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CASE STUDY

Intravascular schwannoma as an extremely unusual cause of vein obstruction: a case report

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The blood vessel lumen is an extremely rare location for a benign peripheral nerve sheath tumor like schwannoma. Less than 10 cases have been previously reported. In this report, we present a case of a 68-year-old woman who had a soft tissue nodule at the posterior calf of her left leg during a physical examination. Pathological examination was performed after complete surgical excision. The patient underwent follow-up for 12 months after surgery without evidence of recurrence or any other complication. This is the first case of intravascular schwannoma reported as a cause of vein obstruction. Microscopically, the tumor was composed of Schwann spindle cells that were immunoreactive for S100 protein and SOX10. This tumor was surrounded by a well-defined vascular smooth muscle wall. Prospective series are required to improve the knowledge on the underlying mechanisms of intravascular schwannoma development.

Key Words: Neurilemmoma; Peripheral nervous system neoplasms; Nerve sheath neoplasms; Peripheral nervous system; Schwann cells

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Schwannoma is a benign neural tumor of Schwann cell origin on the nerve sheath [1]. Schwannomas are also called neurilemomas and are generally located in the deep dermis and subcutaneous tissue, but these can appear at different sites of the body. Spinal intradural extramedullary examples are common, and these form "dumbbell tumors" when expanding through the neural foramina as multiple paraspinal schwannomas. These "dumbbell tumors" are common in neurofibromatosis type 2. Cranial nerve involvement is not uncommon; cerebellopontine angle schwannoma arising from the vestibular division of the eighth cranial nerve is one of the most frequent presentations [2]. Spinal intramedullary; central nervous system (CNS); visceral, such as the gastrointestinal tract; and bone schwannomas are rare [3,4].

Low-power microscopic views of schwannomas are characterized by well-defined margins with frequent encapsulation. These tumors have two different alternating cellular areas in a biphasic growth pattern: the hypercellular areas consisting of spindle cell proliferation, Antoni A areas, and the hypocellular or cystic areas characterized by the presence of macrophages and collagen fibers, Antoni B areas. A frequently recognized morphological feature of schwannomas is the presence of Verocay bodies that consist of palisading nuclei alternating with acellular areas [5]. Immunohistochemically, schwannomas are characterized by diffuse and strong staining for S100 and SOX10 [6,7]. The diagnosis is made based on the classical morphologic characteristics, the biphasic growth pattern, and the diffuse S100 and SOX10 immunoreactivity.

Venous obstruction is the partial or complete occlusion of the blood vessel lumen and can be associated with low blood flow or increased pooling. The most common form of venous obstruction is deep vein thrombosis in the lower limb veins. Stasis results in viscosity increase and formation of microthrombi. This

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is due to multiple factors that slow or obstruct the flow of venous blood. One of the most common causes is endothelial (intimal) damage secondary to intrinsic or external trauma. In a hypercoagulable state, a biochemical imbalance between procoagulant and anticoagulant factors occurs [8].

Intravascular schwannomas are extremely rare. In this report, we present a case of intravascular schwannoma, an unusual cause of deep venous obstruction. To the best of our knowledge, just four case reports had been published in English prior to this report [9–12]. Elucidating the signs and symptoms of this rare form of schwannoma is necessary to avoid misdiagnosis.

CASE REPORT

Case presentation

We present the case of a 68-year-old woman who had a three-year history of non-radiating pain on the medial side of her left leg, 5 cm distal to the popliteal fossa. No CNS disorders were identified at physical examination, and no other related symptoms were observed.

A soft tissue Doppler ultrasound was performed and showed a spindle-shaped to ovoid lesion, the largest diameter of which was 2.3 cm. The mass was in the deep subcutaneous tissue, near the muscular fascia (Fig. 1A, B) and did not display marked internal blood flow (Fig. 1B). The radiological characteristics of the lesion on ultrasonographic examination suggested the presence of a soft tissue tumor of probable neural origin. The lesion was completely surgically removed.

Pathologic characteristics

The macroscopic examination of the resected area revealed the presence of a soft tissue nodule, largest diameter 2.3 cm, with a vaguely spindle morphology and smooth external surface. The cut surface of the mass was grayish brown and had the consistency of rubber.

