

CASE REPORT

Cutaneous microcystic/reticular schwannoma: case report and literature review of an exceedingly rare entity with an unusual presentation

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Abstract

Conventional schwannoma represents a benign peripheral nerve sheath tumor derived from Schwann cells, which usually arises in the fourth or fifth decade of life, in the subcutaneous tissue of the distal extremities, or in the head and neck region of adult patients, with no gender predilection. In addition to the classic type, at least 11 different histopathological subtypes have been described and unawareness of these uncommon histopathological entities may lead to diagnostic pitfalls and risk of mistreatment. Recently described in the scientific literature, microcystic/reticular schwannoma is still relatively unknown to both surgeons and pathologists. The purpose of this paper is to highlight its existence by describing an additional case that occurred in the retroauricular area, and to further characterize its clinical, histopathological and immunohistochemical features. We reviewed the literature and compared the current case with others that have been documented thus far, discussing all possible differential diagnoses.

Keywords: schwannoma, microcystic/reticular schwannoma, immunohistochemistry.

Introduction

Schwannoma, also known as neurilemmoma, is a slow-growing, solitary and usually asymptomatic benign peripheral nerve sheath tumor (BPNST), derived from Schwann cells [1]. It usually arises in the fourth or fifth decade of life, in the subcutaneous tissue of the distal extremities, or in the head and neck region of adult patients, with no gender predilection [2–4]. Pure intra-dermal tumors are rare [5, 6]. Occasionally, schwannomas may also involve a broad variety of anatomic regions, such as the mediastinum, gastrointestinal tract, retroperitoneum, spinal cord, cerebellopontine angle and bone. Besides those arising in the setting of neurofibromatosis type 2 (NF2), most schwannomas are solitary and sporadic lesions, although a small percentage of cases may be associated with von Recklinghausen's disease [7].

Conventional schwannoma is a benign proliferation, usually encapsulated and morphologically characterized by a biphasic growth pattern, traditionally designated by Antoni A areas (highly ordered cellular component that palisades) and Antoni B areas (hypocellular myxoid component). In addition to the classic type, at least 11 different histopathological subtypes have been described [7]. These variants include ancient (degenerated) schwannoma [8], cellular schwannoma [9], plexiform schwannoma [10], melanotic schwannoma [11, 12],

epithelioid schwannoma [13], hybrid schwannoma/neurofibroma [14], hybrid schwannoma/perineurioma [15], gastrointestinal schwannoma [16], neuroblastoma-like schwannoma [17], lipoblastic schwannoma [18], and microcystic/reticular schwannoma [19]. All these histopathological variants highlight the morphological heterogeneity of schwannoma, with no dissimilarities in clinical behavior or general outcome. Unawareness of these uncommon histopathological subtypes may lead to diagnostic pitfalls and risk of mistreatment. The microcystic/reticular variant of schwannoma is a recent addition to this group of tumors, which shows predilection for visceral locations, without Antoni A and Antoni B areas or Verocay bodies [19]. Unlike classic schwannoma, the reticular variant may lack encapsulation and reveals a bizarre microcystic and/or reticular architecture, containing focal infiltrative areas.

Cutaneous presentation of microcystic/reticular schwannoma is extremely rare, with only six cases reported as of September 2017 [19–21].

Here, we report the case of an incidentally diagnosed cutaneous microcystic/reticular schwannoma and discuss the relevant differential diagnoses in this location, with the aim to raise awareness and further characterize the clinical, histopathological and immunohistochemical (IHC) features of this extremely rare tumor.

Case presentation

We report the case of a 43-year-old male with history of cutaneous melanoma admitted to the University Emergency Hospital in Bucharest, Romania, for multiple painless subcutaneous nodules located on the torso, upper extremities and in the retroauricular area. The patient claimed that these masses started to appear and grow in size, several months after the surgical intervention for melanoma. Due to an exceedingly high clinical suspicion of metastatic melanoma, the patient was referred to the Department of Plastic Surgery, where he underwent surgery with complete removal of the aforementioned masses. All specimens were sent separately to the Department of Pathology for histopathological examination.

