Rare multiple schwannomas of the left upper extremity: A case report

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Abstract. Schwannomas are rare benign neoplasms originating from Schwann cells of peripheral nerve sheaths. The current study presents a distinctive case involving multiple schwannomas along the peripheral nerves of the left upper extremity. The patient exhibited multiple gradually enlarging subcutaneous masses distributed along the nerves of the left upper limb, without pain, neurological deficits or a positive Tinel's sign upon physical examination. Preoperative diagnostic imaging, including high-resolution ultrasonography and magnetic resonance imaging, revealed well-circumscribed, homogeneous soft-tissue masses with characteristic features. Despite these findings, imaging modalities demonstrated limited specificity in conclusively differentiating the upper extremity tumors from other soft-tissue neoplasms. Surgical exploration conducted under general anesthesia identified three encapsulated masses with focal capsular discontinuities, adherent to surrounding skeletal muscle and the median nerve. The masses measured 6x5x3, 5x4x3.5 and 5x3.5x3 cm from proximal to distal, respectively. Complete surgical excision was performed with meticulous preservation of adjacent neurovascular structures. Histopathological analysis confirmed the diagnosis of schwannomas. This report also provides an extensive review of the literature addressing the etiology, clinical presentation, diagnostic techniques and treatment strategies for peripheral nerve schwannomas, contributing to a deeper understanding of this rare neurogenic tumor and aiding in its effective clinical management.

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Introduction

Schwannomas, also referred to as neurilemmomas, are the most common type of benign peripheral nerve sheath tumor (BPNST), originating from Schwann cells and present predominantly in the hands and upper limbs (1-4). While PNSTs are rare, schwannomas are the most prevalent type, accounting for nearly 5% of all soft-tissue tumors of the upper limb (5). The global incidence of schwannomas is reported to be 3-4 cases per million individuals (6). As BPNSTs, schwannomas typically grow slowly, with a relatively low incidence of malignant transformation, generally ranging from 1 to 13% (7). Therefore, the prognosis for the vast majority of patients is favorable, and the mortality rate is relatively low. However, for patients at risk of malignant transformation, especially those with pathogenic genes (such as NF2, SMARCB1 and LZTR1), there may be a higher risk of complications (8). Approximately 19% of all cases of schwannomas occur in the upper limb, with the distal region near the elbow being the most common tumor site (9). These tumors tend to originate along major nerves and on the flexor surfaces of the upper and lower limbs (10,11). Surgical intervention has been reported as the primary treatment and is relatively effective for schwannomas (12). However, to the best of our knowledge, studies on multiple schwannomas in the upper limb are scarce. The rarity of this condition and the ambiguity in the diagnostic criteria may lead to an underestimation of the actual incidence of multiple schwannomas. Therefore, it is imperative to conduct

standardized studies on multiple schwannomas in the upper limb, including studies on diagnosis, surgical management and postoperative care. In this context, the present study discusses the case of a patient with multiple schwannomas in the upper limb. This report also includes a brief review of the literature on the pathogenesis, clinical features, diagnosis and treatment of schwannomas, with the objective of providing novel insights into their management.

Case report

A 70-year-old man presented at Guangzhou Red Cross Hospital (Guangzhou, China) in January 2024 with a mass in the left upper limb that had existed for >40 years. Initially, this mass was solid and oval in shape, measuring ~1x2 cm on the medial aspect of the left upper limb. No specific treatment was received for the mass. Over the past 20 years, the mass had progressively enlarged, and new masses have developed near the left elbow and the hypothenar region. The patient reported no pain or tenderness, and all the masses were cystic-solid upon palpation. The results of the neurological examination were unremarkable. The masses were mobile in the transverse plane but not along the longitudinal axis. The overlying skin exhibited no signs of redness, swelling or ulceration, and no increase in skin temperature was noted. No family member had a history of schwannomas. Given these observations, it was plausible to conclude that this case was more likely to represent a sporadic schwannoma.

