

Original Article

Fibrous hamartoma of infancy: a clinical pathological analysis of seventeen cases

Guojun Yu, Yibing Wang, Guangjun Wang, Dawei Zhang, Yong Sun

Department of Burn and Plastic Surgery, Huai'an First People's Hospital, Nanjing Medical University, Huai'an 223300, Jiangsu Province, China

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Abstract: To discuss the clinical and pathological features, differential diagnosis and prognosis of fibrous hamartoma of infancy (FHI), seventeen FHI specimens were analyzed with H&E staining and strepavidin peroxidase (SP) immunohistochemistry to detect distinguishing tissue markers. The long-term outcomes of select cases were also obtained. Among the 17 patients (13 males, 4 females, average age 16 months), FHI manifested as a subcutaneous painless mass, primarily on the back of the neck, the upper arms and buttocks. One recurrence was noted among six follow-up cases. The tumors consisted of three main components: fibrous connective tissue; mature fat; and undifferentiated mesenchymal tissue. Immunohistochemistry revealed that fibrous connective tissue was positive for SMA and actin, mature fat tissue was positive for S-100 protein, and undifferentiated mesenchymal tissue was positive for CD34 and was partially positive for actin and SMA. The tumors were negative for desmin, NSE, bcl-2, β -catenin and Ki-67. In brief, FHI is a benign, fibroblastic/myofibroblastic proliferative lesion. Defined histologic features of FHI as presented here would distinguish FHI from similar invasive tumors including infant fibromatosis, calcifying aponeurotic fibroma, fibrous fatty tumor and embryonal rhabdomyosarcoma. Once clearly identified, FHI is curable with complete resection.

Keywords: Fibrous hamartoma of infancy, clinical features, pathological features

Introduction

Fibrous hamartoma of infancy (FHI) is a benign, superficial soft tissue tumor that typically presents before the age of two years. FHI is a rare tumor with a 0.02% frequency relative to all benign soft-tissue tumors [1]. The disease was first described and named by Reye in 1956 as a subdermal fibromatous tumor of infancy. In 1965, Enzinger further described its unique characteristics and re-named the lesion as fibrous hamartoma of infancy.

FHI lesions have common histological features, but misdiagnosis is possible because clinical knowledge of FHI is limited, its incidence is rare, and because some of its histologic features are dynamic rather than static. To advance the knowledge of FHI, we currently describe the clinical and pathological features of seventeen diverse cases of FHI examined by light microscopy and immunohistochemistry.

Materials and methods

Clinical tissue specimens were obtained from seventeen diagnosed cases of FHI from Affiliated Hospital, Xuzhou Medical College (Jiangsu Province, China) from 1997 to 2010. Specimens were fixed by 4% formaldehyde, embedded in paraffin, H&E stained and observed under light microscopy. In parallel, immunohistochemistry was performed using the strepavidin peroxidase (SP) method. Primary antibodies included those for vimentin, actin, desmin, SMA, S-100 protein, β -catenin, CD34, bcl-2, NSE and Ki-67 purchased from Fuzhou Maixin Biotechnology Development Company (Fuzhou, China).

Results

Clinical features

Among the seventeen cases, the male to female ratio was approximately 3:1 (13 males, 4 females). Onset ranged from birth to nine years

