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A Clinical and Histopathological Analysis of 45 Cases of Cutaneous Neurilemmoma (Schwannomas)

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Abstract

Background: Neurilemmoma (Schwannomas) are the most common peripheral nerve tumors and usually do not undergo malignant transformation, except in some atypical cases. Additionally, the imaging appearance of schwannomas resembles that of neurofibromas, making it difficult to distinguish between the two. Therefore, the clinical diagnosis and treatment of schwannomas may face certain challenges. The management and prognosis of neurilemmomas differ from their malignant counterparts, making correct diagnosis important. **Objective:** This study evaluates the clinical and histopathological characteristics of 45 cases of neurilemmoma. **Methods:** This retrospective study involves 45 cases diagnosed with cutaneous neurilemmoma at the Seventh Affiliated Hospital of Sun Yat-sen University between April 2020 and September 2024. All cases were retrieved from medical records. **Results:** The age range of the 45 patients was 23 to 73 years, with a male to female ratio of 1.6:1. Over half the cases occurred in individuals aged 30 to 59, with most lesions found in the extremities, predominantly in the lower limbs. Disease duration varied from 7 days to 20 years. All tumors were solitary, with diameters ranging from 0.8 cm to 8 cm. Most tumors (33/45, 73.33%) were asymptomatic, though some patients experienced symptoms like pain and numbness. Mass was the most common clinical diagnosis (33/45, 73.33%). Five patients had suspected neurilemmomas prior to surgery. Immunohistochemical staining revealed all positive results for S-100 and SOX-10 markers, while EMA staining showed a negative rate of 93.33%. Most Ki-67 values (19/23, 82.6%) were less than or equal to 5%. **Conclusion:** The diversity of clinical features, pathological manifestations, and immunohistochemical results of schwannoma poses a challenge to accurate diagnosis. A comprehensive understanding of its clinical and pathological characteristics is essential

for accurate diagnosis, and when combined with immunohistochemical analysis, it helps avoid misdiagnosis.

Keywords

Neurilemmoma, Schwannomas, Cutaneous Neurilemmoma, Clinical Feature, Histopathological Characteristics

1. Introduction

Neurilemmoma, also known as schwannoma, is a benign encapsulated peripheral nerve sheath tumor composed of Antoni A and loose myxoid reticular areas arranged in an orderly alternating pattern. Immunohistochemically, the tumor cells exhibit Schwannian cell differentiation and ultrastructural features characteristic of Schwannian cells. The majority of schwannomas are sporadic (90%) [1]. Schwannomas can occur at any age but are most commonly observed in individuals aged 40 - 60, with no significant gender difference [2]. However, central nervous system schwannomas are more prevalent in females, with a female-to-male ratio of approximately 2:1. They typically manifest in the head and neck region and flexion areas of the limbs. Tumors in the mediastinum, retroperitoneum, and pelvic cavity tend to be larger. Most cases present as solitary masses that grow slowly and generally remain asymptomatic. However, some cases may exhibit accompanying pain or other symptoms. Cutaneous schwannomas mostly appear small without direct association with underlying nerves.

Therefore, we analyzed a series of 45 cases of neurilemmoma from the Seventh Affiliated Hospital of Sun Yat-sen University. This study retrospectively examined the clinical and pathological data to establish a foundation for clinical diagnosis and treatment.

2. Materials and Methods

All patients who underwent surgical resection and histology between April 2020 and September 2024 and were diagnosed with neurilemmoma by dermatopathologists were identified by reviewing the medical database of the dermatopathology division of the hospital. The tumors occurred in the bone, gastrointestinal tract, pancreas, liver, retroperitoneum, mediastinum, organs, nasopharynx, larynx, thyroid gland, adrenal gland, lymph nodes, and other sites.

We included 45 patients who 1) were diagnosed with schwannomas, 2) had tumors occurring on the body surface, and 3) had skin signs.