The magnetic resonance imaging (MRI) examination conducted upon admission revealed two ovoid masses located in the ulnar nerve path in the middle to distal part of the left upper arm, with slight hyperintensity on T1-weighted images and heterogeneous hyperintensity on T2-weighted images. The masses were ~4.2x5.8x6.1 and 5.0x5.6x6.5 cm in size. The T2-weighted images revealed target signs, with the masses closely related to the nerve. No signal suppression was noted on fat-saturated sequences, and the enhancement of the masses was heterogeneous, with progressive enhancement on delayed-phase imaging. The adjacent muscles exhibited signs of compression displacement with distinct delineations. In addition, long ovoid nodular lesions with similar signal characteristics were observed on the radial side of the flexor tendon sheath close to the wrist and superficial to the thenar muscles on the volar aspect of the left forearm. These lesions were ~1.4x2.8 and 3.0x3.7x5.1 cm in size, respectively, and exhibited marked heterogeneous enhancement on contrast-enhanced images (Fig. 1).

The patient underwent excision of the left upper limb mass, median nerve exploration and pathological biopsy under general anesthesia with endotracheal intubation. A longitudinal incision was made along the long axis of the tumor, followed by an incision on the skin and subcutaneous tissue. The tumor was bluntly dissected and exposed. A capsule was observed, although it was a focal discontinuity. The tumor adhered to the surrounding skeletal muscle and the median nerve, which was most consistent with a benign neurogenic tumor. Careful dissection of the surrounding nerves, blood vessels and tendons was performed. The tumor dimensions from proximal to distal were 6x5x3, 5x4x3.5 and 5x3.5x3 cm, respectively (Fig. 2). The incision was closed in layers, and the tumors were sent for pathological evaluation. The postoperative course remained uneventful, and complete tumor resection was achieved without any damage to the surrounding nerves. The patient exhibited no sensory or circulatory abnormalities in the surgical region or the distal limb, and no complications occurred. The patient was, therefore, discharged with a healed incision.

Postoperative pathological examination revealed the following gross findings: i) Subcutaneous mass no. 1 in the left upper limb: A grayish-red to grayish-white mass measuring 6x5x3 cm, with the excised surface exhibiting grayish-red to grayish-white coloration and soft consistency. ii) Subcutaneous mass no. 2 in the left upper limb: A grayish-red to grayish-white mass measuring 5x4x3.5 cm in size, with the excised surface exhibiting grayish-red to grayish-yellow coloration, a moderate texture and associations with regions of hemorrhage. iii) Subcutaneous mass no. 3 in the left upper limb: A grayish-red mass measuring 5x3.5x3 cm, with a tail 5 cm in length and ~1 cm in diameter, exhibiting a grayish-red to grayish-yellow excised surface with a soft consistency and solid texture. After tissue sampling, fixation with 10% neutral formalin at room temperature for 8 h, dehydration, embedding with paraffin, sectioning at a thickness of 4 μm and staining, the prepared slides were examined under a Nikon Eclipse CI optical microscope (Nikon Corporation). Hematoxylin and eosin (H&E) staining was performed on the prepared slides. After dewaxing and rehydrating at room temperature, the slides were stained with hematoxylin for 3 min, differentiated and rinsed before being stained with eosin for 9 min. Following rinsing, dehydration and clearing, the slides were baked at 67˚C for 15 min, dried for 10 min and then mounted for observation. H&E staining revealed typical fascicular regions (Antoni A regions) and reticular regions (Antoni B regions). The Antoni A regions contained spindle-shaped cells arranged in fascicular and palisading patterns, with Verocay bodies, with a few regions densely packed, while other regions were more loosely arranged, with visible blood vessels. The Antoni B regions presented with hemosiderin deposition around the blood vessels, along with chronic hemorrhage and cystic changes, suggesting a degenerative schwannoma. Mild nuclear atypia (degenerative changes) was observed in some cells, with no increased mitotic activity. The stroma showed loose myxoid changes, with abundant vascular structures exhibiting congestion and hemorrhage, accompanied by fibrosis, hyaline degeneration and localized calcification, indicating a degenerative schwannoma (Fig. 3A-D). To accurately describe the tumor components, immunohistochemical (IHC) staining was performed on several representative paraffin block sections using the ChemMate Envision method (DakoCytomation; Agilent Technologies, Inc.). IHC was performed using a ready-to-use ChemMate Envision kit from DakoCytomation; Agilent Technologies, Inc., [Kit details: Anti-p53 (DO-7) monoclonal antibody, cat. no. M7001; anti-Ki-67 (30-9) rabbit monoclonal primary antibody, cat. no. 790-4286; S100 antibody, cat. no. CSM-0101] following the manufacturer's instructions. The immunohistochemistry analysis revealed positive expression for S100, p53 (~2%) and Ki-67 (hotspot region ~2%). S-100 immunohistochemical staining showed positivity in both the cytoplasm and nuclei of tumor cells, with some regions primarily exhibiting cytoplasmic positivity,

