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A Clinical and Histopathological Analysis of 147 Cases of Dermatofibroma (Benign Fibrous Histiocytoma)

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Abstract

Background: Dermatofibroma usually occurs on the extremities or trunk as a common and benign skin tumor. The identification of typical dermatofibroma is uncomplicated, although it can be challenge due to its wide range of presentations and histological variations. **Objective:** This study was undertaken to evaluate the clinical and histopathological characteristics of 147 Cases of Dermatofibroma. **Methods:** This is a retrospective study of 147 biopsy specimens of 124 patients who were diagnosed with dermatofibroma in the Department of Dermatology and the Department of Pathology at the Seventh Affiliated Hospital of Sun Yat-sen University between January 2009 and April 2024. All case were retrieved from the saved medical records. **Results:** Ages of the 124 Dermatofibroma-affected individuals ranged from 11 to 61 years with a male-to-female ratio of 1:1.7. Over 80% of the case occurred between the ages of 20 and 49 years, 61.9% of the lesions were found on the extremities. The duration of the cases varied from 17 days to 30 years and half of lesions (58.2%) persisted for less than two years. Over 60% of the lesions were found on the extremities. The diameter of the tumors ranged between 0.3 cm and 5 cm, with most tumors measuring less than or equal to 2 cm (85.00%). Cutaneous masses or dermatofibroma was the most common clinical diagnosis. Most tumors (79.6%) were asymptomatic. Cutaneous masses or dermatofibroma was the most common clinical diagnosis. Prior to the surgical procedure, 57 cases were suspected to be "DF", 55 cases were suspected to be "cutaneous masses". Immunohistochemical staining revealed positive expression of SMA, while the negative rate of CD34 was found to be 66.67%. No diffuse CD34 positivity was observed in all tumors. **Conclusion:** Variations in clinical features, pathological manifestations, and immunohistochemical results of DF pose challenges for accurate diagnosis. A comprehensive understanding of its

clinical and pathological characteristics is crucial for precise identification. Incorporating immunohistochemical analysis can help prevent misdiagnosis.

Keywords

Dermatofibroma, Benign Fibrous Histiocytoma, Clinical Feature, Histopathological Characteristics

1. Introduction

Dermatofibroma, also known as benign fibrous histiocytoma, is one of the most common soft tissue lesions due to the proliferation of benign spindle cells within the dermis [1]. Dermatofibromas often occur on the extremities with an overall predominance of females [2]. The lesion usually presents as slow-growing, pink or tan/brown to black, firm, dermal papules. They are usually less than 2 cm in diameter [3]. The management of this disease primarily involves surgical intervention and conservative measures. The diagnosis of typical dermatofibroma is straightforward, yet challenging due to its diverse manifestations, varied histological variants.

Therefore, we analyzed a series of 147 cases of dermatofibroma from the Seventh Affiliated Hospital of Sun Yat-sen University. The present study retrospectively examined the clinical and pathological data to establish a foundation for clinical diagnosis and treatment.

2. Materials

There are 147 biopsy specimens of 124 patients who were diagnosed with dermatofibroma in the Department of Dermatology at the Seventh Affiliated Hospital of Sun Yat-Sen University between January 2019 and April 2024.

3. Methods

3.1. Clinical Features

The clinical and pathological data of all patients were collected, including age, gender, duration, size, count of lesions, the site of the disease, clinical diagnosis, immunohistochemistry results and other relevant indicators.

3.2. Histopathologic Features

124 patients (with a total of 147 lesions) underwent surgical resection at our hospital. All resected lesions were subjected to routine pathological examination. Specimens were fixed in formalin, embedded in paraffin, and sectioned at a thickness of 4 μm for hematoxylin-eosin staining. The immunohistochemical results, including CD68, smooth muscle actin (SMA), S-100 protein, Ki-67, epithelial membrane antigen (EMA), desmin, CD34, SOX-10 and Actin, were utilized to aid in the differential diagnosis when skin fibroma was suspected.

3.3. Statistical Processing

All data were processed by Microsoft Excel 2021 and SPSS 24.0 software and descriptive statistics were adopted.