Microscopically, the tumor was nodular and composed of spindle cells. This tumor occupied the entire lumen of a venous vessel that had a thickened smooth muscle wall with focal myxoid degeneration and no elastic fibers (Fig. 1D). The lesion was composed of at least two intermingled cellular areas, at least one

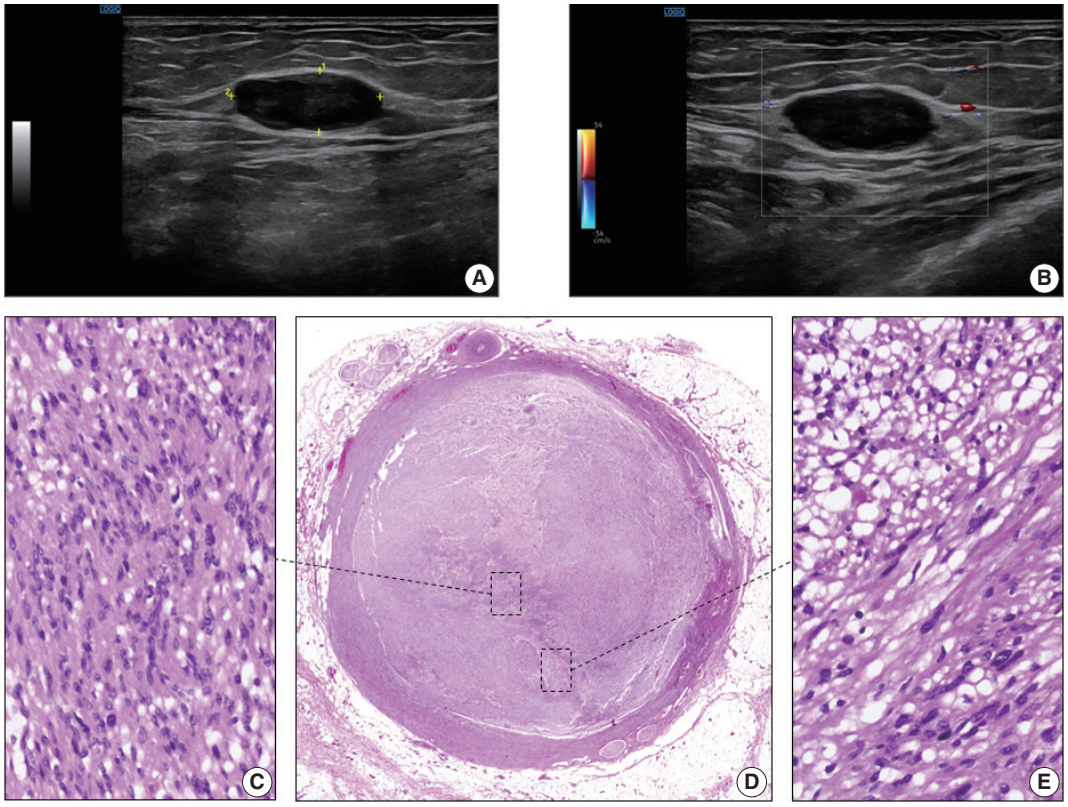

Fig. 1. Ultrasonographic imaging and morphological features. (A) Ultrasonographic characteristics of the tumor showing a 2.3 cm hypoechoic ovoid nodule. (B) Low blood flow around the tumor in the Doppler ultrasound view. (C) Hypercellular areas that consist of cohesive spindle cells (Antoni A zones). (D) The tumor shows an intravascular growth pattern, occupying the entire lumen of the blood vessel. (E) Hypocellular areas that consist of haphazardly arranged spindle cells in a loose myxoid stroma (Antoni B zones).

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of which shared features with the normal peripheral nerve sheath cells. Within these areas, some of the cells had elongated, fusiform, or oval hyperchromatic nuclei with sharp edges and scarce cytoplasm (Antoni A zones) (Fig. 1C); these were arranged to form parallel palisades with interposed filaments (Verocay bodies).

In addition, the tumor had areas composed of less cohesive cells with small, rounded nuclei and large pale cytoplasm in a loose myxoid stroma (Antoni B zones) (Fig. 1E). The lesion was not necrotic or hemorrhagic. Neither mitosis nor atypia was present. The venous vessel within which the tumor expanded was surrounded by tiny mature vessels, the vasa vasorum, and nerves, the nervi vasorum (Fig. 1D).

