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Case Report

Multiple Schwannomas Involving an Unusual Communicating Loop between the Ulnar and Median Nerves in the Axilla: Clinical Implications

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Abstract

Background: Schwannoma and neurofibroma constitute benign peripheral nerve sheath tumors (BPNSTs), which may present as single or multiple lesions. Multiple schwannomas are rare in the peripheral nerves of the upper extremity. Solitary small schwannoma is usually asymptomatic, while larger and multiple schwannomas may have different symptoms due to pressure effects. Median and ulnar nerve communications are often encountered in the upper limb, making these anastomoses clinically important. However, such communications with schwannomas in the axilla are rare.

Case Report: The study protocol was designed per the prevailing guidelines of the Institute on the use of human cadavers for teaching and research. Written informed consent was obtained from the family of the body donor at the time of whole-body donation. The upper extremities, including the brachial plexuses of both sides, were carefully dissected as per the instructions in *Cunningham's Manual of Practical Anatomy*15th edition.

Discussion: Unusual anastomoses in the axilla and two encapsulated, highly vascular fusiform masses were observed. Another fairly large mass was noted on the right chest wall. Histological examination confirmed the masses to be schwannomas.

Conclusion: Asymptomatic schwannomas often remain undiagnosed, and those lying in the axilla can be misdiagnosed. Awareness of such variant anatomy will enable clinicians and surgeons to plan more appropriate diagnostic and therapeutic interventions.

Keywords: Axillary mass, Median-ulnar nerve communications, Multiple schwannomas, BPNSTs, Mammae erraticae

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Introduction

Anatomical variations in different areas of the body have always been important from a surgical and clinical point of view (1). Several variations of the brachial plexus and its branches are described in the literature. One such common variation is the occurrence of communicating branches or anastomoses between the median and ulnar nerves at different sites, which involve crossing over of axons between the two important branches. The four known types of anastomoses between the median and ulnar nerves are (a) Martin-Gruber anastomoses, where there is a communicating ramus from the median nerve to the ulnar nerve in the forearm (b) the reverse Martin-Gruber or Marinacci anastomoses wherein the crossing of axons occurs from the ulnar to the median nerve in the forearm(1), (c) the Riche-Cannieu type involves communication between the recurrent branch of the median nerve and the deep branch of the ulnar nerve in the palm, and (d) Berrettini anastomoses in the hand with intercommunications between the common digital nerves of the median and ulnar nerves (2). The Martin-Gruber type is a common occurrence and has great clinical importance (3). These communications may alter innervations patterns and become even more relevant from a clinical and electro-diagnostic point of view. Benign peripheral nerve sheath tumors (BPNSTs) in the upper extremities are reported in the literature; however, medium to large-sized BPNSTs in the axilla are less commonly observed. BPNSTs can be schwannomas (earlier known as neurilemmoma) with a prevalence of 0.8%–2% or they may be neurofibromas (4). Schwannomas and neurofibromas are common benign tumors originating from Schwann cells in the peripheral nerve sheath. Typically, schwannomas occur eccentrically on the nerve of origin, causing lateral displacement of nerve fibers, and present as solitary, slow-growing mass lesions that either remain asymptomatic or have pressure symptoms such as pain and numbness (5). Whereas schwannomas, which

usually remain attached to the patent peripheral nerve and typically grow within a fibrous capsule, arise from the Schwann cells of peripheral nerves, neurofibromas consist of fibroblasts, perineuronal cells, and other tissue elements of peripheral nerves apart from Schwann cells and involve the nerve in a diffuse manner, which may not be associated with axons. Schwannomas have been reported to occur everywhere in the body, at all ages, regardless of race or gender (6), but are seen to be more frequent in the 2nd–5th decades of life (7). Although extremely rare, association with von Recklinghausen's disease (8) or malignant transformations are also reported at times (9). Schwannomas in unusual sites often go unnoticed, and there are chances of them being misdiagnosed and mismanaged (10). The occurrence of mass lesions in the axilla poses a clinical diagnostic challenge due to multiple etiologies (axillary tail of Spence, mass due to any inflammatory condition, lymphadenopathy, or other benign or malignant masses). It gives rise to diverse symptoms due to the pressure effect or the direct involvement of the nerve fibers. Schwannomas of the brachial plexus in the axilla may be misdiagnosed as mammae erraticae, too (11). Co-occurrence of unusual anastomoses other than the known ones, along with multiple BPNSTs in the axilla region, increases the possibility of iatrogenic injuries and may also affect limb blood flow due to proximity to other neurovascular structures, including the axillary artery and vein. When present simultaneously, multiple similar or related tumors might indicate a known syndrome or warrant genetic and molecular testing for further evaluation.