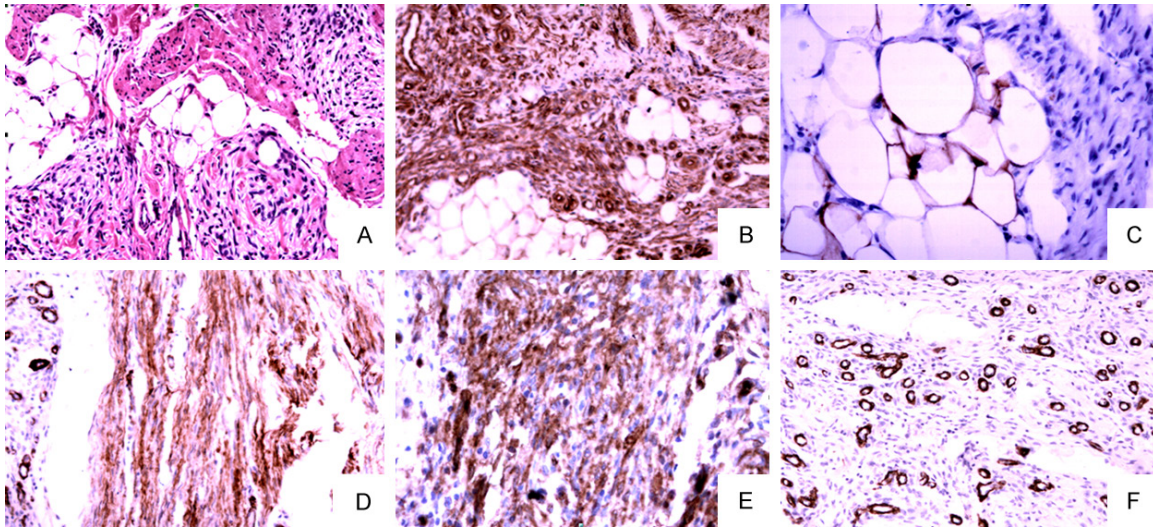


Figure 1. A. Three elements of FHI lesions: fibrous connective tissue; mesenchymal cells; and mature fat. H&E staining, 200 ×. B. Vimentin positive tissue. H&E staining, 400 ×. C. S-100 protein-positive adipose nuclei. H&E staining, 400 ×. D. SMA-positive fibrous tissue. H&E staining, 200 ×. E. CD34-positive undifferentiated mesenchymal tissue. H&E staining, 400 ×. F. SMA marker indicates undifferentiated mesenchymal tissue containing blood vessels. H&E staining, 200 ×.

of age, with an average age of sixteen months. Clinical manifestations included a painless subcutaneous mass with an unclear border and a soft or medium texture. The areas of incidence included: 4 cases in the back of the neck; 3 cases on the upper arm; 2 cases on the buttocks; 2 cases on the head and wrists; 1 case on the axillary; 1 case on the abdomen; 1 case on the scrotum; and 1 case on the knee. B-ultrasound and CT imaging were used to differentiate FHI from others such as lipoma, hemangioma, or fibromatosis, or malignant lesions. Of the six follow-up cases, the time since excision ranged from five months to two years. Five patients were without recurrence, and one patient relapsed after seven months but remained healthy after further excision.

Gross observation

Specimens appeared as gray-red and gray-yellow irregular tissues with a long diameter from 0.8-6 cm. The average diameter was 3 cm with an unclear mass boundary. On average, aspects of the tumors specimens include a pale, sallow color and a medium texture. Some specimens have more fat tissue and a softer texture or more fibrous tissue with a tougher texture.

Microscopic examination

FHI tumors are characterized by three components in varying proportions (**Figure 1A**): (1)

dense fibrous tissue in well-defined bundles of that branch, weave, interweave, and project into fat; (2) primitive mesenchyme arranged in nests, concentric whorls or bands, rich in capillaries with a small distribution of lymphocytes; and (3) mature adipose tissue as islands that are intimately admixed with the first two components. The proportions of these three components varies among specimens. When the age of FHI onset is younger, the tumor contains more undifferentiated mesenchymal components. When the age of FHI tumor onset is older, the lack of undifferentiated mesenchymal components makes the sample more challenging to diagnose, are requires further analysis (different markers) for clarification of other tissue components or further excision and tissue sampling.

Immunohistochemistry

Vimentin is consistently positive in both dense fibrous areas and undifferentiated mesenchymal tissue. Myoblastic differentiation, as indicated by SMA and actin reactivity, is evident in the dense fibrous areas but rarely in the undifferentiated mesenchymal tissue. Vimentin is present in all three tumor components (**Figure 1B**). Mature fat tissue was positive for S-100 protein (**Figure 1C**), fibrous areas were positive for SMA (**Figure 1D**) and actin, and undifferentiated mesenchymal tissue is positive for CD34 (**Figure 1E**) and partially-positive for actin and

SMA. SMA and CD34 markers were present in blood vessels in undifferentiated mesenchymal tissues (**Figure 1F**). Specimens were negative for desmin, NSE, bcl-2, β -catenin and Ki-67.

Discussion

FHI is a rare benign superficial soft tissue tumor that is typically present before the age of two years. Some researchers believe that FHI should be regarded as embryonic dysplasia, or that FHI is a faulty repair response or error during growth and development; these speculations raise doubt about whether FHI is an actual tumor. However, a considerable proportion of FHI lesions are present at birth, and cytogenetic changes in the lesion support that FHI is an authentic tumor [2, 3]. Ultrastructural analysis of FHI lesions confirms the presence of myofibroblasts. The 2002 World Health Organization classification of soft tissue tumors describes FHI tumors as fibroblastic/myofibroblastic cell tumors [1, 4].

FHI typically occurs in infants less than two years of age with an average age of 10 months; onset is rare in older children and does not occur after adolescence. About 25% of patients with FHI lesions had them at birth. The male to female frequency ratio is about 2:1, and there is no demonstrated hereditary link. In the current analysis, the average patient age was slightly older than the average reported age; however, our study sample was intended to portray a broader spectrum of FHI cases.