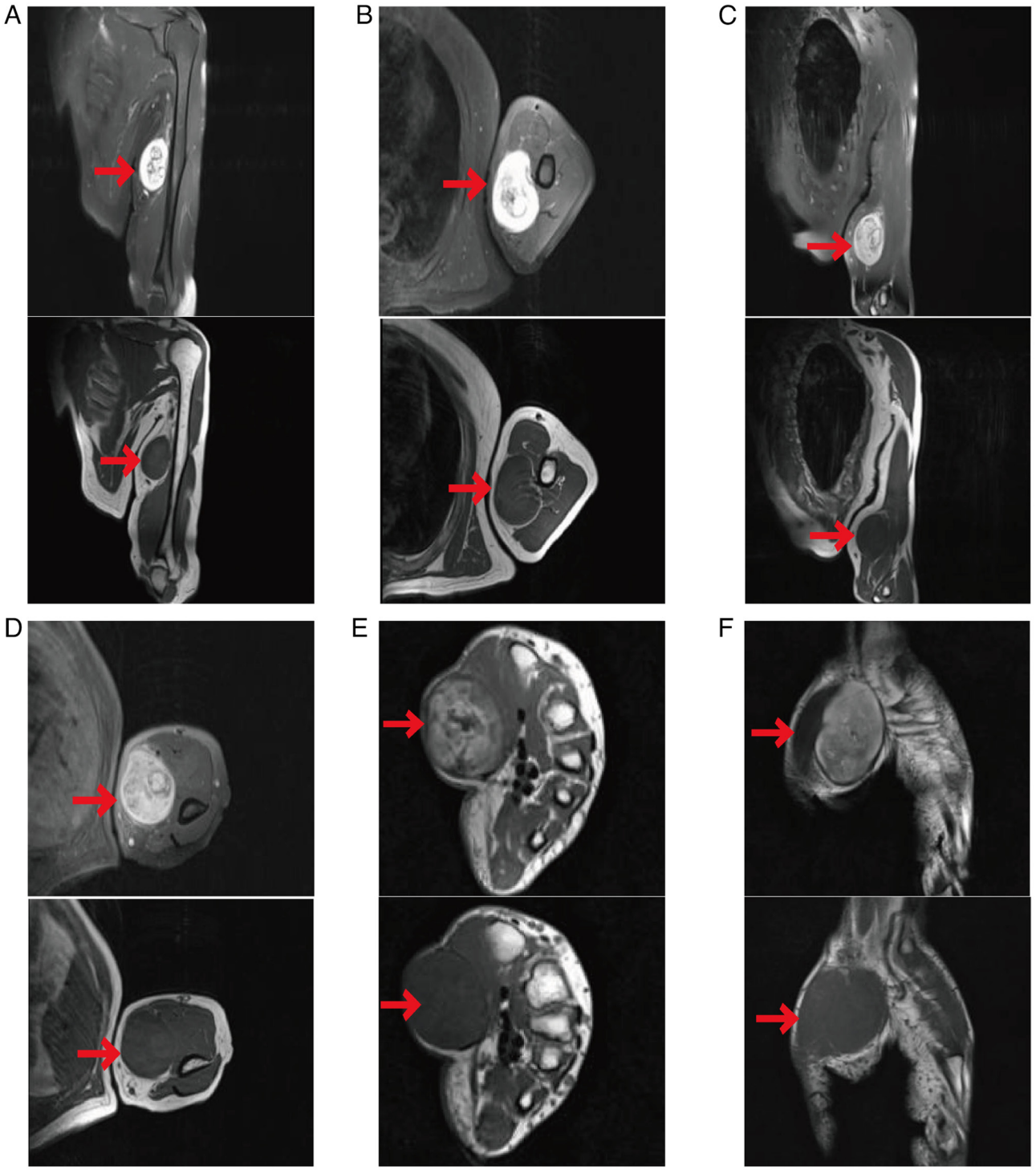

Figure 1. Magnetic resonance imaging analysis of the different planes of the tumor at admission shown as non-contrast and contrast-enhanced sequences. (A) Coronal plane scan of the mass in the proximal left upper arm. (B) Axial plane scan of the mass in the proximal left upper arm. (C) Coronal scan of the distal left upper arm mass. (D) Axial plane scan of the distal left upper arm mass. (E) T1-weighted and (F) T2-weighted images of the left-hand mass at the thenar muscles. The red arrow in each image indicates the tumor.

while others demonstrated both cytoplasmic and nuclear dual positivity, suggesting that the latter may indicate higher tumor activity. p53 immunohistochemical staining demonstrated focal positivity in scattered tumor cells with variable staining intensity, showing colors ranging from light to dark brown. Immunohistochemical staining revealed a Ki-67 proliferation index of 2%, indicating the presence of tumor cells (Fig. 3E-H). Based on the histological morphology of schwannomas in the microscopic examination section of the third edition of 'Diagnostic Pathology: Soft Tissue Tumors' (13), the pathological diagnosis was established as multiple schwannomas of the left upper limb with secondary degenerative hemorrhage. During the 1-year postoperative follow-up period, the patient underwent seven clinical examinations. The surgical wounds healed well without significant complications, and physical examinations revealed no evidence of tumor recurrence.

