Giant Nodular Fasciitis Originating From The Humeral Periosteum: A Diagnostic Challenge

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Case report

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Abstract

Background: Nodular fasciitis (NF) is a self-limiting, benign, fibroblastic, and myofibroblastic tumor that mostly occurs in the subcutaneous superficial fascia, although there are reports of NF occurrences at atypical sites, such as intraneural and intra-articular locations. However, NF originating from the appendicular periosteum is extremely rare, and NF lesions usually are smaller than 4 cm. A large NF lesion of periosteal origin can be misdiagnosed as a malignant bone tumor and may cause overtreatment.

Case presentation: This case report presents a large NF that originated from the humeral periosteum in an adult 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.

Discussion and Conclusions: NF poses a diagnostic challenge especially occurrences at rare sites as it is often mistaken for a sarcoma. Postoperative histopathological examination of whole sectionscan be combined with immunohistochemical staining and, if necessary, the diagnosis can be confirmed by molecular detection, and thus help avoid overtreatment.

Background

Nodular fasciitis (NF) was first described as a pseudosarcomatous fasciitis by Konwaler et al. in 1955[1]. Similar to other soft-tissue sarcomas, NF is a rapidly growing, benign proliferation of fibroblasts and myofibroblasts displaying abundant, spindle-shaped cellsand high mitotic activity[2].NF presents most typically in the upper extremities (46%), trunk (20%), and head and neck (18%)[3].The peak incidences of NF are seen at ages 20 and 40, often presenting with tenderness, and it is a rare disease in children[4].Most NF lesions are small, measuring less than 2 cm in diameter[3, 4]. Periosteal fasciitis is considered a rare subtype ofNF, 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 immunohistochemicalprofile[5–7], 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. reported the rearrangement of the ubiquitin-specific protease 6 (*USP6*) gene on chromosome 17p13 as a recurrent and specific finding in NF[8]. Subsequently in 2013, Amary et al. found *USP6* gene rearrangements in 91% of the 34 NF cases in their study, thereby making *USP6* fluorescein in situ hybridization (FISH) analysis a a reliable and useful ancillary diagnostic test for NF[9].

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

Case Presentation

A right axillary mass was incidentally found in a 46-year-old man approximately 1 month before he was hospitalized. An MRI scan showed high signal intensity of the agglomerated pressure-fat phase near the right axillary region. The MRI images showed a lesion measuring 62 × 58 × 44 mm^3, 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. 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 × 4 × 4 cm^3 that had a reddish gray surface appearance on cross section and relatively tough texture (Fig. 1). Microscopically, the lesion mainly comprised spindle-shapedfibroblast-like cells,with mucinous degeneration, mild atypia of some cells, and 3–4 mitotic figures per 10 HPF. The intraoperative provisional pathological diagnosis was that the mass was a mesenchymal neoplasm; the final diagnosis would be definitively based on the postoperative pathology. The postoperative histopathology of the lesions revealedspindle-shaped tumor cells with abundant extracellular mucoid matrix(Fig. 2B and 2F); similarly, on examination of the frozen sections, some areas showed fibrous hyperplasia and hyaline degeneration(Fig. 1A), whereas other areas had extravasation of red blood cells (Fig. 2D). Tumor cells in areas with relatively high cellularity showed mild atypia(Fig. 2C and 2D) and mitotic figures (Fig. 2C). Immunohistochemistry showed that the specimen stained negative for CD34,S100, andβ-catenin; positive for CD10 and SMA (Fig. 3). FISH analysisrevealed a*USP6* gene fracture rearrangement (Fig. 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%.

Discussion And Conclusions

The published literature describes NF as a benign myofibroblastic proliferation, which was initially reported in 1955 as a pseudosarcomatous fibromatosis or fasciitis[1]. The exact etiology of this proliferative lesion is not known, although local injury or inflammation have been postulated as triggers[10]. 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%)[11].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 those10 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 up, 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 months. This report presents a rare case of clinical NF of the humeral periosteum with a tumor diameter of 7.5 cm.

