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Giant nodular fasciitis originating from the humeral periosteum: A case report

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Abstract

BACKGROUND

Nodular fasciitis (NF) is a self-limiting tumor that mostly occurs in the subcutaneous superficial fascia. NF originating from the appendicular periosteum is extremely rare. A large NF lesion of periosteal origin can be misdiagnosed as a malignant bone tumor and may cause overtreatment.

CASE SUMMARY

A right axillary mass was found in a 46-year-old man and was initially diagnosed intraoperatively as low-grade sarcoma, but later diagnosed as NF after post-resection histopathological evaluation. Furthermore, fluorescence *in situ* hybridization analysis revealed a *USP6* gene rearrangement that confirmed the diagnosis. To the best of our knowledge, this is the first case of NF in the humeral periosteum.

CONCLUSION

NF poses a diagnostic challenge as it is often mistaken for sarcoma. Postoperative histopathological examination of whole sections can be combined with immunohistochemical staining and, if necessary, the diagnosis can be confirmed by molecular detection, and thus help avoid overtreatment.

Key Words: Nodular fasciitis; Periosteum; Differential diagnosis; *USP6*; Fluorescence *in situ* hybridization; Case report

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Core Tip: This article provides a comprehensive overview of the clinicopathological, immunohistochemical, and molecular features of nodular fasciitis originating from the humeral periosteum. To date, this is the first report of nodular fasciitis originating from

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the humeral periosteum and this type of research is critical to further our understanding of these lesions and advance pathological diagnoses.

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INTRODUCTION

Nodular fasciitis (NF) was first described as a pseudosarcomatous fasciitis by Konwaler *et al*[1] in 1955. Similar to other soft-tissue sarcomas, NF is a rapidly growing, benign proliferation of fibroblasts and myofibroblasts displaying abundant, spindle-shaped cells and high mitotic activity. NF presents most typically in the upper extremities (46%), trunk (20%), and head and neck (18%)[2]. The peak incidences of NF are seen at ages 20 and 40, often presenting with tenderness, and it is a rare disease in children[3]. Most NF lesions are small, measuring less than 2 cm in diameter[2,4]. Periosteal fasciitis is considered a rare subtype of NF, with some case reports in the published literature and most of those were published over 20 years ago; only one case of periosteal fasciitis has been published recently, in 2017. The frequently reported sites of periosteal fasciitis are the maxilla and the hand; however, there are no reports of periosteal fasciitis in the limbs, and all reported cases described tumors that were smaller than 5 cm.

As NF has a nonspecific immunohistochemical profile[4], its histomorphological characteristics are the primary diagnostic criteria. Therefore, it remains a challenge to distinguish NF from other spindle cell lesions, particularly those of the myofibroblastic lineage.

In 2011, Erickson-Johnson *et al*[5] reported the rearrangement of the *USP6* gene on chromosome 17p13 as a recurrent and specific finding in NF. Subsequently in 2013, Amary *et al*[6] found *USP6* gene rearrangements in 91% of the 34 NF cases in their study, thereby making *USP6* fluorescence *in situ* hybridization (FISH) analysis a reliable and useful ancillary diagnostic test for NF.

This report presents findings from the first case of large-sized NF originating from the humeral periosteum. We emphasize the importance of highlighting this rare clinical entity, which usually represents a diagnostic dilemma.

CASE PRESENTATION

Chief complaints

Intermittent pain in the right axilla for 1 mo.

History of present illness

The patient had intermittent right axillary pain with no obvious cause of for 1 mo. And he found a lump under his axilla. Magnetic resonance imaging (MRI) showed a lesion measuring 62 mm × 58 mm × 44 mm, with relatively well-demarcated margins, and the lesion encircled the humerus, with localized thinning of the humeral cortex, and was closely related to the radial artery. The clinician recommended surgical treatment.

History of past illness

There was no history of past illness.

Personal and family history

There was no personal and family history.

Physical examination

A tough mass was locally palpable on the medial side of the upper right arm and was approximately 7 cm in size.