4. Results

4.1. Clinical Findings

4.1.1. Age and Gender Distribution

The distribution of gender and age is presented in Table 1. Among the 124 patients with dermatofibroma with ages ranged 11 to 61, there were 46 males and 78 females, resulting in a male-to-female ratio of 1:1.7. The mean age at onset was (36.01 ± 9.82) years old, with a median age of 35 years old. Over 80% of the cases occurred between the ages of 20 and 49 years. The highest incidence was observed in the age group of 30 - 39 years (46.8%).

Table 1. Age and gender distribution of 124 patients with dermatofibroma.

Age	Gender		Total (%)
	Male (%)	Female (%)	
10 - 19	1 (0.8)	3 (2.4)	4 (3.2)
20 - 29	11(8.9)	14 (11.3)	25 (20.2)
30 - 39	22(17.7)	36 (29.0)	58 (46.8)
40 - 49	11 (8.9)	12 (9.7)	23 (18.5)
50 - 59	1 (0.8)	12 (9.7)	13 (10.5)
60 - 69	0 (0)	1 (0.8)	1 (0.8)
Total (%)	46 (37.1)	78 (62.9)	124 (100)

4.1.2. The Duration, Medical History and Presenting Symptoms

The duration of the lesions varied from 17 days to 30 years. Among the tumors observed, 71 (58.2%) persisted for less than two years while 51 tumors (41.8%) persisted for more than two years.

Among the 124 patients, one case presented a clear history of "insect bite", while another case had a documented record of repeated scratching. Most tumors (117 cases) were asymptomatic, with only 15 cases reporting pain, including 2 cases of tenderness, 1 case of tingling, and another case of pain with swelling. Additionally, there were 13 cases presenting pruritus, 2 cases experiencing both pain and pruritus, as well as 2 cases with instances of localized abnormal sensations.

4.1.3. Size and Count of the Lesions

The examination revealed a range in tumor size from 0.3 to 5 cm, with most tumors being smaller than 2 cm (117/147, 85.2%). The majority of cases (110/147, 88.7%) presented with a solitary lesion, while a minority (11.3%) exhibited multiple lesions, including 9 cases with 2 lesions, 3 cases with 3 lesions, 1 case with 4 lesions, and 1 case with 6 lesions.

4.1.4. Distribution of the Lesions

Over 60% of the lesions were found on the extremities (Figure 1(A) and Figure

1(B)). As depicted in Table 2, there was a gradual decline in the incidence of lesions in the lower limbs, upper limbs, shoulder, back, head and face, chest, abdomen and neck. No dermatofibroma was observed on the scalp in our study.

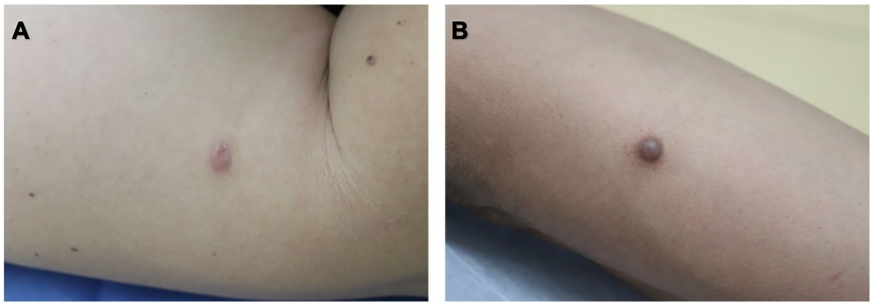

Figure 1. Clinical presentations of dermatofibroma. (A) Case 103, a 1.3 cm * 0.9 cm pruritic, pink nodule on the right arm. (B) Case 138, a 1 cm diameter brown, dome-shaped firm nodule on the left arm.

Table 2. Distribution of 147 cases with dermatofibroma.