Table 1
Published studies reporting periosteal fasciitis

References	Published time	Number of cases	Sex	Age (years)	Symptom presence and duration	Location	Treatment	Size (cm)	*USP6* gene	Follow-up (month)	Recurrence	Injury
Laaveri M [16]	2017	1	Female	7	No	Mandible	Local resection	3	Yes	36	No	No
Rankin G [17]	1991	1	Female	39	No	Hand	Local resection	5	NA	10	No	No
Mostofi RS [18]	1987	1	Male	46	No	Mandible	Local resection	3	NA	30	No	No
Sato M [19]	1981	1	Male	31	Pain for 2 mos.	Maxillary	Local resection	4	NA	8	No	No
McCarthy EF [20]	1976	1	Male	40	No	Ring finger.	Amputation	NA	NA	12	No	No
Johnson MK [21]	1975	1	Male	38	Pain and swelling for 3 mos.	Metacarpal & ring finger	Local resection	NA	NA	12	No	No
Goncalves D [22]	1974	1	Female	23	Pain and swelling for 2 wks.	Index finger	Amputation	NA	NA	60	No	No
Lumerman H [23]	1972	1	Female	31	Pain for 3 days	Mandible	Local resection	2	NA	30	No	No
Carpenter EB, Lublin B [24]	1967	1	Female	32	Pain and swelling for 7 mos.	Proximal and middle phalanges, ring finger	Amputation	NA	NA	12	No	No
Mallory TB[25]	1933	1	Female	28	Pain, swelling for 4 wks.	4th & 5th metacarpals	Incomplete local resection	NA	NA	12	No	No

Note: mos., months; wks., weeks.

Due to its fast and infiltrative growth pattern, NFremains one of the most commonly misdiagnosed benign spindle cell neoplasms[5]. 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 foractin, desmin,calponin,and CD34 (focal),and negative staining for S100 and nuclear β-catenin[12–14]. 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 andpseudolipoblasts 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 fibromyxoidsarcoma[15].Molecular genetics show*FUS-CREB3L2* or *FUS-CREB3L1* gene fusion (Table 2).

Table 2
Primary differential diagnosis

Tumor types	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[26–27]	*MYH9–USP6* 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[15]	*FUS–CREB3L2* or *FUS–CREB3L1* gene fusion
Low-grade myofibroblastic sarcoma	Predominantly in adults, 40–50 year 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[12–14]	Only one showed a circular chromosome
Low-grade myxofibrosarcoma	Elderly patients, over 60 years, 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[28]	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[6]. Recent studies have shown that *USP6* in situ hybridization has higher specificity and sensitivity in the diagnosis of NF[9], 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.

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 should be considered in a rapidly growing nodule with a relatively clear border in the upper limb, despite an atypical site and large tumor volume, because arelatively conservative diagnosis, especially during the surgery, could reduce overtreatment. Postoperative histopathological examination of whole sectionscan be combined with immunohistochemical staining and, if necessary, the diagnosis can be confirmed by molecular detection.

List Of Abbreviations

NF
nodular fasciitis; FISH:fluorescence insitu hybridization analysis; EMA:epithelial membrane antigen; SMA:smooth muscle actin.

Declarations

Ethics approval and consent to participate

This study was approved by ethics committee of The Second Hospital of Jilin University (Changchun, China).

Consent for publication

Written informed consent was obtained from all patients involved in this review.

Availability of data and materials

The datasets used and/or analyzed during the current study are availablefrom the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

P.L.S. designed the review. S.L.Y. collected the data and prepared thedraft. J.L. , M.J. participated in data interpretation.P.L.S. and H.W.G. provided research fund. All authors read and approved the final manuscript.