Case Report

The study protocol was designed per the prevailing guideline of the institute on the use of human cadavers for teaching and research, and consent was obtained from the family of the body donor at the time of whole-body donation. During routine dissection for undergraduate teaching, we observed an unusual variation in the right axillary region in a 65-year-old male cadaver. The cadaver was embalmed with a solution containing a mixture of ethanol, glycerol, formalin, and phenol and stored in a weak formalin solution before taking out for dissection purposes. The upper extremities, including the brachial plexuses of both sides, were dissected carefully using conventional dissection methods.

We noticed uncommon anastomoses between the ulnar nerve and median nerve in the axilla (Figure 1A, B). We also observed two masses in the anastomotic branch found between the ulnar and median nerve. The anastomoses were seen to be originating from the ulnar nerve just proximal to the upper border of the pectoralis minor muscle in the axilla, and the nerve fibers ran downward and laterally to join the median nerve opposite the insertion of the coracobrachialis muscle in the middle third of the humerus (Figure 1A, B).

On gross examination of the communicating ramus, an encapsulated, highly vascular ovoid mass lesion measuring 5 cm × 2 cm × 1.5 cm was noticed in the anastomoses lying deep in the axilla, a major portion of it lying beneath the pectoralis minor muscle and medial to the second part of the axillary artery (Figure 1A). The mass was neither visible nor palpable on gross examination before dissection, probably due to the axillary pad of fat, indicating the location of the mass to be relatively deep. The cut section showed multiple solid grey-white areas and tiny foci showing cystic degeneration (Figure 2B). The second small mass of 1.2 cm × 0.8 cm × 0.3 cm was also noted in the same twig just distal to it, which revealed a similar appearance in its gross cut section. However, another encapsulated, highly vascular reniform mass measuring 12.5 cm × 6.5 cm × 2.5 cm (Figure 1A) was noted in the right chest wall extending from the second to the seventh intercostal space along the mid-axillary line. This reniform mass also showed similar gross features in its cut sections (Figure 2B).

The careful dissection of the axilla and arm region on the opposite side did not reveal any such communicating branch or mass. The other branches of the brachial plexus of both sides were essentially normal. No evidence of atrophy of muscles innervated by the median or ulnar nerve was noted on any side. Histological examination of all the masses confirmed them to be benign schwannomas showing characteristic hypercellular Antoni A areas and myxoid hypocellular Antoni B areas in different proportions (hematoxylin and eosin [H&E]-stained sections) and pathognomonic Verocay bodies (Figure 2C, 2D).

All the tumors were circumscribed by a dense fibrous capsule. The Schwann cells were seen to be either disposed as Antoni A pattern (the so-called hypercellular area comprising of a single form of Schwann cells with basophilic nuclei in ill-defined cytoplasmic background intermixed in a collagenous matrix) or as Antoni B pattern (composed of loosely organized Schwann cellswith indistinct cytoplasm scattered among the abundant mucous matrix, the characteristic hypocellular area). Cellular atypia was not observed. H&E-stained sections also demonstrated parallel arrays of alternating palisades (alternating rows of aggregated elongated nuclei with acellular areas represented by Schwann cell cytoplasmic processes), identified as the diagnostic Verocay bodies. There was no evidence of past surgical procedures in the region. The observed gross anatomical variation and associated masses were photographed, and histological images were photomicrographed. The current report was unrelated to the cause of death.