Location	Set	n (%)	Total (%)
Head and Face	Face	4 (2.7)	5 (3.4)
	Ear	1 (0.7)	
Neck	Neck	4 (2.7)	4 (2.7)
Trunk	Chest	8 (5.4)	47 (32.0)
	Abdomen	3 (2.0)	
	Shoulder	11 (7.5)	
	Back	11 (7.5)	
	Waist	1 (0.7)	
	Buttocks	12 (8.2)	
Extremities	Arm	27 (18.3)	91 (61.9)
	Hand	1 (0.7)	
	Leg	61 (41.5)	
	Foot	3 (2.0)	
Total (%)		124 (100)	124 (100)

4.1.5. Clinical Diagnosis of the Lesions

57 lesions (38.8%) were diagnosed as dermatofibroma (DF), while 90 lesions (61.2%) were identified as other diseases or distinguished from other conditions. Among those without a preoperative diagnosis, 55 cases (37.4%) were initially classified as cutaneous masses, whereas the remaining cases were differentiated from dermatofibrosarcoma protuberans, keloid, pigmented nevus, skin cysts (epidermoid cyst and sebaceous cyst), sebaceous nevus, subcutaneous lipoma, steatocystoma multiplex and seborrheic keratosis.

4.2. Histopathologic features

4.2.1. Pathological Presentation

General Observation: The tumor is located in the dermis, with some skin damage invading the subcutaneous tissue. It is firm in texture and the cut surface is often

brown or gray or red in color.

Mirrored View: Spindle-shaped fibroblasts and myofibroblasts are observed in the dermis layer of the skin, arranged in an interwoven or striated pattern. The cells show small cellular heterogeneity and no evident nuclear division. Collagen bundles can be seen forming at the periphery (**Figure 2(A)** and **Figure 2(B)**). Scattered among the spindle cells are foamy tissue cells, multinucleated giant cells, and thin-walled blood vessels. Focal infiltration of chronic inflammatory cells, such as lymphocytes and plasma cells, and deposition of hemosiderin, are commonly observed.

4.2.2. Immunohistochemistry

This study included 19 cases of immunohistochemical examination. Specific findings were as follows: the positivity rate of SMA staining was 100% (8/8); The negativity rate of Desmin staining was 55.5% (5/9), with 2 positive cases, and individual and focal positivity each with 1 case. The negativity rate of CD34 staining was 66.67% (9/15), with a positivity rate of 33.33% (5/15), including 1 case with margin positivity, 1 case with partial positivity, 1 case with focal positivity, 1 case with positivity in endothelial cells (**Figure 2(C)**), and 1 case with positivity in spindle cells. No diffuse CD34 positivity was observed in all tumors. Ki-67 staining was less than 5%, with 60% (3/5) having 1%. The positive rate of CD68 staining was 34.8% (11/13). 4 cases were positive, 2 cases were partially positive, 1 case was weakly positive, 2 cases were positive in tumor cells, and 2 cases were positive in tissue cells. All cases showed variable amounts of CD68-positive tissue cells (**Figure 2(D)**). The negativity rate of S-100 protein staining was 100% (5/5). The negativity rate of Actin staining was 100% (3/3). The negativity rates of EMA and SOX-10 staining were 100.00% (1/1; 2/2, respectively).

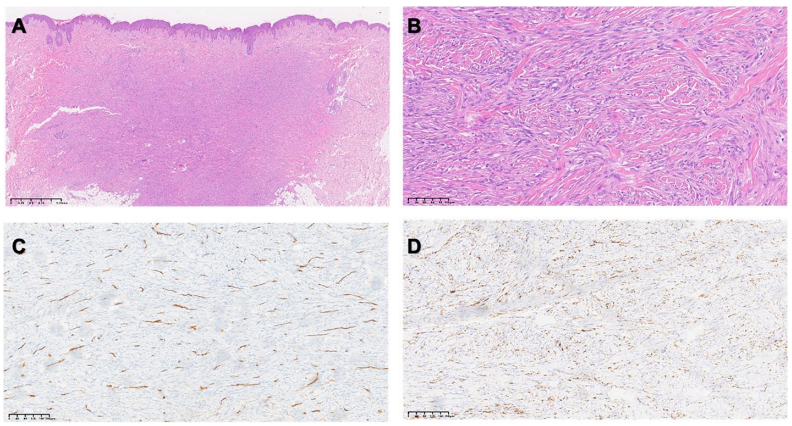

Figure 2. Histopathological view. (A) The tumor is located within the dermis layer of the skin, with a thin layer of connective tissue separating it from the epidermis, as observed under low magnification. Magnification × 4, HE. (B) The tumor is composed of spindle-shaped fibroblast-like cells and tissue cell-like cells with unequal proportions. The tumor cells are interlaced with coarse collagen fibers, and the cells show no obvious dysplasia. Magnification × 20, HE. (C) Tumor cells are CD34 negative and vascular endothelial cells are positive. Magnification × 10. IHC was performed using standard EnVision method. (D) Tumor intratumoral tissue cells CD68 positive. Magnification × 10. IHC was performed using standard EnVision method.