2.1. Clinical Features

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

2.2. Histopathologic Features

All resected lesions underwent routine pathological examination. Immunohistochemical results were used for differential diagnosis. The expression of S-100 protein, particularly its location, and CD34, which indicates the fibroblast component, can be used to distinguish neurofibroma. GFAP helps differentiate glial tumors such as astrocytoma and oligodendroglioma. Smooth muscle actin (SMA) and Desmin can help discriminate leiomyoma. Vimentin is used to identify skin fibroma. EMA is an epithelial differentiation marker used to identify tumors of epithelial origin. The Ki-67 index evaluated the proliferative activity of tumor cells. Other immunohistochemical results, including epithelial membrane antigen (EMA), CD68, CD47, STAT6, ERG, Actin, PGP9.5, and CK, aided in the differential diagnosis.

2.3. Statistical Processing

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

3. Results

3.1. Clinical Findings

3.1.1. Age and Gender Distribution

Age and gender distribution is presented in Figure 1. Among the 45 patients with schwannoma, aged 23 to 73, there were 28 males and 17 females, resulting in a male-to-female ratio of 1.6:1. The mean age at onset was 46.0 ± 12.1 years, with a median age of 45 years. The highest proportion (24.4%) was observed among individuals aged 40 - 49. The age of onset was predominantly concentrated in the range of 30 - 59 years (31/45, 68.8%).

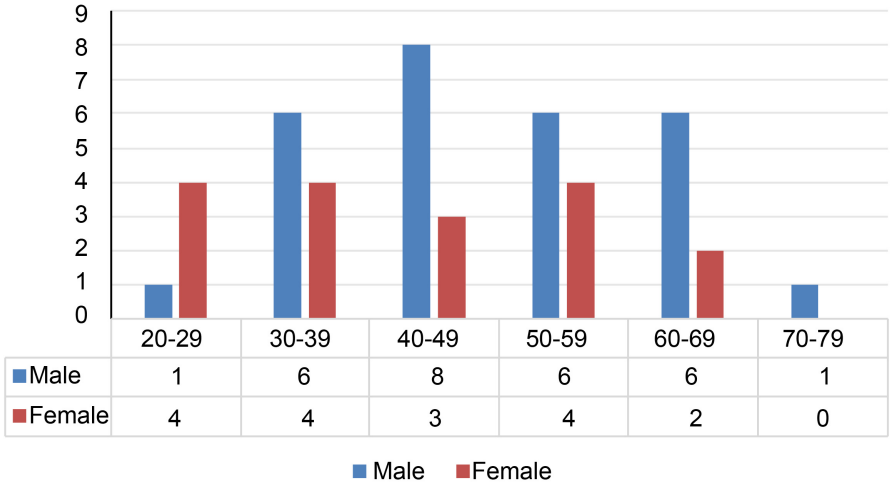

Figure 1. Age and gender distribution of 45 patients with neurilemmoma.

3.1.2. The Duration and Presenting Symptoms

Most tumors (33/45, 73.33%) were asymptomatic, while 12 cases (26.7%)

experienced pain, including 6 with tenderness and 4 with soreness. Eight cases had accompanying symptoms: one facial tumor with intermittent needle-like pain and limited mouth opening; one buttock tumor aggravated by prolonged sitting and driving, causing pain radiating from the buttock to the thigh, sometimes with numbness; one with ipsilateral upper limb numbness; one with ipsilateral upper limb convulsive pain; one with ipsilateral muscle weakness; and one with numbness and tingling in the finger where the tumor was located. Additionally, there was slight limitation in elbow joint extension in one case, and another reported finger pain at the affected site.

3.1.3. Size and Count of the Lesions

All observed tumors were solitary, with lesion diameters ranging from 0.8 cm to 8 cm.

3.1.4. Distribution of the Lesions

As depicted in Table 1 and Figure 2, the lesions were predominantly observed on the extremities in 14 cases (51.1%), followed by the neck in 10 cases (22.2%), the face in 5 cases (11.1%), the trunk (Figure 3(A)) in 5 cases (11.1%) and the scalp (Figure 3(B)) in 2 cases (4.4%).

Table 1. Distribution of 45 cases with neurilemmoma.