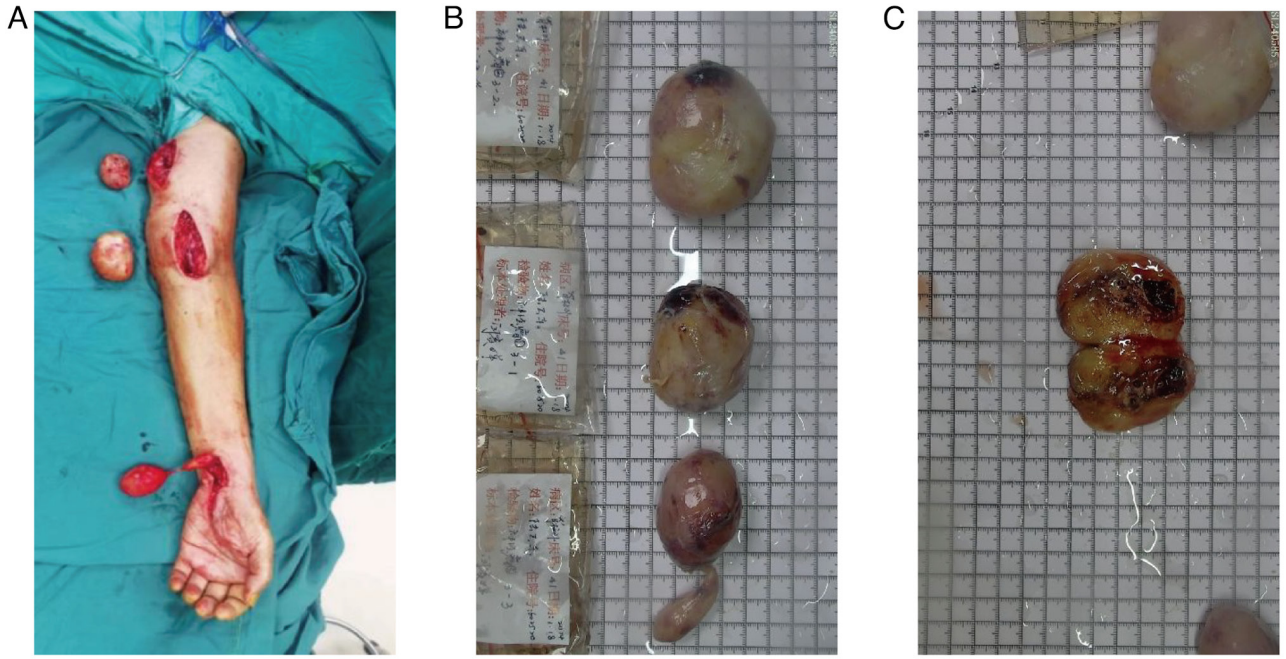

Figure 2. Macroscopic view of the tissue of the detected mass. (A) Intraoperative view of the mass, with the capsule mostly intact, partially incomplete, and partial adhesion of the mass to the surrounding skeletal muscle and median nerve. (B) Gross examination of the specimen at the time of pathological submission, revealing that the tumor was round, encapsulated and well circumscribed, with grayish-red to grayish-yellow coloration, a soft consistency and a solid texture. (C) The cut surface of the tumor revealed cystic degeneration and hemorrhage.