All the subcutaneous masses were histopathologically confirmed as metastases of melanoma, except the one located in the retroauricular area. Upon revising the clinical history, the patient admitted that the retroauricular nodule appeared and persisted for several years before the diagnosis of melanoma. In this case report, we will discuss only the retroauricular nodule.

Gross examination of the surgical sample, which measured 2/1.5/1.5 cm, was well circumscribed with a vague lobular appearance. Cut sections were white with alternating yellowish areas, rubbery, and appeared to be homogeneously solid with focal myxoid patches. The specimen samples were fixated with 10% buffered formalin and were processed by conventional histopathological methods using paraffin embedding, sectioning and Hematoxylin–Eosin (HE) staining.

Histopathological examination of standard-stained HE slides revealed an unencapsulated, somewhat infiltrative tumor. The spindle-shaped neoplastic cells had scant eosinophilic cytoplasm and bland hyperchromatic round to oval nuclei, with no prominent nucleoli. Intranuclear cytoplasmic inclusions were occasionally present. No cytological atypia, mitoses or necrosis were observed and a large proportion of the tumoral mass was represented by cells arranged in a microcystic fashion. The tumor cells were forming lace-like, retiform or pseudoglandular structures measuring between 10 µm and 120 µm in diameter, containing abundant basophilic myxoid/mucinous material. The stroma of the tumor contained basophilic myxoid material with some hyalinized collagen fibers and focal lymphoplasmacytic infiltrate (Figures 1–3).

In order to help establish an accurate final diagnosis, IHC tests were performed. To begin with, the paraffin blocks were cut and the resulting 3-µm thick sections were mounted on slides covered with poly-L-lysine. Afterwards, the sections were deparaffinized in successive toluene and alcohol baths, rehydrated (three successive alcohol baths with decreasing concentration: 96%, 80% and 70%) followed by a final bath with distilled water for 10 minutes. For IHC staining, we used an indirect triserial Avidin–Biotin complex method (deparaffinization in toluene and alcohol series), rehydration, washing in phosphate-buffered saline (PBS), incubation with normal serum, for 20 minutes, incubation with primary antibody

overnight, DAKO Labeled Streptavidin–Biotin (LSAB) kit, washing in carbonate buffer and development in 3,3'-diaminobenzidine (DAB) hydrochloride/hydrogen peroxide nuclear counterstaining with Mayer's Hematoxylin. We used the following antibodies from Biocare: S100 (mouse monoclonal, clone 15E2E2 + 4C4.9, 1:100 dilution), SOX10 (mouse monoclonal, clone BC24, ready-to-use), CD99 (rabbit monoclonal, clone EP8, 1:100 dilution), transducin-like enhancer of split 1 (TLE1) (from Abcam, rabbit polyclonal, clone ab15587-200, 1:250 dilution), protein gene product 9.5 (PGP9.5) (mouse monoclonal, clone 31A3, 1:250 dilution), epithelial membrane antigen (EMA) (mouse monoclonal, clone E29, 1:100 dilution), CD31 (rat monoclonal, clone Mec13.3, 1:50 dilution), CD34 (mouse monoclonal, clone QBEnd/10, 1:100 dilution), glial fibrillary acidic protein (GFAP) (mouse monoclonal, clone GA-5, 1:50 dilution), smooth muscle actin (SMA) (mouse monoclonal, clone 1A4 – also known as asm-1, 1:100 dilution), cytokeratin (CK) AE1/AE3 (mouse monoclonal, clone AE1/AE3, 1:100 dilution), CK7 (mouse monoclonal, clone OV-TL 12/30, 1:200 dilution), p63 (mouse monoclonal, clone 4A4, 1:200 dilution), Melan A (mouse monoclonal, clone A103, 1:25 dilution), human melanoma black 45 (HMB45) (mouse monoclonal, clone HMB45, 1:100 dilution), Ki67 (mouse monoclonal, clone MIB-1, ready-to-use), proliferating cell nuclear antigen (PCNA) (mouse monoclonal, clone PC10, 1:100 dilution), vimentin (rabbit monoclonal, clone SP20, 1:50 dilution) and calponin (mouse monoclonal, clone CALP, 1:100 dilution).