Location	Set	n (%)	Total (%)
Scalp	scalp	2 (4.4)	2 (4.4)
Face	forehead	1 (2.2)	5 (11.1)
	orbit	1 (2.2)	
	eyelid	1 (2.2)	
	cheek	1 (2.2)	
	lip	1 (2.2)	
Neck	neck	10 (22.2)	10 (22.2)
Trunk	buttocks	3 (6.7)	5 (11.1)
	perineum	1 (2.2)	
	shoulder	1 (2.2)	
Extremities	hand	2 (4.4)	23 (51.1)
	arm	8 (17.8)	
	leg	11 (24.4)	
	foot	2 (4.4)	
Total (%)		45 (100)	45 (100)

3.1.5. Clinical Diagnosis of the Lesions

Clinical diagnosis revealed that mass was present in 33 patients (73.33%). The remaining cases were considered as neurogenic tumors (3 cases), dermatofibroma (1 case), sebaceous cyst (1 case), ganglion cyst (1 case), and hemangioma (1 case), with 5 patients diagnosed with schwannoma.

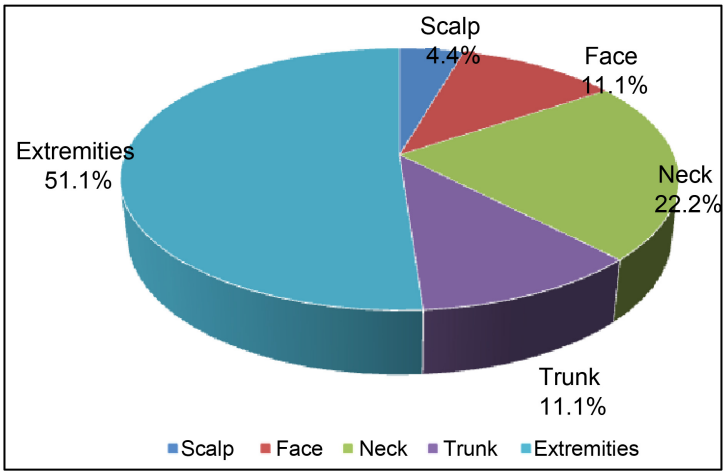

Figure 2. Distribution of 45 case with neurilemmoma.

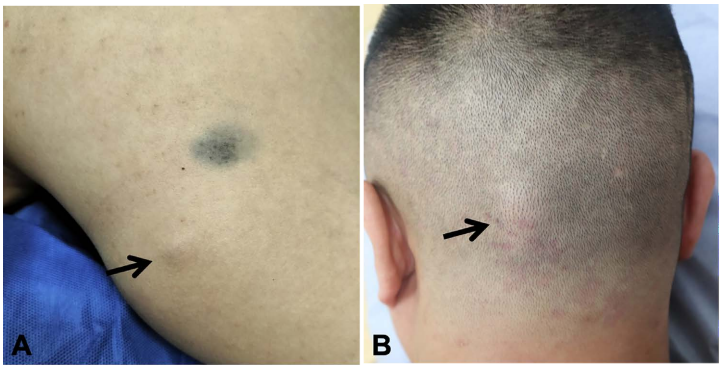

Figure 3. Clinical presentations of neurilemmoma. (A) Case 44, a 0.9 cm subcutaneous mass was present on the left shoulder; (B) Case 19, a 2.5 cm × 2.0 cm × 1.5 cm subcutaneous mass of scalp.

3.2. Histopathologic Features

3.2.1. Pathological Presentation

Microscopically, the tumor exhibited well-defined margins with an intact fibrous capsule (Figure 4(A)). The tumor cells displayed a spindle-shaped or wavy morphology and were organized in fascicles or staggered patterns. In certain regions, the cells were densely arranged, while in others, they appeared sparsely distributed, with oval or fusiform nuclei. Within the fascicular region, the spindle-shaped or short spindle-shaped tumor cells formed palisades or fascicles (Figure 4(B)), exhibiting minimal cellular atypia and an absence of mitotic figures.