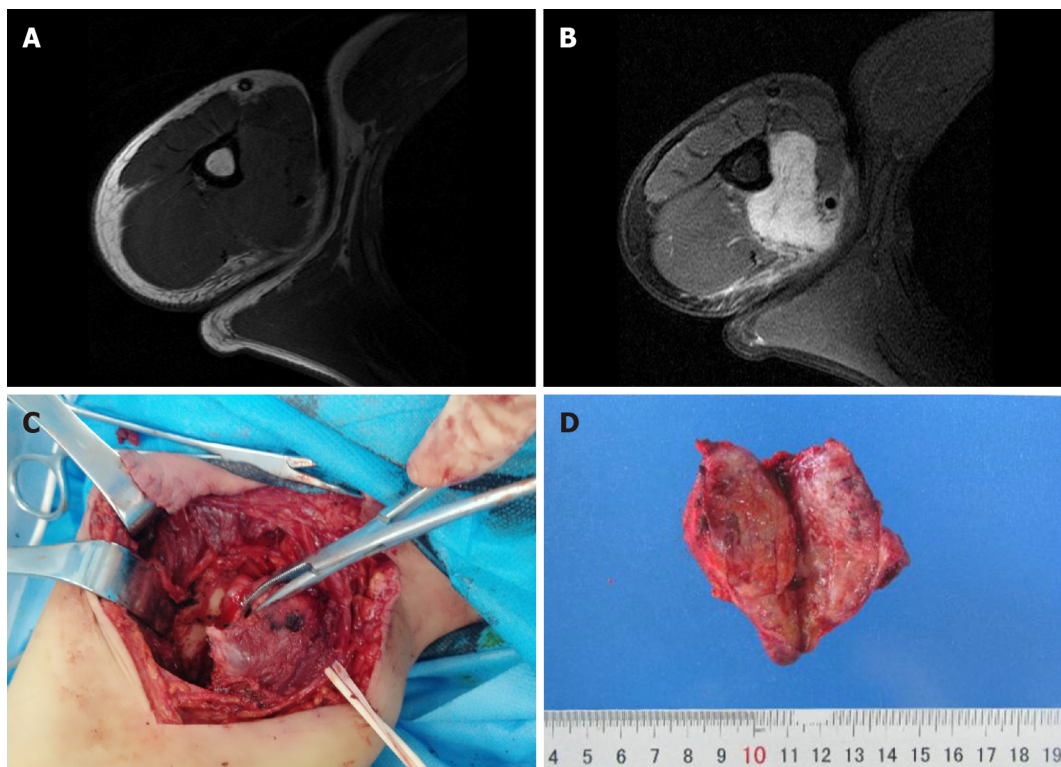


Figure 1 Imaging and gross examination. A: Magnetic resonance imaging showed patchy low signal in the medial humerus (T1WI); B: Magnetic resonance imaging showed a high signal intensity on the humerus, with local thinning of the humeral cortex (T2WI); C: The root of the mass extended laterally below the biceps brachii and was closely related to the humerus; D: The mass was nodular, with a diameter of 7.5 cm, a relatively clear boundary, and a reddish gray appearance on cross section.

Laboratory examinations

No abnormalities were found in routine laboratory tests.

Imaging examinations

An MRI scan showed a high signal intensity in the agglomerated pressure-fat phase near the right axillary region. The MRI images showed a lesion measuring 62 mm × 58 mm × 44 mm, with relatively well-demarcated margins. The lesion encircled the humerus, with localized thinning of the humeral cortex, and was closely related to the radial artery.

FINAL DIAGNOSIS

NF.

TREATMENT

Surgical tumor resection.

Diagnostic work-up

The differential diagnosis of sarcoma was made, and the patient underwent surgical tumor resection. Intraoperatively, we identified a mass with an approximate diameter of 7 cm that was closely related to the humerus, with a relatively clear boundary that separated it from the surrounding tissue. The tumor was completely separated from the periosteum. The surgical specimen was intraoperatively subjected to rapid histopathological examination. Gross examination revealed a gray nodule measuring 7.5 cm × 4 cm × 4 cm that had a reddish gray surface appearance on cross section and relatively tough texture (Figure 1). Microscopically, the lesion mainly comprised spindle-shaped fibroblast-like cells, with mucinous degeneration, mild atypia of some cells, and 3-4 mitotic figures per 10 high power fields. The intraoperative provisional