IHC staining of the surgically resected tumor showed strongly diffuse nuclear and cytoplasmic immunopositivity for S100 protein (Figure 4). The tumor cells also revealed diffuse nuclear immunopositivity for SOX10 and TLE1 (Figure 5). PGP9.5 showed focal positivity (Figure 6). Cystic spaces containing basophilic myxoid/mucinous substance were lined exclusively by S100-positive Schwann cells, which appeared negative on immunostaining for EMA, CD31 and CD34. The tumor also featured diffuse immunoreactivity for GFAP and lacked immunoreactivity for epithelial markers such as CK AE1/AE3, CK7 and, as already mentioned, EMA (Figure 7). The tumor also lacked immunoreactivity for myoepithelial markers, such as SMA, p63 and calponin. Variable amounts of CD34-positive fibroblasts and vascular structures were present in between the microcystic/reticular spaces (Figure 8). No EMA-positive perineurial cells were present between or at the periphery of the microcystic/reticular structures. Melan A and HMB45 were negative. Ki67 immunopositivity was roughly 5%, while PCNA revealed much higher diffuse nuclear positivity (Figure 9). Vimentin immunostaining showed diffuse cytoplasmic immunopositivity in all tumoral cells (Figure 10). Corroborating histopathological and IHC features, the diagnosis of microcystic/reticular schwannoma was considered most likely.

After complete surgical excision with clean resection margins, the patient is well with no evidence of tumor recurrence or metastasis on follow-up after six months.

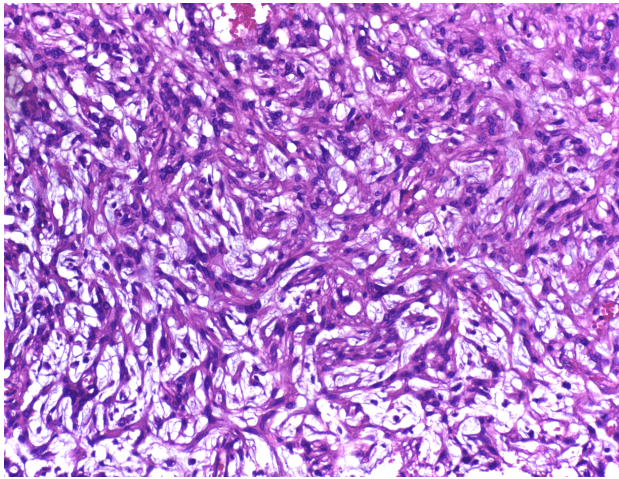


Figure 1 – Histopathological aspect of the surgically resected tumor showing numerous microcystic structures formed by spindle cells with bland nuclei (HE staining, ×200).

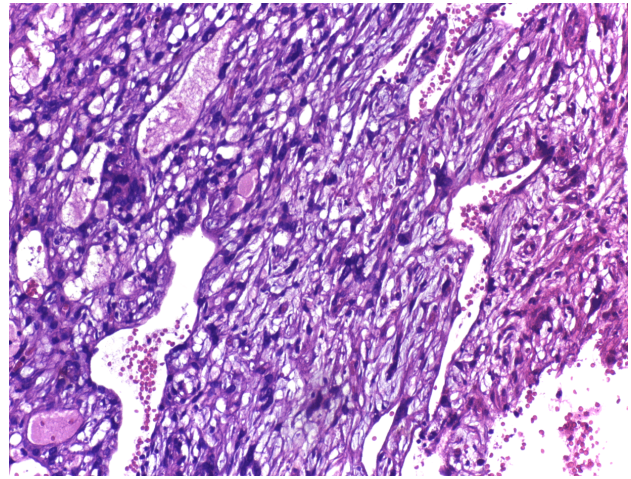


Figure 2 – Histopathological aspect of the surgically resected specimen showing spindle cells with scant eosinophilic cytoplasm and bland-looking nuclei with no mitotic activity (HE staining, ×100).