3.2.2. Immunohistochemistry

This study involved immunohistochemical examination of 28 cases with the following results: The positive rate of S100 staining was 100% (Figure 4(C)); the positive rate of SOX-10 staining was 100% (21/21) (Figure 4(D)); 5 cases were stained for GFAP, with positive results in 3 cases (2 cases showing focal+ staining, 1 case showing patchy+ staining), and 2 cases showing negative results; the positive rate of Vimentin staining was 100% (3/3). The negative rate of SMA staining

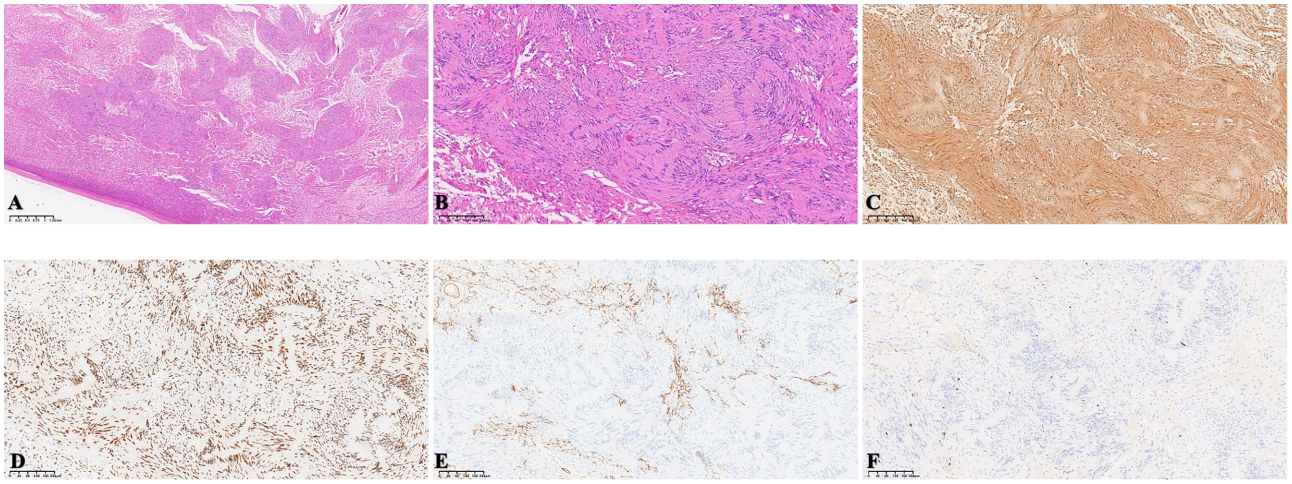

Figure 4. Histopathological view. (A) The boundaries of the tumor are well-defined, with a complete fibrous envelope visible; alternating fascicular and reticular zones are seen within the tumor. (B) Spindle-shaped or short spindle-shaped tumor cells in the fascicular zone are arranged in a fenestrated or fascicular pattern, with little cellular anisotropy and no nuclear schizophrenic image. (C) Diffuse expression of S-100 by tumor cells. (D) Diffuse expression of SOX-10 by tumor cells. (E) Negative expression of CD34 in tumor cells. (F) Tumor cell proliferation index less than 1%.

was 93.33% (14/15); the negative rate of CD34 staining was 95.8% (23/24) (**Figure 4(E)**), with 1 case showing partial weak positivity; the negative rate of EMA staining was 93.33% (14/15), with 1 case showing focal positive staining; the negative rate of CD68 staining was 100% (3/3); the negative rate of CD47 staining was 33.3% (1/3), with 2 cases showing partial positivity; the negative rate of Desmin staining was 100% (9/9); the negative rate of STAT6 staining was 100% (4/4); the negative rate of Actin staining was 100% (2/2); PGP9.5 was positive in 2 cases, with 1 case showing partial positivity; CK was negative in 100% (2/2) of cases; ERG was negative in 100% (2/2) of cases. Ki-67 staining was positive in 23 cases, with most cases showing less than 5% (**Figure 4(F)**), and 4 cases (4/23, 17.4%) showing 10%.