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Figures

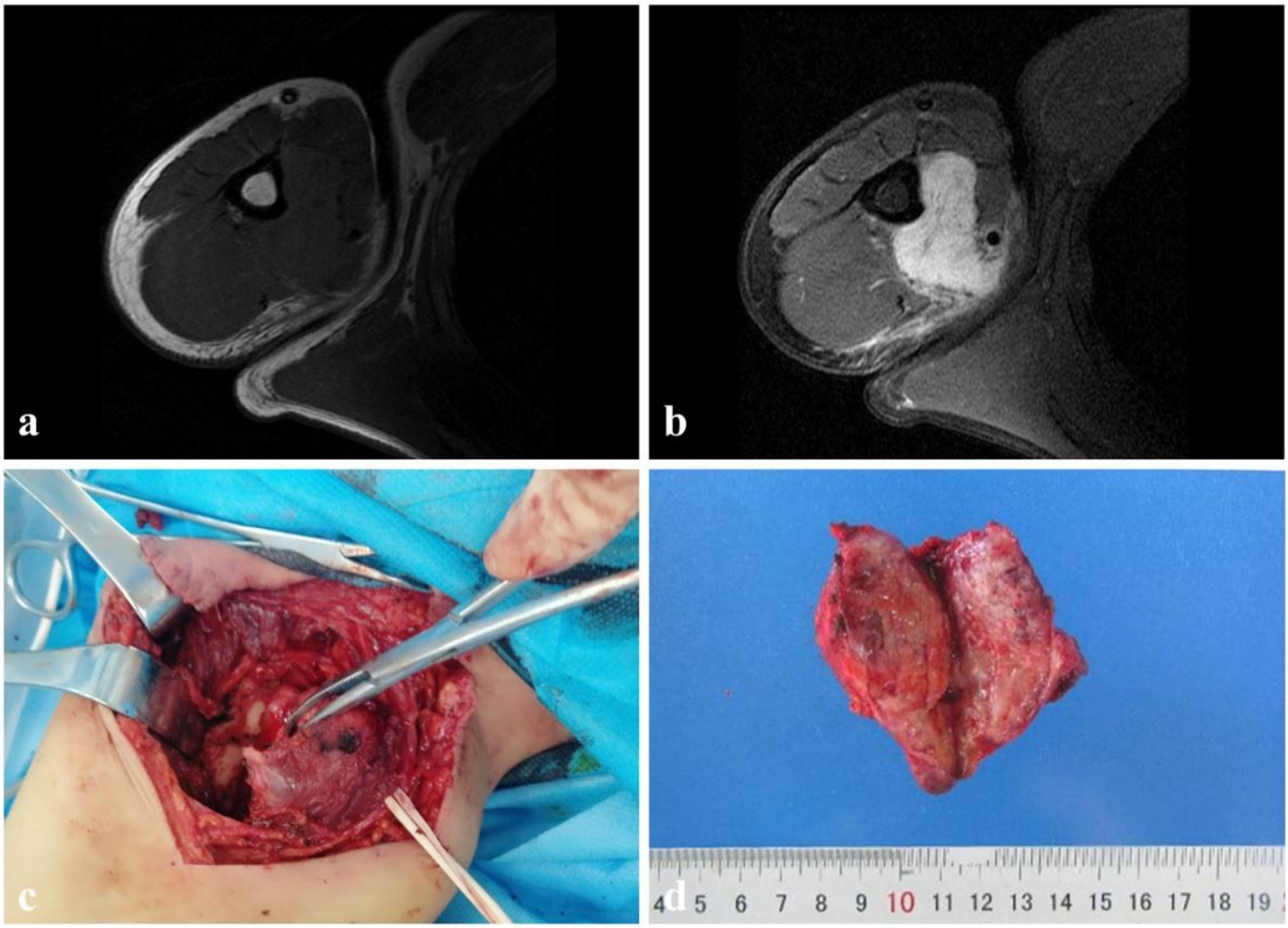

Figure 1

Imaging and gross examination.a and b. MRI showed a lesion encircling the humerus, with local thinning of the humeral cortex. c. The root of the mass extends laterally below the biceps brachii and is closely related to the humerus. d. The mass was nodular, with a diameter of 7.5 cm, with a relatively clear boundary, and areddish gray appearance on cross section.