Discussion

Anastomoses between the median and ulnar nerves are of

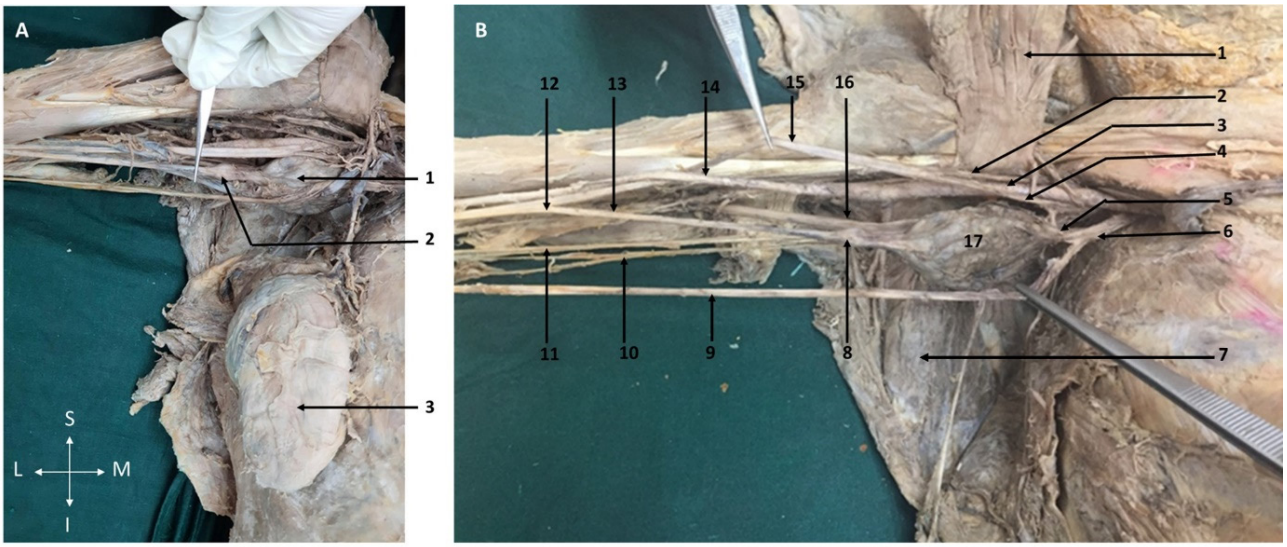

Figure 1. (A) Dissected right axilla showing all the three schwannomas; axillary (1 & 2) and pectoral (3). (B) Dissected right axilla showing variant communicating anastomoses between ulnar and median nerve with schwannomas; 1-pectoralis minor, 2-lateral root of the median nerve, 3-2nd part of axillary artery, 4-medial root of the median nerve, 5-anastomotic branch arising from ulnar nerve, 6 & 9-ulnar nerve, 7-subscapularis, 8-small axillary schwannoma in the communicating ramus, 10-medial cutaneous nerve of arm, 11-medial cutaneous nerve of forearm, 12-junction of the anastomotic branch to the median nerve, 13-anastomotic branch, 14-brachial artery, 15-median nerve, 16-radial nerve, 17-large axillary schwannoma

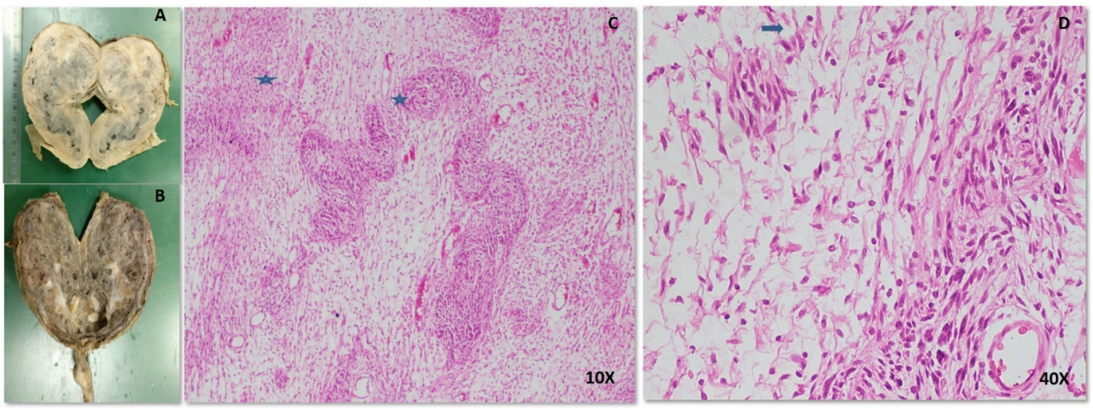

Figure 2. (A, B) Cut section of the masses (chest and axillary masses, respectively) showing solid grey-white areas with tiny cystic degenerations; (C, D) Histological characteristics: (C) Benign tumor showing alternating hypercellular (Star) and hypocellular areas (intervening area) in typical palisading arrangement (Verocay body), (D) Hypocellular area shows loose spindle-shaped cells (arrow) floating in a myxoid background