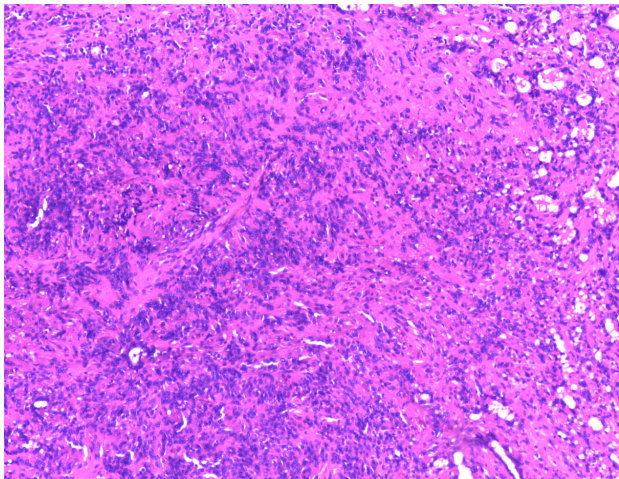


Figure 3 – Histopathological aspect of the surgically resected specimen showing cellular Antoni B areas located at the periphery of the tumor (HE staining, ×100).

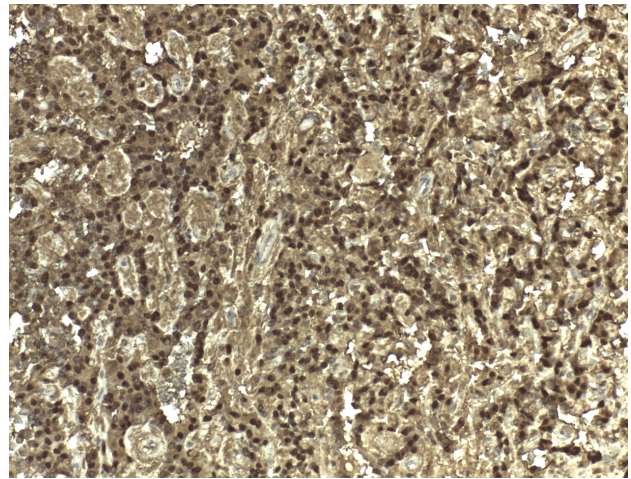


Figure 4 – Immunostaining for S100 showing diffuse nuclear and cytoplasmic positivity in all tumoral cells (IHC staining with DAB chromogen, ×200).

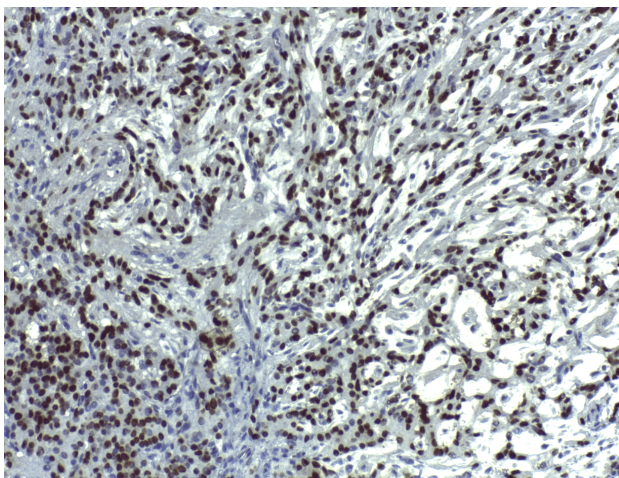


Figure 5 – Immunostaining for SOX10 showing diffuse nuclear positivity in all tumoral cells (IHC staining with DAB chromogen, ×200).