FHI tumors occur mainly on the armpit area, scapula and upper arm followed by the thigh, groin, buttocks [5], back, forearms, scrotum and the head/face [6-9]. FHI is very rare in the fingers [2], wrist [10] and the lower extremities [7]. Almost all FHI tumors are solitary, moveable nodules with unclear borders and are located in the deep dermis or subcutaneous layer. Occasionally, the tumor involves the fascia or muscle surface, but does not generally involve the deep muscle. FHI lesions can grow rapidly before the age of five followed by a slower growth rate, but the lesions do not stop growing or resolve on their own [9, 11].

FYI tumors are often misdiagnosed as enlarged lymph nodes, lipoma, neurofibroma, hemangioma or dermatofibroma [10]. Some tumors with atypical hair growth on the surface may be mis-

diagnosed as a nerve cell nevus rather than FHI [5]. X-ray, color Doppler ultrasound and MRI may be used to diagnose soft-tissue tumors. X-rays can differentiate normal bone and tissue calcification and color Doppler ultrasound can reveal areas of hyperechogenicity. MRI can reveal multiple lobes within the tumor which is characteristic of lesions with a higher fat content [12, 13]. Despite an occasionally large mass of FMI tumors, the surrounding tissue does not have pressure signs and the adjacent normal structures such as local blood vessels and nerves are not adversely affected [9].

FHI tumors are typically 3-5 cm, but can be up to 15 cm with unclear border and uncapsulated. Its texture and color varies due to the proportion of fat. Efem et al. observed FHI lesion samples from six patients from 6 months old to 10 years old. They postulated that older FHI lesions show some capsule formation [9].

The histological structures observed here are characteristic for FHI lesions with their required three elements: staggered dense fiber bundles, formed by the spindle-shaped fibroblasts, myofibroblasts and collagen fibers; mesenchymal cells containing myxoid matrix or an asterism of small round-shaped primitive mesenchymal cells; non-mitotic mature adipose tissue interspersed between the other two structural elements.

Immunophenotyping data also supports previous observations. Three FHI components expressed vimentin, mature fat cells expressed S-100 protein, and spindle cells and primitive mesenchymal cells expressed actin and SMA, suggesting that the myofibroblasts were differentiated. As with other studies, FHI lesions were negative for desmin. Immature mesenchymal cells also expressed CD34 and SMA. The presence of CD34 indicated that tumors were well-vascularized [1-3, 7, 8, 12, 14].

Collectively, FHI lesions have uniform pathological features and are easier to diagnose closer to lesion onset. However, if the composition of the tumor changes over time, it is often confused with other lesions and/or diseases. The diseases discussed next may be confused with FHI.

When FHI onset is at an older age in children and adolescents, lesions are more common on

their hands and feet. Calcifying aponeurotic fibromas may appear as nodules or as an ill-defined infiltrating mass in subcutaneous tissue. However, histologic analysis reveals diffuse fibroblastic growth with spotty calcification and scattered osteoclast-like giant cells, features that are unique from FHI lesions.

When the percentage of fat in FHI lesions is high, the lesion may often misdiagnosed as fibrous lipoma, especially when there is a low count or no count of immature mesenchymal cells. However, unlike FHI, fibrolipoma has clear boundary and can be lobulated due to a mucus-like matrix.

Infant fibromatosis has an invasive character and is difficult to completely resect, easily recurs, and occurs deeper in tissues, mainly in striated muscle. Microscopic observation reveals differentiated fibroblasts and their diffuse infiltration among the cells and fibers of striated muscle. These features are distinct from FHI lesions.

FHI lesions that are rich in undifferentiated mesenchymal, tissue, especially lesions excised from the head and neck, can be confused with embryonal rhabdomyosarcoma. However, embryonal rhabdomyosarcoma is a highly malignant tumor of striated muscle derived from primitive mesenchymal cells. These lesions show alternating loosely cellular areas with myxoid stroma and densely cellular areas with spindle cells. Immunohistochemistry can also distinguish FHI from embryonal rhabdomyosarcoma; the latter is positive for myoglobin, myosin, myogenin and other markers not characteristic of FHI.

FHI tumors are benign and rarely relapse with complete initial excision. More than 16% of recurrence is due to incomplete initial excision [10], but this recurrence is still curable with reoperation [7, 9]. Delayed operation will not increase the risk of malignant transformation. Also, delayed excision will not harm the ability to excise the tumor. Compared to a younger tumor that exhibits an unclear mass boundary, a more established tumor is more prone to encapsulation which facilitates successful excision [9].

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yibing Wang, Department of Burn and Plastic Surgery, Huai'an First People's Hospital, Nanjing Medical University, 6 Beijing Road West, Huai'an 223300, Jiangsu Province, China. E-mail: wangyb1228@163.com

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