phylogenetic and embryologic significance as comparable communications exist in mammals, especially in primates (12,13). These anastomoses are believed to be the vestige of the common ventral nerve trunk supplying the flexor muscles of the upper extremity. The median and the ulnar nerves traverse through the flexor compartment of the arm but do not receive any branches from this locality (14). Many authors have reported the prevalence of median-ulnar nerve communications in various anatomic, surgical, and electrophysiological studies (1,2,15-17). Median and ulnar nerve communication in the arm is known in fetuses (18), but such communications and coexisting BPNSTs in adults have not been reported to the best of our knowledge. Schwannomas are predominantly seen along the distribution of cranial nerves, but a modest predilection is observed for the peripheral nerve in the extremities too. They are slow-growing, asymptomatic, and non-aggressive in nature, most of which are less than 5 cm in diameter. Although benign, malignant transformation does occur, especially in long-standing neurofibromatosis (NF-1) cases. Various authors have described schwannomas in the peripheral nerves innervating the upper extremities (Table 1).

Here, we report a cadaveric case of multiple schwannomas involving the unusual communicating branch from the ulnar to the median nerve in the axilla, along with a giant concealed schwannoma in the right chest wall involving intercostal and long thoracic nerves. The third schwannoma, which was larger, smooth, and oval in shape from side to side and not palpable as a swollen mass on initial examination, was found on the right side of the chest wall. Multiple schwannomas are seen in association with major peripheral nerves, different plexuses (brachial or lumbosacral), spinal nerve roots,

Table 1. Schwannoma in the peripheral nerves of the upper extremity in different population groups

Involved nerve	Authors	Number of schwannomas reported	Population group
Deep motor branch of the ulnar nerve	Cavanagh and Pincott, 1977(5)	1	British
Multiple nerves of the upper limb	Artico et al, 1997(6)	64	Italian
Long thoracic nerve of Bell	Tian et al, 2019 (7)	1	Chinese
Multiple nerves of the upper limb	Pertea et al, 2022 (19)	17	Romanian
Median nerve	Ardeleanu et al, 2020 (20)	1	Romanian
Ulnar nerve	Fodor, Samuila and Bodog, 2020(21)	1	Romanian
Median nerve	Hakan et al, 2019 (22)	1	Turkish
Median nerve	Xarchas et al, 2020 (23)	3	Greek
Brachial plexus	Vučemilo et al, 2018 (24)	1	Croatian
Ulnar nerve	Tabrizi et al, 2020 (25)	1	Iranian
Median nerve	Nishida et al, 2014 (26)	1	Morocco
Median nerve	Dusad et al, 2016 (27)	1	Indian
Radial nerve	Battaglia et al, 2017 (28)	1	American
Median nerve	Padasali et al, 2015 (29)	1	Indian
Median nerve	Rammohan et al, 2014 (30)	1	Indian
Median nerve	Anghel et al, 2014 (31)	1	Romanian
Median nerve	Kütahya et al, 2013 (32)	2	Turkish
Multiple nerves of the upper limb	Tang et al, 2013 (33)	8	Hong Kongese
Brachial plexus	Kumar and Akhtar, 2011 (34)	1	Indian
Multiple nerves of the upper limb	Kwon et al, 2009 (35)	56	Korean
Median nerve	Aydin, Kotan and Keles, 2007 (36)	1	Turkish
Brachial plexus	Chen et al, 2008 (37)	1	Japan
Multiple nerves of the upper limb	Knight et al, 2007 (38)	80	British

and cranial nerves (mostly vestibulocochlear) (39,40).

Multiple schwannomas involving nerves other than the vestibular nerves are called schwannomatosis, which have similarities with neurofibromatosis. They can be distinguished from each other by the differences in clinicopathological features, e.g., café-au-lait spots and the presence of neurofibromas in neurofibromatosis (41). The laboratory distinction between the two can be made via histological and immunohistochemical staining methods using H&E and S-100 immunostaining (42). Axillary schwannomas in association with brachial plexus branches are extremely rare and may create challenges in diagnosis and treatment (43). Due to the almost identical characteristics of different masses, distinguishing schwannomas from other masses may create a difficult situation for the doctor. Up to 6% of schwannomas can be diagnosed preoperatively with the help of clinical examination, imaging studies, and fine needle aspiration cytology (44). The peripheral nerve tumors occurring in the extremities, including those observed in neurofibromatosis type 1 (NF-1), are mostly benign.