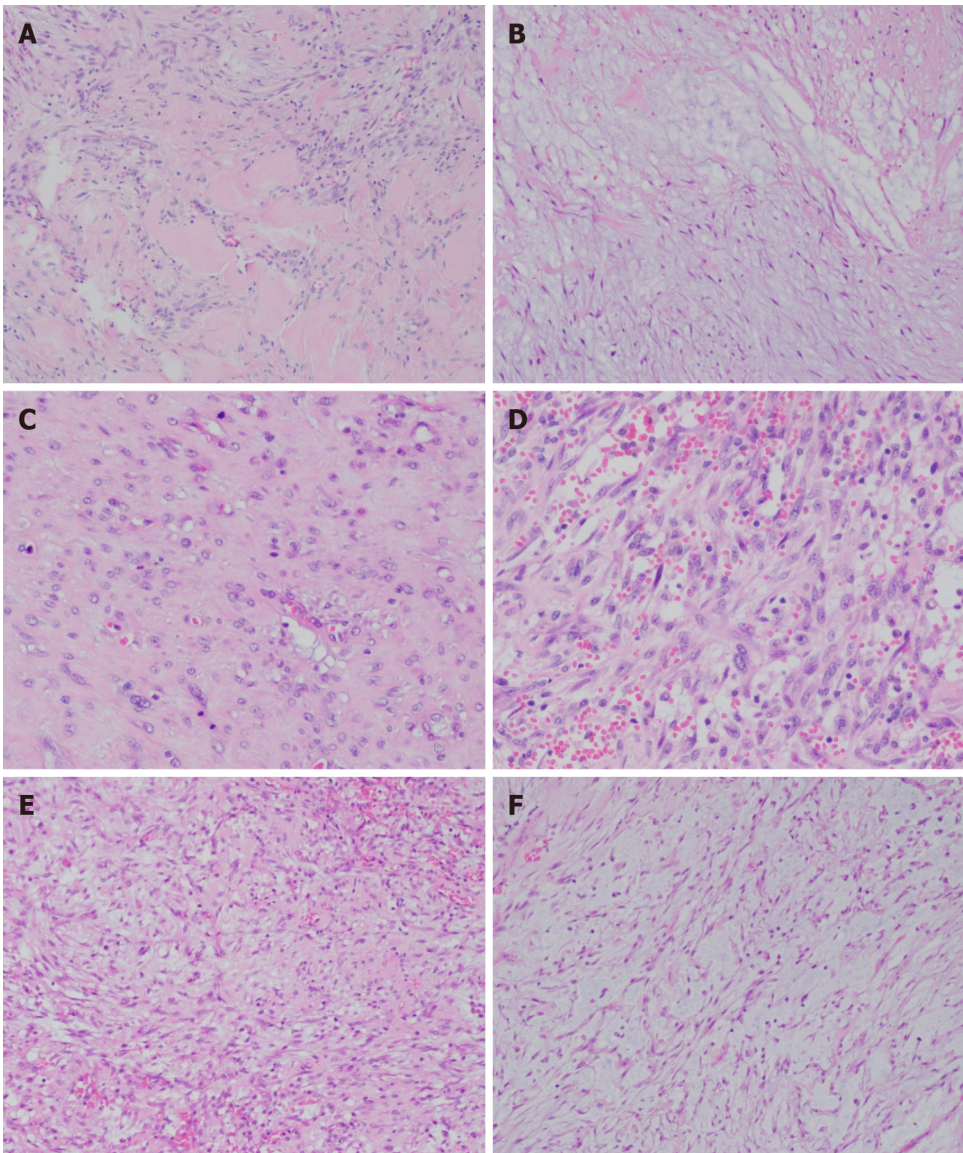


Figure 2 Hematoxylin-eosin staining. A: Localized fibrous tissue hyperplasia and hyaline degeneration [hematoxylin and eosin (HE), $\times 100$]; B: Some areas showed extracellular mucoid matrix (HE, $\times 100$); C: Mitotic figures (HE, $\times 200$); D: Tumor cells are abundant and there is apparent extravasation of red blood cells (HE, $\times 200$); E: Spindle-shaped and fibroblast-like tumor cells (HE, $\times 100$); F: Spindle-shaped tumor cells with stromal mucous degeneration (HE, $\times 100$).

pathological diagnosis was a mesenchymal neoplasm; the final diagnosis would be definitively based on the postoperative pathology. The postoperative histopathology of the lesions revealed spindle-shaped tumor cells with abundant extracellular mucoid matrix (Figure 2B and F); similarly, on examination of the frozen sections, some areas showed fibrous hyperplasia and hyaline degeneration (Figure 1A), whereas other areas had extravasation of red blood cells (Figure 2D). Tumor cells in areas with relatively high cellularity showed mild atypia (Figure 2C and D) and mitotic figures (Figure 2C). Immunohistochemistry showed that the specimen stained negative for CD34, S100, and β -catenin and positive for CD10 and SMA (Figure 3). FISH analysis revealed a *USP6* gene fracture rearrangement (Figure 4) with signal patterns as follows: 1G1R1F 16.5%, 1G1R 8.5%, 2F 35.5%, 1F 25.0%, 1G1F 7.0%, and 1R1F 7.5%.