4. Discussion

The schwannoma is a prevalent, indolent neoplasm that arises from the Schwann cells surrounding peripheral nerves and exhibits well-defined encapsulation [3]. This pathological condition was first described in 1908 by Josef Verocay, a pathologist from Prague [4]. It is also called neuroschwannoma, neurilemmoma, or neurinoma of Verocay [5]. Multiple cutaneous schwannomas, also referred to as schwannomatosis, may or may not be accompanied by lesions of the spinal and other peripheral nerves. Neurilemmoma can occur spontaneously or be triggered by traumatic events or other stimuli. Cytogenetic investigations have identified the NF2 gene as a tumor suppressor gene for schwannoma [6], with approximately 60% of cases exhibiting inactivating mutations in the NF2 gene [7]. The most prevalent genetic characteristic of both sporadic and familial schwannomas is the presence of loss-of-function mutations in the NF2 gene, located on chromosome 22q12.2, which encodes Merlin. Merlin functions as a connector between the cell

membrane and cytoskeleton, regulating intracellular signaling pathways. Additionally, it plays various roles within cells, including the activation of oncogenic signaling pathways. Western blot analysis and immunohistochemistry revealed an absence of Merlin protein in schwannomas with NF2 loss-of-function mutations, suggesting that the lack of Merlin protein may play a crucial role in schwannoma development [6]. In recent years, with the continuous expansion of genomic and genetic understanding, there has been a gradual increase in research on the genetic mechanisms underlying schwannoma. Studies have revealed that mutations in genes such as SMARCB1, PRKAR1A, LZTR1, COQ6, and BAF170 are closely associated with the pathogenesis of schwannoma [6] [8] [9]. Furthermore, recent genetic analysis of schwannomas has identified recurrent mutations in ARID1A, ARID1B, and DDR1 genes, as well as a novel SH3PXD2A-HTRA1 fusion occurring in a subset of schwannomas [10]. 90% of schwannomas are sporadic [1] [11], and 10% are associated with syndromes, including neurofibromatosis type 2 (3%), schwannomatosis (2%), meningiomatosis (5%), and, rarely, neurofibromatosis type 1. Many of these tumors are incidentally found on imaging, so their precise prevalence may be underestimated due to a lack of identifiable symptoms [12].

Neurilemmoma typically manifests as an isolated subcutaneous nodule or mass, usually measuring 3 - 4 cm, exhibiting slow growth, and generally devoid of symptoms. However, if the tumor involves nerve tissue, pain or numbness may occur in the corresponding regions [11], particularly in cases of large volume and schwannomatosis. The tumor that affects small nerves can be freely displaced except at the point of contact. Conversely, the movement of a tumor that affects large nerves is restricted due to attachment along the nerve's longitudinal axis. Tumors located in the paraspinal region can induce sensory disturbances. Those situated in the posterior mediastinum often extend into the spinal canal, compressing the spinal cord and leading to motor symptoms or dyskinesia. Most schwannomas found on the skin are small and generally not attached to nerves. Schwannomas occurring within solid organs are relatively rare, with most found in the gastrointestinal tract and occasional instances involving the kidney and pancreas. Few cases occur within bone structures. Auditory vestibular nerve (eighth cranial nerve) involvement is frequent in patients with neurofibromatosis type 2 [13].

Schwannomas are generally equally distributed between genders in most studies [14] [15]. They usually occur between the ages of 30 - 50, with rare cases in children, especially congenital ones. However, a study by Shrikrishna et al. found a higher prevalence in males (3:1), with the highest incidence in the second decade of life [16]. Our study revealed a male-to-female ratio of 1.6:1, indicating a higher incidence in males, which deviates from existing literature. Our study focused exclusively on surface tumors, excluding those in bones, the gastrointestinal tract, pancreas, nasopharynx, and larynx, which may have led to the unequal gender ratio. Few studies focus on cutaneous neurilemmomas, so our study may provide new insights for clinical management and research. Some schwannomas may be asymptomatic and too small to require surgical resection, leading patients to opt

for conservative follow-up instead, resulting in a lack of specimens. Additionally, treatment options may vary based on gender. These factors may contribute to the observed differences in gender distribution. In terms of age, the greatest incidence in our study was between the third and fifth decades, consistent with other authors' findings [17] [18].