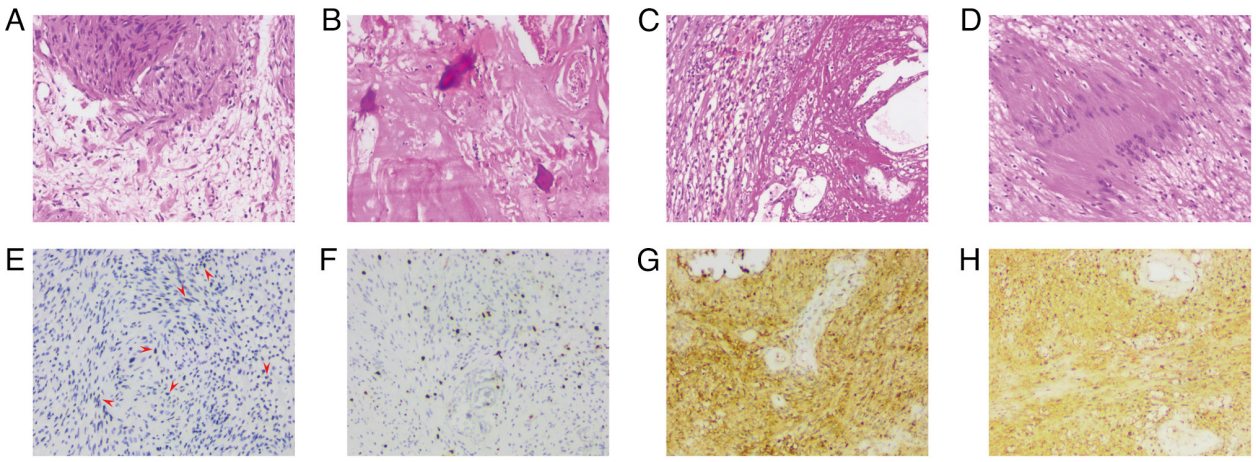

Figure 3. Tumor H&E and immunohistochemistry staining. (A-D) H&E staining and (E-H) immunohistochemical staining images of schwannomas (all x100 magnification). (A) The diagnostic morphology of the schwannoma revealed typical fascicular regions (Antoni A regions) and reticular regions (Antoni B regions). The Antoni A regions contained spindle cells arranged in fascicles or interwoven patterns, and Verocay bodies were also observed; the lower region exhibited a loose pattern, with visible blood vessels. (B) Noticeable hyaline degeneration of the tumor stroma and punctate calcification were present, indicating a degenerative schwannoma. (C) The Antoni B region presented with hemosiderin deposition around the blood vessels, along with chronic hemorrhage and cystic changes, suggesting a degenerative schwannoma. (D) Antoni A regions exhibited spindle cells in fascicular or interwoven arrangements, and Verocay bodies were present. (E) p53 immunohistochemical staining demonstrated focal positivity in scattered tumor cells with variable staining intensity. Red arrows point to some of these positively stained cells or cell clusters, which are colored in varying shades from light to dark brown. (F) Immunohistochemical staining revealed a Ki-67 proliferation index of 2%, indicating the presence of tumor cells. (G and H) Immunohistochemical staining for S-100 revealed positivity in the cytoplasm and nuclei of the tumor cells. Cytoplasmic positivity is mainly shown in (G), while (H) exhibits both cytoplasmic and nuclear dual positivity, suggesting that the latter may indicate higher tumor activity. H&E, hematoxylin and eosin.

Discussion

Schwannomas are non-invasive tumors of the peripheral nerve sheath. Studies have indicated that schwannomas are the most common PNSTs in the upper limb, with an incidence rate of 64% (12). No significant sex or ethnicity differences have been noted in this context (14). In a 22-year epidemiological study conducted by Sandberg *et al* (12), which studied a total of 68 tumors in 53 patients, the median nerve was revealed to be the most frequently affected nerve, followed by the ulnar and digital nerves.