OUTCOME AND FOLLOW-UP

The patient had an uneventful recovery after surgery and no further treatment was given. There was no recurrence during the 20-mo follow-up period.

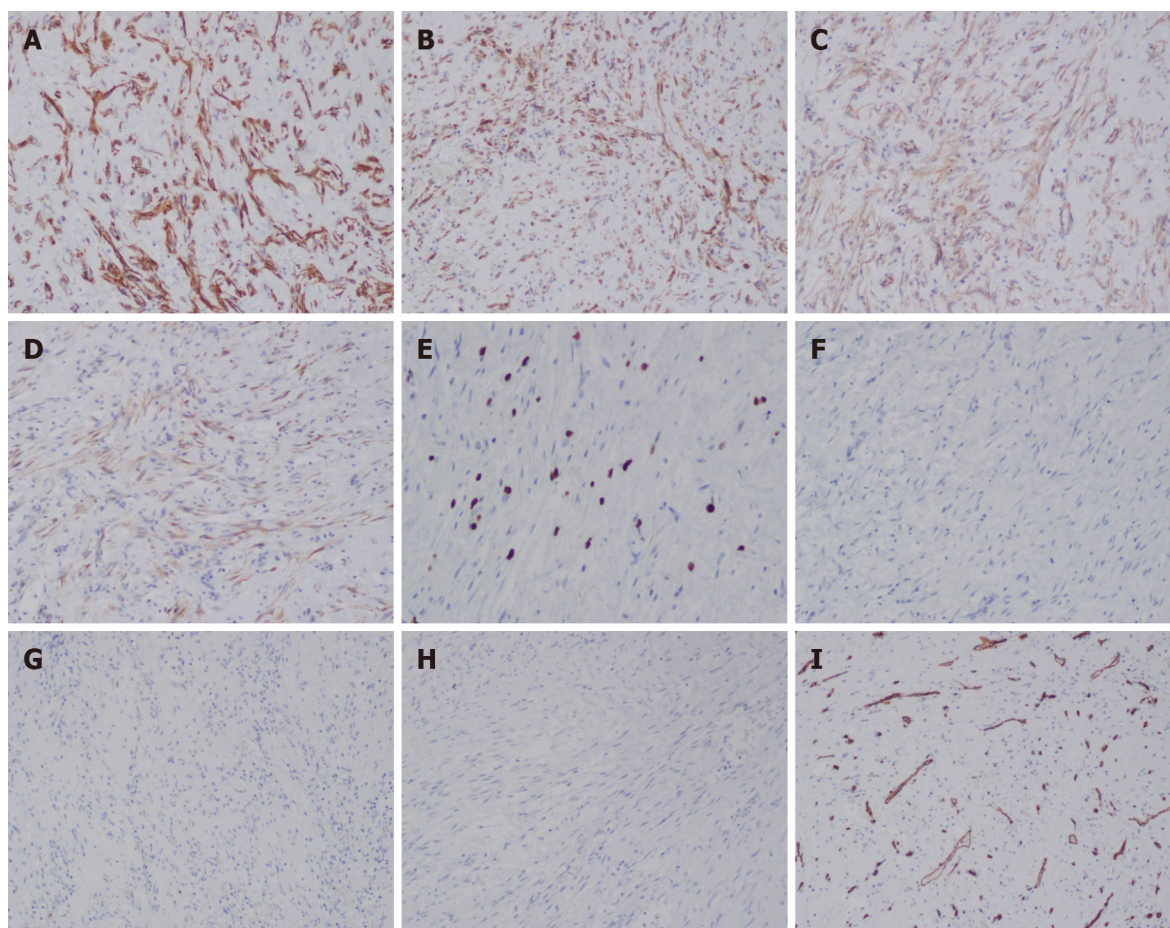


Figure 3 Immunohistochemical staining. A: Tumor cells stained positive for SMA; B: Tumor cells stained positive for CD10; C: The cytoplasm tested positive for β -catenin; D: Tumor cells stained positive for calponin; E: The Ki67 index was 10%; F: Tumor cells stained negative for desmin; G: Tumor cells stained negative for EMA; H: Tumor cells stained negative for S-100; I: Tumor cells stained negative for CD34 (EnVision, $\times 100$).

