Clinicopathological and genetic findings of infantile nodular fasciitis

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To the Editor: Nodular fasciitis (NF) has been described as a rapidly growing benign soft tissue tumor with fibroblastic/myofibroblastic proliferation. It commonly involves the upper extremities of adults aged 20 to 40 years. Due to its rapid growth rate, high cellularity, and brisk mitosis, these lesions are easily confused with soft tissue sarcomas in the diagnosis-making process. Recent findings indicated that recurrent gene rearrangement of ubiquitin-specific protease 6 (USP6), located at 17p13.2, favors the clonally proliferative nature of NF. USP6 rearrangements have been discovered in approximately 90% of NF cases and >65% of NFs harbor myosin heavy chain 9 (MYH9)-USP6 fusions with a type I (exon 1–exon 1) or type II (exon 1–exon 2) pattern. Thus, USP6 rearrangements have been adopted as a valuable diagnostic biomarker for discriminating challenging cases from their histologic mimics. NF is frequently seen in adulthood but extremely rare in infants. Here, we evaluated the clinical, pathologic, and genetic features of infantile NF to understand the tumorigenesis mechanism underlying this entity.

This study was approved by the West China Hospital Institutional Review Board. A systematized nomenclature of medicine search of the hospital surgical pathology Institutional Review Board. A systematized nomenclature of medicine search of the hospital surgical pathology institutional review boards was performed. A total of 11 cases were identified from July 2008 to August 2020. The diagnosed age ranged from 4 to 23 months (median 11 months). Imaging data (including ultrasound and computed tomography) were available in four cases and unclear boundaries were shown in three of these cases (75%). All patients underwent surgical excision and the resected tumors were 1.4 to 4.0 cm (median 1.5 cm) in the largest dimension. Totally, five lesions were located in the subcutis, four in the muscle, one was identified in the parotid gland connective tissue, and one case lacked in-depth information. The resection of most specimens showed an ill-defined, firm nodule with a gray-white appearance. Histologically, muscular invasion was observed in five of the 11 patients [Figure 1A]. All tumors were mainly composed of spindle cells arranged in a fascicular pattern [Figure 1B]. Most cases (7/11) presented abundant fat spindle cells with a small amount of lymphocyte infiltration, while some lesions showed spindle cells with medium density and apparent inflammatory cell infiltration. Most cases (7/11) presented with microscopic changes. Red blood cell extravasation was not obvious in most cases (9/11). Scattered osteoclastic giant cells were observed in five of the 11 (45.5%) patients. The mitotic figures ranged from 1 to 13 per 10 high-power fields (HPFs) in these cases [Figure 1C]. Immunohistochemical staining was conducted, and all the cases with available data were positive for smooth muscle actin (SMA) [Figure 1D] and negative for desmin. The MIB-1 index was available in nine cases and ranged from 8% to 25%. The details of the clinicopathological data are shown in Supplementary Table 1, http://links.lww.com/CM9/A736.

Fluorescence in situ hybridization was performed to detect USP6 gene rearrangement (ZytoVision, Bremerhaven, Germany). Nine of the 11 cases (81.8%) showed positivity for USP6 rearrangement, and the percentage of split red-green signals ranged from 15% to 78%; among these cases, eight showed balanced rearrangement with one-fusion (1F), one-green (1G), and one-red (1G) (1F + 1G + 1R) signal patterns [Figure 1E]. In contrast, one case showed unbalanced rearrangement, of which 55% of cells showed a one-fusion and one-red (1F + 1R) [Figure 1F] signal pattern. Two cases were negative for USP6 rearrangement. Notably, the tissues of seven cases with USP6 rearrangement were retrievable for reverse
transcription-polymerase chain reaction (RT-PCR) and Sanger sequencing. The RT-PCR primers for detecting common fusion types of USP6 are listed in Supplementary Table 2, http://links.lww.com/CM9/A736. The results showed that only one case was positive for MYH9-USP6 with a type I [Figure 1G] and type II [Figure 1H] pattern, while six were negative for MYH9-USP6 in either type I or type II pattern [Supplementary Table 3, http://links.lww.com/CM9/A736].

No other treatment was provided after the simple surgical excisions. Follow-up information was available for 81.8% (9/11) of the patients who underwent tumor excision, with a median follow-up duration of 51 months (range: 5–121). Among these nine patients, there were two patients who developed local recurrence in 5 months after surgery; among which one was performed with re-excision and has been alive without evidence of recurrence for 19 months after the second operation, while another one has been alive with relapsed tumor for 3 months. All the other seven patients were disease-free after surgery.

This report presented 11 infantile NFs and reviewed the published literature to deeply understand this entity’s characteristics. Although a few previous studies have reported NF in childhood and summarized the clinical and pathological features, none of them focused on infantile patient groups.[5,6] After carefully reviewing the previous literature, it was found that patients <2 years old have been sporadically reported in previous studies by other researchers [Supplementary Table 4, http://links.lww.com/CM9/A736]. In the current study, the lesions were most frequently found in the head and neck, which may differ from those in adults or even in older children. Although NF has been suggested to be a trauma-related lesion, no patients in this study were reported to have a trauma...
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identifications in the English literature. Unbalanced rearrangements were
showed much higher cellularity and brisk mitoses (13/10 HPF). To further understand the role of an unbalanced
USP6 rearrangement and clinicopathological features.

In clinical work, accurate histopathologic diagnosis is crucial, as misdiagnosis may lead to aggressive or excessive
treatment. In our series of cases, most cases showed high
Cell sarcomas, such as infantile
USP6 status, combined with the clinicopathologic, molecular,
and genetic characteristics of infantile NF histologic mimics, can be useful in the diagnosis-making process.[3]

Surgical resection is a common treatment for NF and recurrences are rare.[1] However, in our cohort, the longest
duration period was up to 12 months, and no signs of
regression were observed. Two of the nine patients in
the present study showed recurrence in 5 months postoperatively.
Both these two lesions of the two patients were revealed as masses in the auricle of the ear. Local resection
was performed to remove these masses. The recurrence
may have resulted from the positive margin because of the
difficulty of achieving complete surgical excision around
the ear.[3] Therefore, we suggest that complete surgery is
the optimal treatment for infantile NF, if possible.

In conclusion, we have summarized the clinicopathological
features and identified USP6 rearrangements and MYH9-
USP6 fusion in a series of infantile NFs, which increases
our knowledge in this field. We argue that this entity may
have some special characteristics, but further studies with
large cohorts are still needed to obtain a more comprehensive characterization in the future.

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**Conflicts of interest**
None.

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