Research has shown that schwannomatosis and neurofibromatosis type 2 (NF2) are both characterized by multiple schwannomas but represent distinct genetic entities. NF2 is

caused by mutations in the NF2 gene, whereas schwannomatosis is associated with germline mutations in SMARCB1 or LZTR1 (15). In the epidemiological study on schwannomas by Forde *et al* (16), the prevalence of LZTR1-related schwannomatosis and SMARCB1-related schwannomatosis was ~1 in 527,000 and ~1 in 1,100,000, respectively, which is 8.4 to 18.4 times lower than the prevalence of NF2. This highlights the significant role of NF2 in the genetic diagnosis of schwannomas (17). In the present case, due to the need for outsourcing high-throughput sequencing, the associated costs and the patient's personal preferences, genetic sequencing could not be performed to confirm the presence of any alterations in the NF2 gene.

The clinical presentation of schwannomas varies notably. Certain reports indicate that these tumors may be painless, although this lack of pain may be attributed to their slow growth, indirect compression of the nerve and absence of sensory innervation in the tumor (18-21). A comprehensive retrospective analysis by Iwashita, which examined 1,202 patients with 1,271 schwannomas, demonstrated a notably low incidence of pain. The histopathological classification of the patients revealed several distinct types: Common (n=932), degenerative (n=238), cellular (n=19), plexiform (n=35), pigmented (n=2), myxoma (n=16) and organoid (n=30), with pain manifestation predominantly observed in myxoma and organoid variants (19). Additionally, symptoms such as pain, sensory abnormalities and a positive Tinel's sign are often associated with the location of the tumor. As the tumor grows and compresses more sensitive nerve regions, the patient may experience pain or other symptoms. A review of the literature on patients with schwannomas in the hand and wrist revealed that the interval between symptom onset and surgery ranged from a few months to 37 years (14). Tumors located in the finger regions tend to cause symptoms earlier than those located in the wrist and the palm. In the present case, the combination of the patient's 40-year clinical history and subsequent histopathological findings from H&E staining strongly indicated a degenerative variant of schwannoma (19).