5. Discussion

Dermatofibroma (DF), known as fibrous histiocytoma (FH), is the most frequent fibrohistiocytic skin tumor. Accounts for approximately 3% of the skin lesion specimens received by a single dermatopathology laboratory [1], This neoplasm appears most often in middle age, on the extremities or trunk, rarely on the head or on fingers and toes [4]. They most commonly occur on the legs, elbows, or trunk of middle-aged women. They can vary in color from violet to dark and may also be flesh-colored [5] [6]. Local trauma (e.g., an insect bite) has occasionally been reported as a precipitating factor. Local trauma (e.g. insect bite, vaccination or trauma) [7] has been reported as a precipitating factor.

Dermatofibroma usually presents as a slowly growing, firm dermal nodule, which is generally solid and slightly raised, ranging in diameter from a few millimeters to 1 cm, rarely exceeding 2 cm. During palpation, skin lesions can be found connected to the subcutaneous fatty tissue. When the skin lesion is lightly pinched, the tumor often partially sinks in, which is referred to as a dimple sign.

In this study, the gender ratio was 1:1.7, the median age of onset was 35 years old. Most of the cases occurred between the ages of 20 and 49 years. The lesions located in the limbs, especially in the lower limbs, which is consistent with the literature reports [2]. However, unlike the previous reports, the most common diameter in our study was 1 - 2 cm (51.0%). Indeed, some prior Korean studies have reported the most common diameter to be 1 - 5 mm [2].

Currently, it is unclear whether skin fibromas are caused by reactive inflammatory processes due to mechanical stimuli or whether they are true tumor. Local trauma, such as insect bites, has occasionally been reported as a triggering factor. Some believe that skin fibromas are a reaction of the skin to injury, inflammation, and repair, while others believe they are benign tumors that originate from skin fibroblast cells [5] [8]. Although the controversy regarding the reactivity or neoplastic nature of dermatofibroma has not been fully resolved, most evidence in recent years has been more supportive of a neoplastic process [8].

This disease can occur naturally or have a history of insect bites or trauma. A large part of the cases is related to minor local injuries, especially insect bites. Among the patients in this group, one case had a history of insect bites, and another case appeared after repeated scratching, possibly due to subjective unawareness of the minor trauma.

Fibroma skin lesions are usually solitary [2], but about 10% of individuals have multiple skin lesions [9]. Multiple DF is commonly seen in patients with autoimmune diseases such as systemic lupus erythematosus (SLE), Sjogren's syndrome [10], *Lupus profundus* [11], dermatomyositis, as well as in immunodeficient patients with acquired immunodeficiency syndrome and patients during immunosuppressive treatment [12] [13]. It is also observed during pregnancy [14]. However, more than 2 lesions were present in 11.3% of the patients in our study, but none of the patients with multiple lesions had a related history.

Dermatofibroma is also known as benign fibrous histiocytoma (BFH) [3].

Benign fibrous histiocytoma is a type of benign mesenchymal tumor that occurs in the dermis. It is composed of undifferentiated mesenchymal cells or fibroblasts arranged in short intersecting, storiform, or fascicular patterns. The lesion often contains varying amounts of foam-like tissue cells, hemophagocytic cells, multinucleated giant cells/reed-sternberg cells, and chronic inflammatory cells. The key distinction between malignant fibrous histiocytoma and benign fibrous histiocytoma lies in the tumor's capacity for invasive growth and the presence of evident cellular atypia.