Immunohistochemistry

The tumor had typical immunohistochemical characteristics of a schwannoma. A diffuse and strong positivity for S100 protein (clone EP32, monoclonal antibody, ready-to-use on Leica BOND III system, Leica Biosystems, Newcastle Upon Tyne, UK) (Fig. 2A–D) and SOX10 (clone EP268, monoclonal antibody, ready-to-use on Leica BOND III system, Master Diagnóstica, Grenada, Spain) (Fig. 3A, B) was found in the tumor spindle cells. We also observed a normal nuclear expression level of H3K27me3 (clone C36B11, monoclonal antibody, 1:400 on Leica BOND III system, Cell Signaling Technology, Danvers, MA, USA) in the tumor cells (Fig. 3D). These markers were also positive in the nervi vasorum inside and around the vein wall. The tumor cells were negative for CD34 (clone QBEnd/10, monoclonal antibody, ready-to-use on Leica BOND III system, Leica Biosystems) (Fig. 3C), smooth muscle actin (SMA) (clone Alpha sm-1, monoclonal antibody, ready-to-use on Leica BOND III system, Leica Biosystems) (Fig. 2E, F), and CD31 (clone JC70A, monoclonal antibody, ready-to-use on Leica BOND III system, Leica Biosystems). CD34 (Fig. 3C) and CD31 highlight the endothelial elements inside the tumor and the vein endothelium surrounding the tumor. CD34 was also positive in some fibroblastic cells of the tumor stroma (Fig. 3C). SMA was positive in the smooth muscle cells of the vein wall, small vessels present in the vasa vasorum, and vessels inside the tumor (Fig. 2E, F).

DISCUSSION

Schwannoma is a nerve sheath tumor entirely or nearly entirely composed of differentiated neoplastic Schwann cells that are associated in some cases with different conditions such as