Nevertheless, the calculated lifetime risk of malignant transformation ranges from 8–13% (25). Most schwannomas are reported in the median nerve, and their occurrence in the ulnar nerve is infrequent (45). Visser also reported schwannomas in the superficial radial nerve (46). Our findings are uncommon, and awareness about the uncommon anatomy may help physicians and surgeons in diagnosis and management.

Somatic mutations in the NF-2 (neurofibromatosis type 2) gene and a loss of heterozygosity of chromosome 22 are commonly implicated with schwannoma occurrence (47). However, many schwannoma cases lack demonstrable genetic mutations (48). NF-1 and NF-2 are the two other varieties of neurofibromatosis, and the clinical features of all these entities at presentation may be the same or may overlap. Meningiomas have also been reported in approximately 5% of schwannomatosis cases, and they were found to be SMARCB1-gene-positive (48). Identification of a heterozygous germline pathogenic variant in the SMARCB1 gene or the LZTR1 gene, are utilized for establishing the diagnosis of schwannomatosis. The SMARCB1 gene (OMIM 601607) is a member of the SWItch/Sucrose non-fermentable (SWI/SNF) complex located on the long arm of chromosome 22, centromeric to the NF2 gene (OMIM607379). The SMARCB1 gene encodes for a protein subunit of the SWI/SNF protein complex, which regulates gene expression by chromatin remodeling. Although the exact role of the SMARCB1 gene is not fully understood, it is thought to act primarily as a tumor suppressor gene, the heterozygous mutant variant of which is held responsible for schwannomatosis.

The LZTR1 gene (leucine zipper-like transcription regulator 1) (OMIM 600574) is located on the long arm of chromosome 22, centromeric to SMARCB1, and is believed to also act as a tumor suppressor gene (49). It is also linked with sporadic cases of schwannomatosis. The autosomal-dominant conditions such as schwannomatosis and NF-2 have a genetic predilection for developing multiple schwannomas. In fact, the NF2 gene is described to be the most common genetic predisposing factor for schwannomas. Multiple schwannomas can indicate an association with tumor suppressor genes and thus demand genetic testing (50). Pathmanaban et al highlighted in their study that many young adults with sporadic schwannoma harbored important inheritable predisposing mutations (50). Therefore, genetic testing can be a valuable opportunity to detect the propensity of future additional tumor occurrence in young adults with sporadic schwannoma. These genetic traits should be suspected in a proband with two or more diagnosed non-vestibular schwannomas with a positive family history of schwannomatosis.

Conclusion

Multiple schwannomas in unusual sites may create a significant challenge to accurate diagnosis. Hence, a clinician or surgeon dealing with such masses in the axilla should be aware of the possibility of a schwannoma in the differential diagnosis. Also, this kind of unreported communicating median-ulnar branch may be suddenly encountered during surgical exploration in the axilla. Therefore, care must be taken while performing any surgical, anesthetic, or radio-diagnostic intervention in the area to prevent inadvertent damage to anastomoses carrying important motor or sensory fibers. Apart from that, such unknown neural connections can affect the results of nerve conduction studies or electromyography. The incidental finding of these schwannomas in the axilla should be distinguished from schwannomatosis or neurofibromatosis at an earlier stage via histological, molecular, and genetic testing, which can add value to the prognosis and disease management.

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Conceptualization: Dibakar Borthakur, Rajesh Kumar, Rima Dada.
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Methodology: Dibakar Borthakur, Rajesh Kumar, Kishore Sesham.
Supervision: Kishore Sesham, Harisha Kusuma, Rima Dada.
Writing–original draft: Dibakar Borthakur, Rajesh Kumar, Rima Dada.
Writing–review & editing: Dibakar Borthakur, Rajesh Kumar, Kishore Sesham, Harisha Kusuma, Rima Dada.

Competing Interests

The authors declared no conflict of interest.

Ethical Approval

Consent for using the donated cadaver for research and education purposes was obtained from the donor's family at the time of whole-body donation.

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