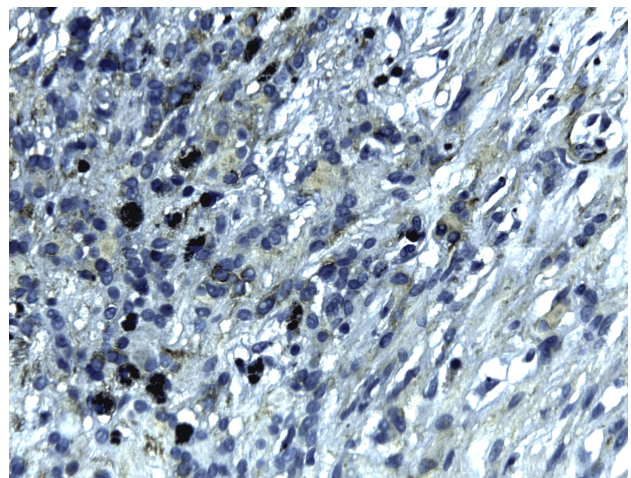


Figure 6 – Immunostaining for PGP9.5 showing focal nuclear positivity at the periphery of the tumor (IHC staining with DAB chromogen, ×400).

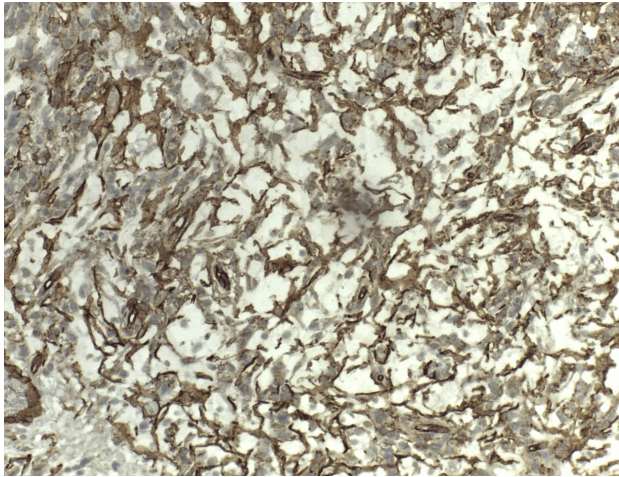


Figure 7 – Immunostaining for GFAP showing diffuse cytoplasmic positivity in all tumoral cells (IHC staining with DAB chromogen, ×200).

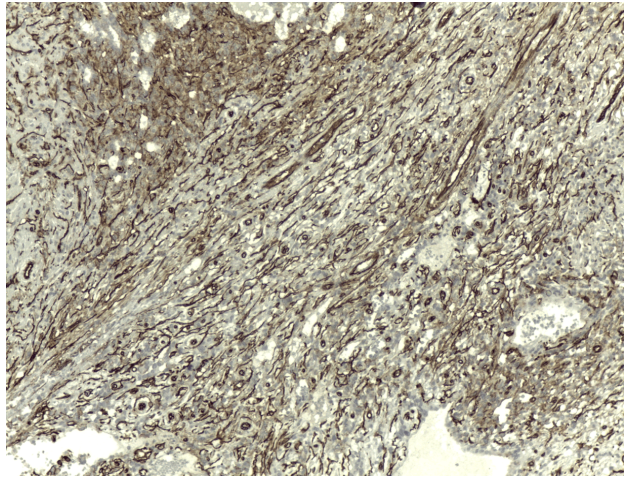


Figure 8 – Immunostaining for CD34 showing diffuse positivity in the fibroblasts and vascular structures between the microcystic/reticular spaces (IHC staining with DAB chromogen, ×100).

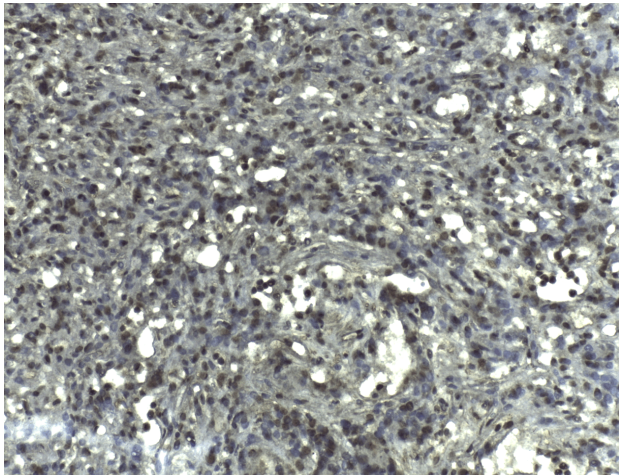


Figure 9 – Immunostaining for PCNA showing variable nuclear positivity in the spindle-cell component (IHC staining with DAB chromogen, ×200).