Schwannoma rarely recurs locally, generally does not metastasize or destroy local tissues, and malignant transformation is rare compared to neurofibroma [11]. It usually manifests as an epithelioid malignant peripheral nerve sheath tumor (MPNST), a round cell malignancy, or angiosarcoma when malignant transformation occurs [5] [19]. Schwannomas are commonly found in the limbs (especially the lower limbs), followed by the head and neck (including the mouth, orbit, and salivary glands), with about 25% - 45% reported in the head and neck region [20]. More than half of the tumors in our study were in the extremities, and 37.3% were found in the head, face, and neck, consistent with previous reports.

On computed tomography (CT) or magnetic resonance imaging (MRI), schwannomas in various anatomic locations are typically well-demarcated round or oval masses. Calcification and cystic changes may be seen in larger tumors [21]. Most schwannomas present as heterogeneous, hypodense masses on CT scan images, exhibiting isointensity with muscle on T1-weighted MRI images and displaying high signal intensity on T2-weighted MRI images [22] [23]. These imaging manifestations can help differentiate them clinically from other diseases. The tumors typically have a spherical to ovoid shape, with a smooth surface and intact capsule. However, tumors found in the central nervous system, parenchymal organs, and mucous membranes (such as the nasal cavity, paranasal sinuses, and nasopharynx) generally lack a capsule. Most of these tumors are smaller than 10 cm in diameter, averaging around 3.0 - 4.0 cm. On cut surface examination, these tumors often appear pale yellow or grayish-white and exhibit translucency and shine.

Schwannomas are diverse in their histologic presentations, frequently displaying varying degrees of degenerative changes such as lipid deposits, cysts of different sizes, hemorrhages, and calcifications. Histologically, schwannomas show a clear periphery with a complete fibrous capsule derived from the perineurium and epineurium. Classical schwannomas are composed of characteristic alternating fascicular areas (Antoni A) and reticular areas (Antoni B). The proportion of Antoni A and B varies in different cases, with either a transition between the two areas or a clear boundary. The fascicular area (Antoni A) consists of short fascicles of Schwann cells arranged in parallel. These cells have spindle-shaped nuclei, sometimes with pseudoinclusions, especially in smears, but the nucleoli are usually inconspicuous. They had abundant, pale eosinophilic cytoplasm with indistinct cell borders. Sometimes, the tumor cells arranged in an onion-skin-like or whorl-like structure or formed Verocay bodies. This is the most prominent characteristic of schwannoma. In intraoperative frozen section analysis, the fascicular region often serves as the morphological basis for diagnosing schwannoma.

Occasionally, mitotic figures can be observed within the fascicular area. The reticular region (zone B) consists of loosely arranged and disordered Schwann cells with round or ovoid nuclei that are hyperchromatic and sometimes contain intranuclear pseudoinclusion bodies. The main features of this tumor include scattered slow inflammatory cells and small blood vessels. Within the reticular area, large and irregular blood vessels are present, with thrombus formation being common in their lumens. The vessel walls are thickened and often accompanied by varying degrees of collagen degeneration; occasionally, hemosiderin deposition and focal foamy histiocytic reaction can be seen surrounding these blood vessels [6]. Microcapsules may form within the reticular area, leading to cysts of different sizes when cystic degeneration is evident. In some cases, a significant amount of mucus can be found in the stroma, resembling schwannoma or other mucinous soft tissue tumors at low magnification. Additionally, some tumors exhibit large rosettes surrounded by layers of small round schwannoma cells with dark nuclei, similar to neuroblastoma tumor cells; this variant is known as neuroblastoma-like schwannoma [24]. Epithelioid tumor cell morphology may also be observed in certain instances of schwannomas. Rarely, schwannomas can coexist with other types of tumors, such as Langerhans cell histiocytosis.

Immunohistochemical examination is necessary for the pathological diagnosis of schwannoma. S-100 is the most commonly used marker to indicate nerve sheath differentiation, and EMA and SOX-10 are also frequently used diagnostic markers. Epithelial membrane antigen (EMA) outlines the perineural cells at the periphery but is negative in tumor cells. The tumor cells express S-100, SOX-10, vimentin, CD57, PGP9.5, and GFAP in about half of the cases. Fibroblasts near the tumor capsule, around blood vessels, and in the degeneration zone express CD34 but are negative in the cell-rich zone. It has been empirically shown that the growth fraction measured by the Ki67 staining index is 2% - 5%, but values up to 15% can be reached in focal site [6].