DISCUSSION

The published literature describes NF as a benign myofibroblastic proliferation, which was initially reported in 1955 as a pseudosarcomatous fibromatosis or fasciitis[1]. The NF lesion typically develops in the subcutaneous superficial fascia of the upper limbs (46%), especially over the volar aspect of the forearm, followed by the head and neck (20%), trunk (18%), and lower extremities (16%). There are no gender differences in NF incidence, and all reported lesions measure less than 5 cm in diameter.

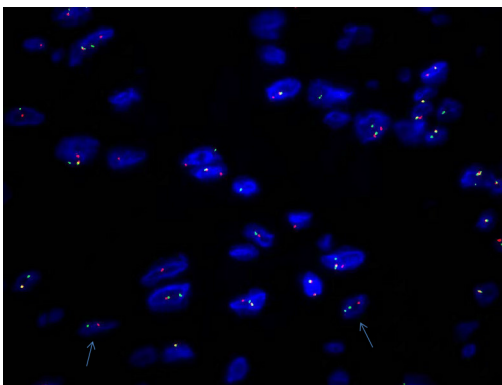
Periosteal fasciitis, a subtype of NF, is characterized by periosteal overgrowth and reactive new bone formation. There are only a few case reports (10 cases) of periosteal fasciitis in the literature, most of which were reported in the 1970s and 1980s, although one case was recently reported in 2017. Among those ten cases (four males; six females), four occurred in the jaw (one in the maxilla, three in the mandible) and six in the hand. The largest reported tumor diameter was approximately 5 cm. Most of the cases were diagnosed by histomorphological features, and FISH was undertaken in only one case in the recent literature and showed *USP6* gene-related heterotopia. All patients were followed, and there are no reports of recurrence (Table 1). In our case, NF was initially diagnosed by histomorphology and immunohistochemistry; however, because of the unusually large tumor and its periosteal origin, we undertook a *USP6* FISH examination. The results showed *USP6*-related ectopia, which further confirmed a diagnosis of NF. The patient has shown no recurrence on follow-up for 10 mo. This report presents a rare case of clinical NF of the humeral periosteum with a tumor diameter of 7.5 cm.

Due to its fast and infiltrative growth pattern, NF remains one of the most commonly misdiagnosed benign spindle cell neoplasms. A common differential diagnosis of NF is low-grade malignant myofibroblastic tumors because, despite their large size, the tumor cells are characterized by mild atypia; positive staining for actin, desmin, calponin, and CD34 (focal), and negative staining for S100 and nuclear β -

Table 1 Published studies reporting periosteal fasciitis

Ref.	Number of cases	Sex	Age (yr)	Symptom presence and duration	Location	Treatment	Size (cm)	USP6 gene	Follow-up (mo)	Recurrence	Injury
Lääveri <i>et al</i> [11], 2017	1	Female	7	No	Mandible	Local resection	3	Yes	36	No	No
Rankin <i>et al</i> [12], 1991	1	Female	39	No	Hand	Local resection	5	NA	10	No	No
Mostofi <i>et al</i> [13], 1987	1	Male	46	No	Mandible	Local resection	3	NA	30	No	No
Sato <i>et al</i> [14], 1981	1	Male	31	Pain for 2 mo	Maxillary	Local resection	4	NA	8	No	No
McCarthy <i>et al</i> [15], 1976	1	Male	40	No	Ring finger	Amputation	NA	NA	12	No	No
Johnson and Lawrence [16], 1975	1	Male	38	Pain and swelling for 3 mo	Metacarpal and ring finger	Local resection	NA	NA	12	No	No
Goncalves [17], 1974	1	Female	23	Pain and swelling for 2 wk	Index finger	Amputation	NA	NA	60	No	No
Lumerman <i>et al</i> [18], 1972	1	Female	31	Pain for 3 d	Mandible	Local resection	2	NA	30	No	No
Carpenter and Lublin [19], 1967	1	Female	32	Pain and swelling for 7 mo	Proximal and middle phalanges, ring finger	Amputation	NA	NA	12	No	No
Mallory [20], 1933	1	Female	28	Pain, swelling for 4 wk	4 th and 5 th metacarpals	Incomplete local resection	NA	NA	12	No	No

NA: Not available.

