently being intensively investigated (4). In contrast, some nodular fasciitis lesions are self-limiting and spontaneously regress (7,8). Guo *et al* reported a case of 'malignant nodular fasciitis', which recurred several times and even metastasized to soft tissues (4). In the latter case, molecular analyses revealed the presence and amplification of the serine/threonine-protein phosphatase 6 catalytic subunit (PPP6)-USP6 fusion gene, which resulted in upregulated transcription of USP6 mRNA. In addition, Guo *et al* suggested that USP6 amplification may underlie the biology of many unclassifiable low-grade spindle-shaped cell/myofibroblastic sarcomas.

Nodular fasciitis often poses a diagnostic challenge to pathologists, as it does not express any specific immunohistochemical markers, and until recently, the diagnosis of such lesions was based on histological features alone. In 2011, rearrangement of the USP6 gene was reported as a recurrent and specific finding of nodular fasciitis (2). USP6 gene rearrangement was found in 92% of cases of nodular fasciitis, and the sensitivity and specificity of FISH for detecting USP6 were reported to be 86 and 100%, respectively (2,9). The detection of USP6 fusion genes may be useful for diagnosing nodular fasciitis lesions.

As for the treatment of nodular fasciitis lesions, surgical excision is usually curative. Some clinicians recommend that nodular fasciitis lesions should initially be observed because of the self-limiting nature of the disease (8). We recommend excising such lesions, especially when they are symptomatic, and marginal resection seems to be sufficient for achieving local control. Intralesional or piecemeal resection may be employed when the lesion is located adjacent to nerves, although it may increase the risk of tumor growth (5).

In conclusion, we reported a rare case of aggressive nodular fasciitis of the hand. The lesion increased rapidly in size, and obtainment of a histological diagnosis was challenging, as the lesion exhibited non-specific immunohistochemical findings. The detection of the MYH9-USP6 fusion gene supported a diagnosis of nodular fasciitis. In spite of its aggressive characteristics, the tumor was locally controlled via marginal excision, and no metastasis was detected postoperatively.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the present study.

Authors' contributions

CS drafted the manuscript. AI and HK performed the histological examination. JM and HK supervised and reviewed the contents of the manuscript and the data and image analysis. CS, TG, AI, JM, and HK contributed to acquisition, analysis, and interpretation of data, and writing and revision of the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the ethics committee of Saitama Cancer Center (approval no. 1119).

Patient consent for publication

The consent for publication of the manuscript and the related images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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