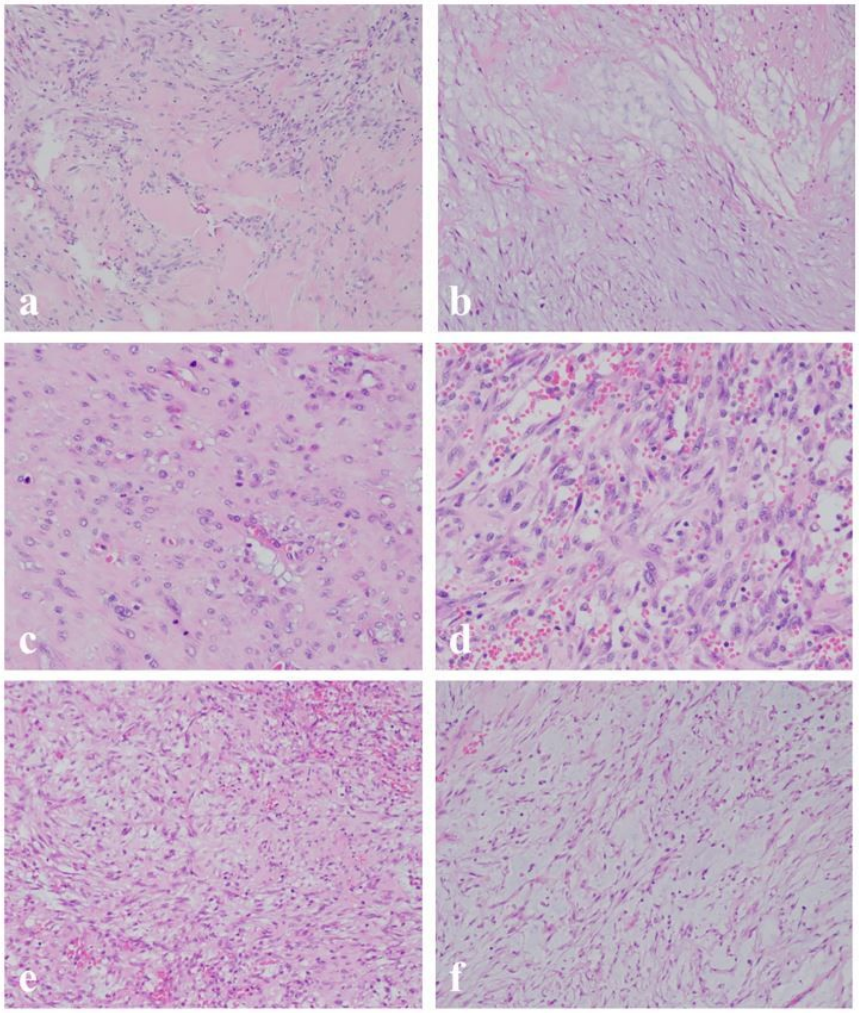

Figure 2

Hematoxylin-eosin staining.a. Localized fibrous tissue hyperplasia and hyaline degeneration (hematoxylin and eosin [HE], ×100).b. Some areas showed extracellular mucoid matrix (HE, ×100).c. Mitotic figures (HE, ×200).d. Tumor cells are abundant and there is apparent extravasation of red blood cells (HE, ×200). e. Spindle-shaped and fibroblast-like tumor cells(HE, ×100).f. Spindle-shaped tumor cells with stromal mucous degeneration (HE, ×100).