According to the clinicopathological classification, there are also some rare variants of dermatofibroma, including cellular dermatofibroma, epithelial dermatofibroma, and aneurysm/hemosiderin dermatofibroma. These atypical subtypes (e.g., cellular, epithelioid, aneurysmal) may exhibit local recurrence following surgical resection [15] [16]. Additionally, there are lipid-containing dermatofibromas, atypical dermatofibromas (dermatofibromas with monster cells), metastatic dermatofibromas and other even rarer types. Metastatic benign dermatofibroma is an extremely uncommon variant that can display clinical and pathological features resembling those of cellular-, aneurysmal-, or atypical-type dermatofibromas [17]-[19]. In a case series involving 16 patients with metastases reported in the literature review study mentioned earlier [17], lung involvement was observed along with lymph nodes infiltration as well as soft tissue and liver involvement, six patients succumbed to the disease, unfortunately. The factors, including large size, high cellularity, aneurysmal changes, marked cellular pleomorphism, high mitotic activity, tumor necrosis, and repeated local recurrences or metastatic dissemination, indicate a significant risk of metastatic dissemination [16].

Dermatofibroma is usually diagnosed relatively easily, with clinical presentation and tissue pathology being the main methods for diagnosing dermatofibroma. Immunohistochemical staining may be performed if necessary to improve the diagnostic rate.

The immunohistochemical results of DF have specificity. All patients examined with immunohistochemistry show positive staining for SMA. The positive rate for CD68 is 30.8%. The negative rates for CD34, Actin and S-100 protein staining are 66.67% and 100%, respectively. No diffuse CD34 positivity was observed in all tumors, which are consistent with previous literature reports.

Clinical features, pathological manifestations, and immunohistochemical results vary among different subtypes of DF, which poses certain challenges for clinicians and pathologists in diagnosing the disease. Furthermore, as one of the common skin histopathological lesions, dermatofibroma often needs to be differentiated from other spindle cell tumors.

Including:

1) Nodular fasciitis

Nodular fasciitis typically occurs during the third or fourth decade of life. Most cases manifest as a solitary, rapidly proliferating tumor that can attain a diameter of 2 - 3 cm within a span of 2 - 6 weeks [20]. In terms of frequency, the most

prevalent sites for these tumors are the upper limbs (39% - 54%), trunk (15% - 20%), lower limbs (16% - 18%), and head and neck region (7% - 20%) [21]. As a type of benign fibroblastic/myofibroblastic tumor, the majority of cases occur in the subcutaneous superficial fascia, while some cases can be located in deep muscle tissue, and very few occur in the dermis. The tumor cells are relatively uniform and mainly composed of proliferating spindle-shaped myofibroblasts. The tumor cells are loosely arranged and can often show clefts or cystic-like structures, demonstrating a characteristic feathery or culture-like growth pattern. Extravasation of red blood cells may be present in the stroma. Immunohistochemical markers show diffuse expression of A-SMA in spindle cells, and FISH testing can reveal a USP6 gene translocation [22] [23].

2) Atypical fibroxanthoma

It is a special subtype of fibrous tissue tumor, characterized by the scattered distribution of large, deeply stained nuclei, irregular nuclear shapes, pleomorphic, spindle-shaped or bizarre cells in the background of classic fibrous tissue tumor under the microscope. The proportion of these pleomorphic regions varies depending on the case. Nuclear mitoses are often seen in the tumor, ranging from 1 to 15/10 high-power fields (HPF), with an average of 3 to 4/10 HPF. Pathologic mitoses can be seen in some cases. A few cases may also have features of aneurysmal fibrous histiocytoma morphology.

3) Mixed neurilemmoma/neurofibroma

Neurofibroma primarily occurs in adults, with extraneural (soft tissue) lesion commonly presenting as subcutaneous nodules affecting the limbs or trunk of middle-aged adults [24]. Yet intraneural neurofibroma typically manifest in the peripheral nerve trunks of young adults' upper limbs [25]. Due to their location within the nerve, patients may experience local neurological symptoms and muscle atrophy. Mixed neurilemmoma are mainly composed of fat spindle and slender spindle cells mixed together, locally, there can be slightly enlarged, deeply stained Schwann cells. The characteristic immunohistochemical features of neurofibroma [26] encompass diffuse expression of EMA in the slender spindle cells (perineurium cells), along with a combination of Schwann cells expressing S-100, SOX10, GLUT1.