Figure 4 Fluorescence *in situ* hybridization analysis showing a USP6 rearrangement as separated red and green signals.

catenin[7-9]. However, FISH shows no USP6 gene-related ectopia, and myofibroblastic tumors have a high recurrence after surgical resection.

Sometimes, it may be difficult to distinguish low-grade myxofibrosarcoma from NF, especially in cases with small tumor volume and without specific immunohistochemical markers. Nonetheless, curvilinear thin-walled blood vessels and pseudolipoblasts suggest the possibility of a myxofibrosarcoma, and FISH examination shows no USP6 gene-related ectopia.

Low-grade malignant fibromyxoid sarcoma is another differential diagnosis of NF. The identification can be comprehensively evaluated by immunohistochemical staining and molecular detection. Immunohistochemistry shows EMA positivity from focally to 80%, and MUC4 positivity has high sensitivity and specificity for the detection of fibromyxoid sarcoma[10]. Molecular genetics show FUS-CREB3L2 or FUS-CREB3L1 gene fusion (Table 2).

Table 2 Primary differential diagnosis

Tumor type	Epidemiology	Clinical features	Size	Histopathology	Immunophenotype	Genetics
Nodular fasciitis	Young adults, no gender difference	Grows rapidly, painless, recurrence is rare	Median size, ≤ 2 cm (always < 5 cm)	Spindle-shaped fibroblasts, growth in S- or C- shaped, interstitium is loose and myxoid, visible exosmosis of erythrocytes	Positive: SMA, Calponin, CD10; negative: S100, CD34, nuclear β-catenin	<i>MYH9-USP6</i> gene fusion
Low-grade fibromyxoid sarcoma	Typically affect young adults, no gender difference	Slow growth, no pain, easy recurrence	Median size, 5 cm (1-20 cm)	Original glue and myxoid region are mixed, spindle cell, small blood vessels, early formation of collagen rosettes	EMA positive from focally to 80%, MUC4 positive has high sensitivity and specificity	<i>FUS-CREB3L2</i> or <i>FUS-CREB3L1</i> gene fusion
Low-grade myofibroblastic sarcoma	Predominantly in adults, 40-50 yr see more, slight predominance in males	Enlarging mass, painless, easy recurrence	Median size, 4 cm (1.4-17 cm)	Diffusely infiltrative growth, spindle cells arranged in a storiform pattern or fascicles	Positive: actin, desmin, calponin, CD34 (focal); negative: S100, nuclear β-catenin	Only one showed a circular chromosome
Low-grade myxofibrosarcoma	Elderly patients, over 60 yr, slight predominance in males	Slowly enlarging, painless, easy recurrence	Larger volume (range variable)	Spindle cells, mild atypia, curvilinear thin-walled blood vessels, pseudolipoblasts	Positive: SMA, negative: Desmin and histiocyte-specific markers	No specific aberration

Immunohistochemical staining has no specific significance in the identification of NF; however, it can be used as an auxiliary and differential diagnostic tool because spindle cells in NF often diffusely express SMA, and are negative for desmin. Recent studies have shown that *USP6 in situ* hybridization has higher specificity and sensitivity in the diagnosis of NF[6], particularly in cases with uncharacteristic morphology.

Furthermore, NF can be accurately diagnosed by combining tumor morphological characteristics, immunohistochemical findings, and *USP6* detection, thereby avoiding misdiagnosis and overtreatment of patients.

CONCLUSION

NF poses a diagnostic challenge as it is often mistaken for a sarcoma, or easily misdiagnosed as a sarcomatous lesion such as malignant fibrous histiocytoma or fibrosarcoma, because of its rapid growth, rich cellularity, and poorly circumscribed nature. NF is a tumor with rapid growth and relatively clear boundary, but it is sometimes difficult to distinguish from low-grade sarcoma under the microscope. When the tumor location is atypical and volume is large, the possibility of the disease should also be considered, especially during the operation, which can avoid excessive treatment. Postoperative histopathological examination of whole sections can be combined with immunohistochemical staining and, if necessary, the diagnosis can be confirmed by molecular detection.

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