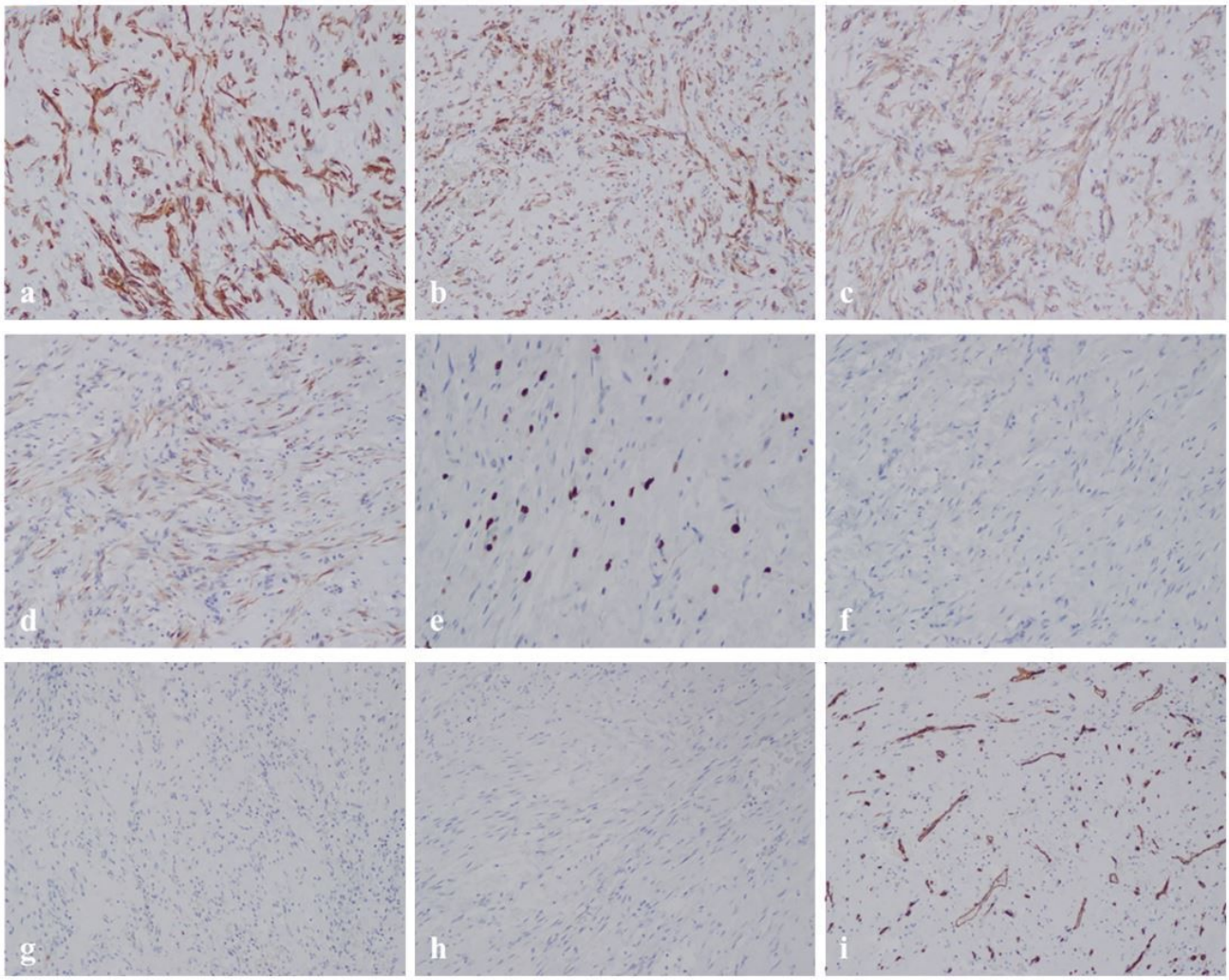

Figure 3

Immunohistochemical staining.a.Tumor cells stained positive forSMA; b.Tumor cells stained positive forCD10;c. The cytoplasm tested positive for β-catenin; d. Tumor cells stained positive forcalponin; e. Ki67 showed tumor cells were proliferating actively 10%; f. Tumor cells stained negative fordesmin, g. Tumor cells stained negative forEMA; h. Tumor cells stained negative forS-100;i. Tumor cells stained negative forCD34 (EnVision, ×100).