When considering differential diagnoses, it is important to identify benign tumors that could be confused with schwannomas. The tumors that should be distinguished from schwannomas include neurofibromas, neuroblastomas and ganglioneuromas. Clinically, no distinct standard exists for differentiating schwannomas from neurofibromas. However, the literature suggests that the primary distinction between the two lies in the age of the patients in which they occur, as while neurofibromas predominantly originate in individuals aged 20-30 years, schwannomas are more common in those aged 30-50 years (12,14). Nevertheless, distinguishing schwannomas from other tumors based solely on clinical history and imaging findings remains considerably challenging.

Ultrasound examination may be utilized to establish a preoperative diagnosis of soft-tissue tumors in the extremities. According to reports, an accuracy rate of up to 77% may be achieved when ultrasound is used as an initial diagnostic modality (22). Ultrasound, however, is unable to differentiate between schwannomas and other tumors, as all tumors typically present as similar hypoechoic masses with posterior acoustic enhancement. Typically, uncharacterized soft-tissue masses in the upper limb that are suspected to be related to PNSTs require further evaluation through MRI examination, which reportedly has 75% diagnostic accuracy in the case of these tumors (23). Schwannomas typically present a homogeneous central low signal and a peripheral high signal, referred to as the target sign, although this is not exclusive to schwannomas (22). While MRI is more accurate for determining tumor location and establishing the differential diagnosis of schwannomas, it does not achieve 100% diagnostic accuracy. In addition, fine-needle aspiration or open biopsy is unsuitable for a definitive diagnosis, as these procedures may lead to scarring and potential fascicular injury during subsequent excision (11). Therefore, despite the availability of appropriate clinical and imaging evidence, the definitive diagnosis of schwannomas continues to rely on histopathological examination.

Currently, no pharmacological therapies are recommended as alternatives to surgery for the treatment of schwannomatosis (24). In asymptomatic schwannomas that are stable in size, a period of observation may be appropriate. In the management of benign schwannomas, therapists prefer to perform complete excision of the tumor along with its capsule, as recurrence is often observed in different regions of the same nerve in the affected limb rather than at the surgical site (25). The optimal surgical approach involves microsurgical techniques for intralesional dissection and meticulous tumor removal aimed at preserving nerve structures while minimizing traction on the surrounding nerve bundles (2,14,26,27).

Overall, a review of the relevant literature and the findings of the present case indicate that patients with schwannomas commonly present with soft-tissue masses, which may be accompanied by symptoms that develop due to nerve compression. Schwannomas originate from Schwann cells located within the nerve sheath and are often easily separable from the nerve. The present report highlights the fact that schwannomas can be multifocal and affect different regions of the body. A thorough examination of the peripheral nerves in patients with schwannomas is therefore essential, and a complete dissection should be performed to obtain a biopsy and thereby confirm that the tumor is not malignant. The potential for tumor recurrence underscores the necessity for routine follow-up examinations of affected patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DY conceived and designed the study, and revised the manuscript. HC collected and analyzed the patient's clinical, imaging and pathological data, and drafted the manuscript. XY and PW performed the surgeries, provided detailed surgical descriptions, and contributed to the refinement of the manuscript's conception, design and content. WY, YL, WL, YT, and JL contributed to the writing of specific sections of the manuscript, assisted in the development of the study's methodology, analyzed data and prepared the pathological images for analysis. YX and HM contributed to the overall study design, critically reviewed the manuscript for important intellectual content, and oversaw the processing and presentation of the figures. YY independently analyzed the radiological images, identified key diagnostic features and drafted the radiological findings section of the manuscript. LL performed the histopathological examination, conducted the immunohistochemical staining, interpreted the results and drafted the pathology section of the manuscript. HC, XY, PW and DY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript, and have agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided specific written informed consent for publication, which included the acquisition of clinical data and images.

Competing interests

The authors declare that they have no competing interests.

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