4) Juvenile xanthogranuloma

Juvenile xanthogranuloma is the most prevalent form of non-Langerhans cell histiocytosis primarily, which affects infants and young children, although adults and the elderly can also be affected [27]. Cutaneous lesions are commonly found on the face, neck, and upper trunk, with potential involvement of internal organs and other body systems. Clinically, it typically presents as solitary or multiple yellow-red papules or nodules localized to the skin. It is composed of multiple sheets of mononuclear-like tissue cells and scattered Langerhans giant cells under a microscope. It primarily expresses tissue cell markers. In the advanced stages of the disease, there may be a presence of numerous spindle-shaped cells, which morphologically resemble fibrous tissue cell tumors.

5) Giant cell fibroblastoma

The tumor mainly occurs in the dermis and is composed of short spindle-shaped cells that grow diffusely and infiltratively. There is often a narrow acellular zone between the superficial part of the tumor and the covering epidermis, and it can also be adjacent to the epidermis. The deep part of the tumor often infiltrates into the subcutaneous adipose tissue, and tumor cells infiltrate along the interlobular septa of the fat, forming a characteristic honeycomb or lace-like infiltrating image. The tumor cells are often arranged in a fascicular pattern, with moderate cell density, and the number of nuclear divisions varies (0-10/10HPF) among different cases; and the tumor cells diffusely express CD34, difficult cases can undergo FISH testing, which shows PDGFB gene rearrangement [28].

6) Dermatofibrosarcoma protuberans (DFSP)

Dermatofibrosarcoma protuberans is a rare mesenchymal tumor, accounting for only 0.1% of all skin tumors [29]. It typically occurs in individuals aged between 30 and 50 years, with the trunk being the most common location, followed by the upper limbs [30]. DFSP can be triggered by exogenous factors such as parasitic diseases, hemangiomatous lesions, previous trauma, burns, or surgical scars [31], which usually have an insidious onset. Clinically, DFSP presents as asymptomatic violaceous nodules or plaques that grow slowly over time [32]. Histologically, these tumors are primarily located in the dermis and consist of short spindle cells exhibiting diffusely infiltrative growth. There is often a narrow acellular band separating the superficial part of the tumor from the overlying epidermis or closely associated with it. The tumor cells frequently invade along interlobular septa, forming a characteristic honeycomb-like or lace-like infiltration pattern. They exhibit storiform arrangement with moderate cell density and variable mitotic count ranging from 0 to 10 per high-power field (HPF). Additionally, immunohistochemical staining shows diffuse expression of CD34 in tumor cells while fluorescence in situ hybridization (FISH) testing can be performed for cases where diagnosis is challenging. The test reveals PDGFB gene translocation indicative of DFSP subtype [28]. Local recurrence for DFSP is reported at 13.7%, while metastasis and mortality rates stand at 1.1% and 0.8%, respectively. Fibrosarcoma transformation, could observed in approximately 3% - 20% of cases, lead to increased risks of local recurrence (29%), metastasis (14.4%), and death (14.7%) compared to typical DFSP cases alone [33]. Due to its significant subclinical expansion potential and destructive nature locally, early diagnosis and treatment play crucial roles.

Although spontaneous resolution is rarely reported, dermatofibromas are usually benign, static, asymptomatic lesions that exhibit little to no growth. No treatment is typically necessary for asymptomatic, stable, common dermatofibromas. Surgical excision is not recommended for common dermatofibromas due to the potential for a scar that may be more noticeable than the original lesion. For patients seeking treatment for cosmetic concerns, cryotherapy using liquid nitrogen, as a preferable alternative to surgical excision, is recommended. Cryotherapy has

demonstrated some success in treating protruding lesions, resulting in either resolution or flattening of the lesion and yielding satisfactory cosmetic outcomes [34] [35]. Atypical variants (e.g., cellular, epithelioid, aneurysmal) may recur locally after surgical excision and, in exceptionally rare cases, metastasize. Therefore, complete resection with a clear margin and regular follow-up should be performed in such atypical variants.

Summing up, the clinical and pathological manifestations of skin fibromas are relatively typical, but in the clinical diagnosis and treatment process, they need to be distinguished from other histologically similar lesions. Mastering their clinical and pathological features is the key to diagnosis. Combining immunohistochemistry testing and molecular analysis can avoid misdiagnosis and improve diagnostic accuracy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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