The diagnosis can be easily made based on typical histopathological and immunohistochemical findings, but it is crucial to distinguish it from the following diseases:

1) Neurofibromas

Neurofibromas are among the most common tumors of nerve sheath origin. Most cases are solitary without other systemic symptoms. However, multiple lesions are not uncommon and are a key feature of neurofibromatosis type I. Unlike schwannomas, neurofibromas predominantly affect the skin and can occur anywhere. Schwannomas, particularly plexiform neurofibromas seen in neurofibromatosis type I, have a tendency to become malignant. The characteristic histopathological findings of neurofibromas are well-defined but nonencapsulated dermal or subcutaneous tumors. These tumors contain a large number of small nerve fibers compared to schwannomas. They are composed of a mixture of Schwann cells, fibroblasts, and perineurial cells. Fibroblasts play an important role in the proliferation of Schwann cells. The tumor cells are diffusely and strongly positive

for S-100 protein [25] often localized in the nucleus, and there are frequently CD34 positive fibroblasts present. The tumor is often interspersed with inflammatory cells, especially mast cells, which are a feature of this disease.

2) Myxoma of nerve sheath

The tumor mainly occurs in the extremities [25], particularly in the hand/fingers, knee/tibia, and ankle/foot. It typically affects men between 40 and 50 years old and presents as an isolated skin-colored nodule that rises above the skin surface, with local recurrence rates as high as 47%. Histologically [26], it appears as a well-circumscribed, multinodular or lobulated tumor without a capsule. It consists of scattered lobules separated by fibrous septa, composed of epithelioid, astrocytic, spindle-shaped, or ring-shaped cells with pale cytoplasm and unclear boundaries, embedded in many myxoid mechanisms. Immunohistochemical staining shows that the tumor cells are positive for S-100, and glial cells are positive for GFAP and CD57 to varying degrees.

3) Leiomyoma

The lesions were frequently observed in various anatomical regions, including the head, face, neck, trunk, limbs, and genitals, with a predilection for the lower limbs. The predominant symptom reported was pain or tenderness. The tumor cells exhibited abundant proliferation and an intricate arrangement of smooth muscle bundles. These cells displayed spindle-shaped morphology and formed fascicular or woven patterns with eosinophilic cytoplasm. The nuclei appeared fusiform, dachshund-like, or blunt at both ends. The neoplastic cells are of smooth muscle origin and thus should stain positive for smooth muscle actin and desmin [27].

4) Dermatofibroma

Dermatofibroma (DF) is a common skin lesion that tends to occur in young and middle-aged people, more frequently in women. It can be found on any part of the body but is more common on the limbs [28]. DF often appears as a single brown skin nodule. Histologically, the tumor is composed mainly of fibroblasts and histiocytes, with uniform spindle cells arranged in interwoven or storiform patterns. Foam-like histiocytes, multinucleated giant cells, and thin-walled blood vessels are scattered among the spindle cells. Immunohistochemical staining shows that the tumor cells are positive for Vimentin and CD10 but negative for S-100 and CD34.

5) Sebaceous cyst

Sebaceous cysts can occur on any part of the body, usually appearing on the scalp, face, neck, trunk, and buttocks. Most are solitary and manifest as raised, round nodules on the body surface, feeling tough to the touch. Histopathological examination shows that the cyst wall is composed of squamous epithelium with a granular cell layer containing lamellar keratins.

Malignant transformation of schwannomas is extremely rare. For instance, low-grade malignant peripheral nerve sheath tumors often arise from the malignant transformation of neurofibromas. Such patients typically have concurrent

neurofibromatosis type I. The primary treatment approach involves surgical resection, with a particular focus on preserving nerves during the procedure. Recurrence is rare after complete resection.

In summary, the clinical and pathological manifestations of schwannoma are characteristic. However, it is imperative to differentiate it from other histologically similar lesions in clinical diagnosis and treatment. A comprehensive understanding of its clinical and pathological characteristics is crucial for accurate diagnosis.

Conflicts of Interest

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

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