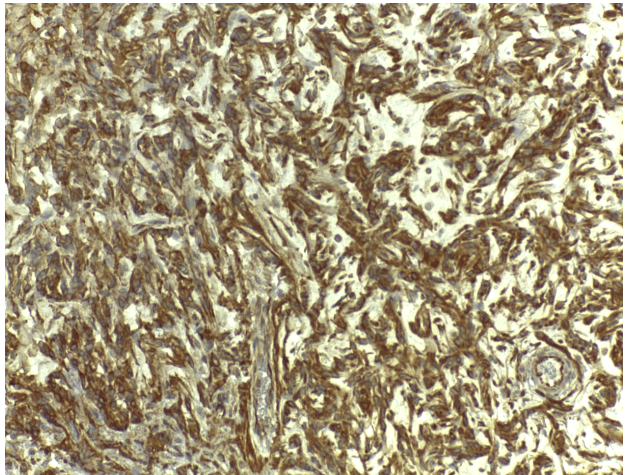


Figure 10 – Immunostaining for vimentin revealing diffuse cytoplasmic positivity across the entire tumor (IHC staining with DAB chromogen, ×200).

☐ Discussions

Schwannomas are benign, non-recurring tumors, which can feature a plethora of histological appearances and several variants have been well described in the scientific literature.

Microcystic/reticular variant (MRV) of schwannoma was initially described in 2008, by Liegl *et al.*, as a distinctive histopathological variant of schwannoma, with predilection for visceral locations, particularly the gastrointestinal tract [19–20, 22–25]. Similar tumors have been reported in the respiratory tract, adrenal glands, deep soft tissue of the face and upper back, cervical spine, parotid gland, pancreas, mesentery and skin. As observed in our case, these tumors reveal a predilection for women and tend to be relatively small in size. Liegl *et al.* described MRV as a lesion with striking microcystic and reticular growth pattern, composed of anastomosing and intersecting spindle cells with scant eosinophilic cytoplasm, set in a collagenous to myxoid stroma. The lesions are diffusely positive for S100, usually lack encapsulation and may show entrapment of normal structures at the

periphery, as seen in the current case. The tumors also generally lack typical organization into Antoni A and Antoni B areas and thick walled hyalinized vessels may be very rare. Our case showed reticular arrangement of cells and extensive cytoplasmic vacuolization as well. Artifactual overlapping of extravasated red blood cells in some areas was reminiscent of intracytoplasmic vascular lumina, raising the differential diagnosis of epithelioid hemangioendothelioma, but CD34 and CD31 were negative. Recognition of the presence of pseudoglandular elements in these tumors is important to distinguish them from other tumoral lesions, some of them with malignant potential, such as myxoid sarcoma. Microcystic structure with pseudo-epithelial lining composed of Schwann cells resulting in a pseudoglandular fashion is nowadays considered to be a degenerative change in these particularly rare tumors. The overall histopathological appearance of this case raised a wide spectrum of differential diagnoses. The main differentials for this location included lymphangioma, reticular perineurioma, nerve sheath myxoma, myxoid variant of cellular neurothekeoma, cutaneous lipomatous neurofibroma, myoepithelial tumors and extraskeletal

myxoid chondrosarcoma. All these differential diagnoses are discussed in the following paragraphs.

Lymphangiomas are developmental malformations of lymphatic tissue. Most cases appear in childhood, but some may arise secondary to lymphatic obstruction caused by surgery, radiation or infection. Histologically, lymphangiomas may be composed of small and large communicating cysts or sponge-like areas with small cavernous spaces. The sequestered tissue does not communicate normally with the lymphatic system and the spaces are filled with proteinaceous fluid containing lymphocytes and red blood cells. In our case, the cells lining the spaces were negative for D2-40, so lymphangioma was excluded.