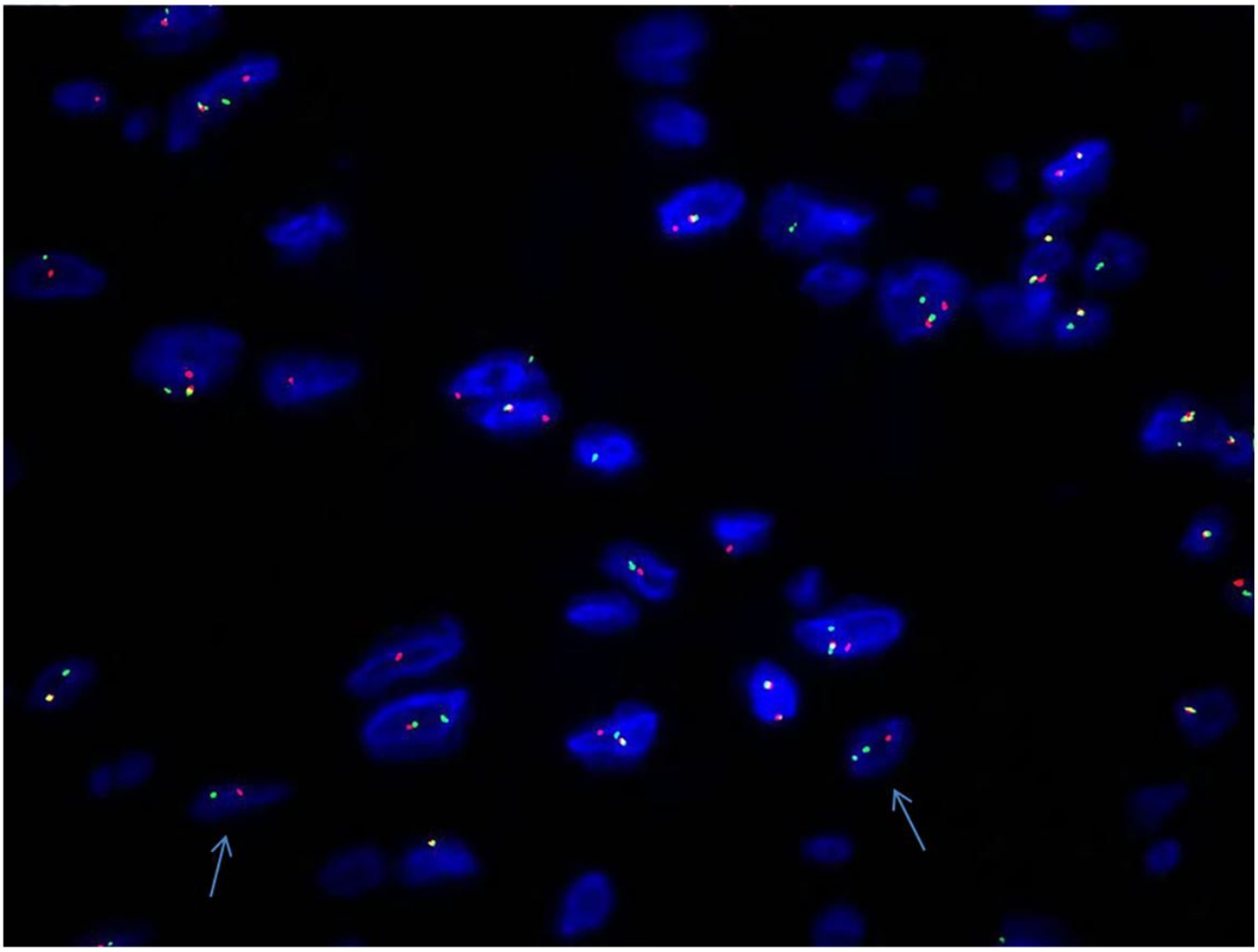

Figure 4

Fluorescence in situ hybridization (FISH) analysis showing USP6 rearrangement as separated red and green signals.