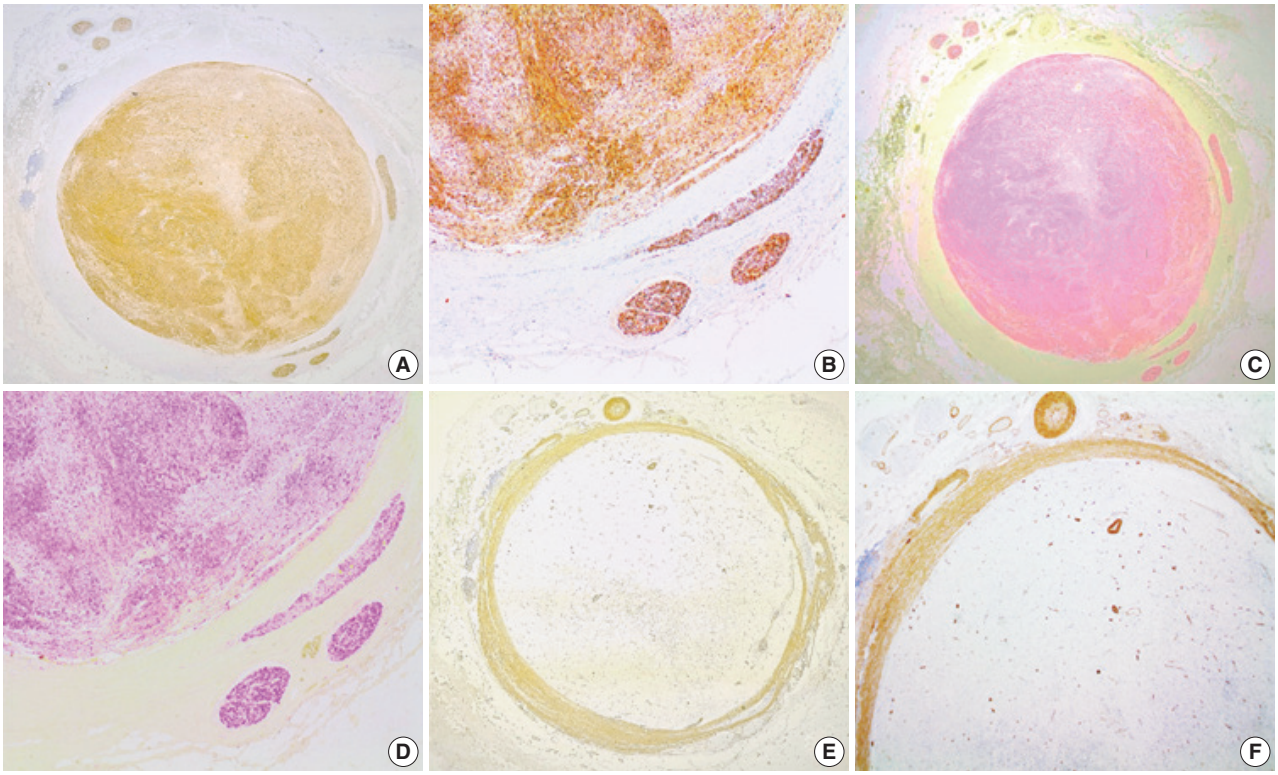

Fig. 2. Positivity for S100 protein in intravascular tumor cells (A–D) and nervi vasorum nerves (B, D). The smooth muscle cells of the vein wall show smooth muscle actin positivity (E, F).

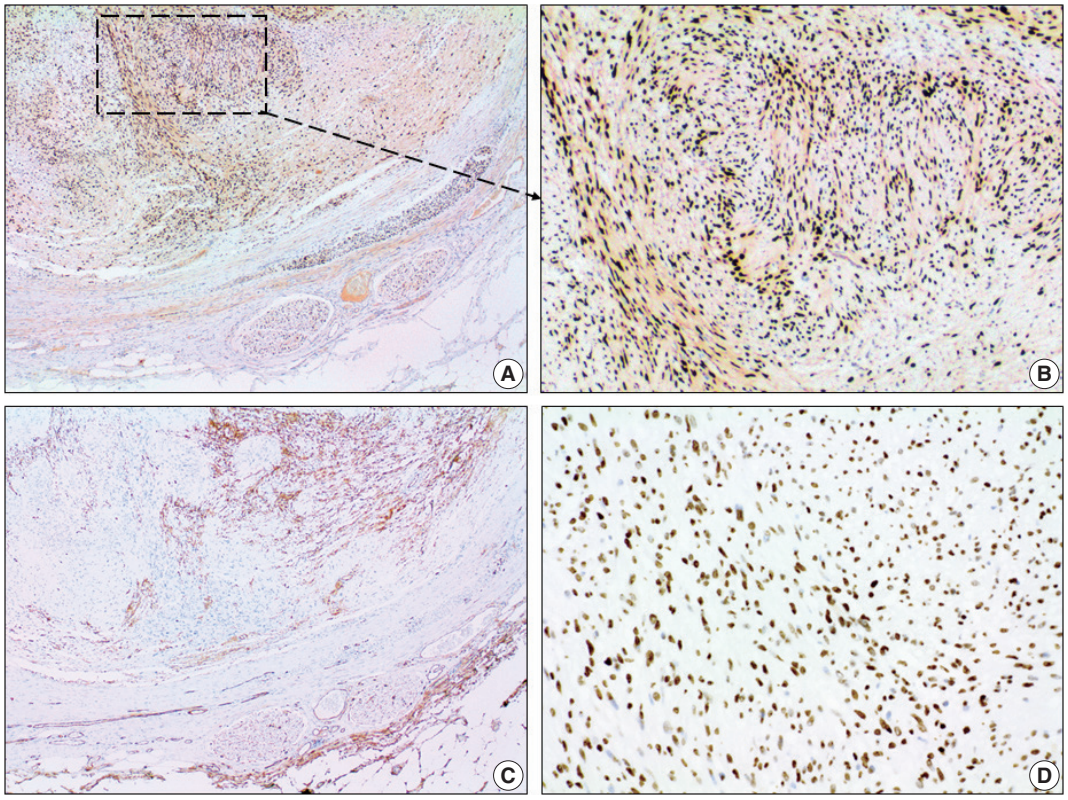

Fig. 3. Immunohistochemical characteristics. (A, B) The intravascular tumor cell positivity for SOX10. (C) Some fibroblastic cells of the tumor stroma, the endothelial cells of capillaries inside the tumor, the endothelium of the vein intima, and the vasa vasorum are CD34-positive. (D) The nuclear immunoreactivity for H3K27me3 is intact in tumor cells.

type 2 neurofibromatosis and schwannomatosis [1].

The incidence of intravascular schwannomas is unknown. The first published case of a schwannoma in a vein lumen was reported in 2011 by Gaudi et al. [5,9].

Venous obstruction is most commonly seen in the form of deep venous thrombosis [8,13]. To the best of our knowledge, a complete obstruction of a deep vein by an intravascular schwannoma has not been previously reported. This is the third reported case of an intravascular schwannoma located in the posterior calf and the first case of a schwannoma in a deep vein of the left leg. Our case showed some clinical similarities with the cases previously reported by other authors, such as the presence of localized pain, a long evolution period (3 years in our case), and recent size enlargement [9-12]. However, unlike previously reported cases in which the age range was 44–56 years and the tumor size range was 0.3–1.5 cm, our patient was older, 68 years, and the tumor was larger, 2.3 cm.

Various theories have been proposed to explain intravascular schwannoma onset. Some of these theories include the nerve origin being native to the vessel wall, tumor embolization, or direct tumor growth extension [9-11]. In some cases, the schwannomas show vascular alterations that display reactive vessel proliferation and tumor vessel permeability that allow for the schwannoma extension to vascular territories [14]. We theorize a nervi vasorum origin due to the proximity of the intravascular tumor to the nervi vasorum nerves (Fig. 4) seen in our case (Fig. 2A–D). Nervi vasorum, or "vessel nerves," are small nerves organized as a network and located in the outer and middle layers of the blood vessels [15,16]. Nervi vasorum play an important role in the maintenance of an appropriate tonus of vascular smooth muscle cells and regulate local blood pressure in doing so [17]. This vascular nerve system participates in the regulation of vasoconstriction and vasodilation and is generally composed of sympathetic fibers. Some of these trigger vasodilation and others induce vasoconstriction depending on the nature of the neurotransmitter and receptors located on the target cell, while parasympathetic stimulation triggers vasodilation.

The correct interpretation of histopathologic features by the pathologist is key to distinguish schwannomas from other tumors on the differential diagnosis list that includes neurofibroma, intravascular leiomyoma/leiomyosarcoma, intravascular lobular capillary hemangioma, intravascular fasciitis, and malignant pe-

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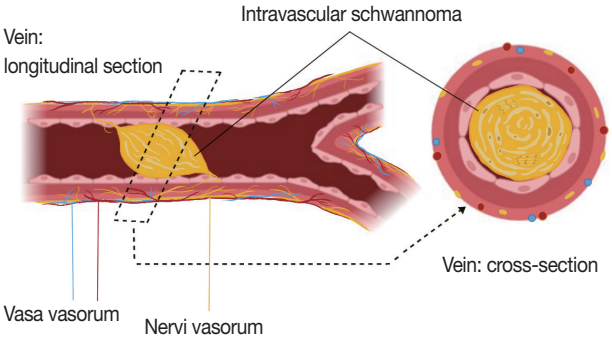

Fig. 4. Anatomical illustration image to explain the hypothetical nervi vasorum origin of intravascular schwannoma and to demonstrate the different biological structures involved. A longitudinal section view of a vessel with a schwannoma of intravascular growth and its hypothesized relation with the peripheral nerve sheath elements of the nervi vasorum network (left). Cross-section view of a blood vessel with a complete lumen obstruction by an intravascular schwannoma (right). Created in BioRender and Clip Studio Paint.

ripheral nerve sheath tumor.

The treatment of choice for schwannomas is surgery in the vast majority of symptomatic cases when the integrity of near organs is not compromised; but, in some cases, the surgical option depends on the tumor location [18,19]. There are no widely accepted treatment guidelines for this tumor. In all previously reported cases, surgical removal in these benign cases, as with conventional cases of schwannomas in other locations, has been the treatment of choice.

The patient is symptom-free after 12 months of follow-up from the surgery and continues to be monitored.

Recognizing the histopathologic features of this rare entity in an intravascular location is important to prevent misdiagnosis [11].

More studies with a large prospective series and molecular studies are required to elucidate the mechanisms underlying the development and the clinical and biological behavior of intravascular schwannomas.

Ethics Statement

Informed written consent was obtained from the patient. This case report was approved by the ethics committee of the University Hospital of Salamanca (2023 02 387).

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Code Availability

Not applicable.

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Conflicts of Interest

The authors declare that they have no potential conflicts of interest.

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