Reticular perineurioma is a rare subtype of perineurioma, occurring most frequently between the fourth and fifth decade of life, preferentially in females, with predilection for distal extremities [26–28]. Histologically, the tumor is composed of spindle perineurial cells with fusiform nuclei and eosinophilic cytoplasm with thin processes arranged in a lace-like reticular pattern, exhibiting immunoreactivity for EMA and consistently lacking S100 reactivity [27]. However, staining for EMA may also be absent or focal and weak, most likely due to low antigen presentation in the thin elongated cytoplasmic processes [27, 28]. Rarely, mitoses and mild to moderate nuclear atypia may be present. The intervening stroma reveals marked degenerative, myxoid or edematous changes, with formation of pseudocystic cavities. The scientific literature contains multiple case reports of hybrid peripheral nerve sheath tumors, which combine histological features from both reticular perineurioma and schwannoma [29], or less frequently, neurofibroma [30] with or without pseudoglandular degenerative changes. This fact further demonstrates the heterogeneity of peripheral nerve sheath tumors and their capability to differentiate along more than one cell lineage. Also, it is of paramount importance to distinguish those variants from the extremely rare true glandular benign peripheral nerve sheath tumors and their malignant counterpart.

Nerve sheath myxoma is a benign nerve sheath tumor with Schwann cell differentiation, which typically appears in the fourth decade of life, with no gender predilection. It represents a controversial tumor due to its presumed relationship with neurothekeoma, but recent gene studies strongly suggest that nerve sheath myxomas and neurothekeomas are distinct entities. Grossly, nerve sheath myxomas present as solitary, multinodular, non-painful and slow-growing tumors, located in the dermis and/or subcutaneous tissue of the lower extremities, particularly the fingers [31]. Histologically, the tumor is usually well circumscribed, characterized by multiple nodules with low cellularity and abundant myxoid matrix, containing small epithelioid, ring-like, stellate or spindled neoplastic Schwann cells, which grow in cords and nests or form syncytial-like aggregates [32, 33]. Mitotic figures are uncommon and nuclear atypia is absent or mild. Immunohistochemically, neoplastic Schwann cells show diffuse immunopositivity for S100 protein, coupled with GFAP and CD57 positivity in the majority of cases. Nerve sheath myxomas may contain few EMA-positive perineurial cells within the fibrous capsule, occasionally

with CD34-positive interstitial fibroblasts [31, 32]. Although microcystic/reticular schwannoma and nerve sheath myxoma feature obvious IHC overlapping, there are clear differences in their pattern of growth – microcystic/reticular structures being absent in nerve sheath myxomas.

Cutaneous lipomatous neurofibroma represents a special subtype of neurofibroma characterized by variable amounts of mature fat in an otherwise classical neurofibroma [33]. Adipocytes are present in less than 10% of cutaneous neurofibromas, either as small groups of mature fat cells or as a diffuse distribution within the neoplastic spindle cell component. Whether mature fat in neurofibroma is an integral component of the tumor or represents and outcome of degenerative and/or metaplastic change has not been completely elucidated. However, upon careful histopathological examination, cutaneous lipomatous neurofibroma is significantly different both citologically and architecturally from microcystic/reticular schwannoma [34].

Cutaneous myoepithelioma is usually comprised of cords or nests of epithelioid, ovoid, or spindle cells with variably reticular architecture and a chondromyxoid or collagenous stroma [35]. It differs from microcystic/reticular schwannoma by the variegated morphology and coexpression of epithelial and myogenic markers.

Extraskelatal myxoid chondrosarcoma (EMC) was first described by Enzinger & Shiraki, in 1972, as a rare soft-tissue sarcoma, which primarily occurs in the deep soft tissue of the extremities, especially within the skeletal muscles and tendons. Histologically, it is characterized by a well-circumscribed multilobular growth of oval to short spindle cells, typically arranged in short anastomosing strands or cords with microcystic or reticular pattern, set in the background of abundant myxoid matrix [36, 37]. However, a uniform reticular pattern as in reticular schwannoma has not been described. The cells are characterized by hyperchromatic nuclei and tiny nucleoli, some featuring nuclear grooves. Immunohistochemically, EMC is generally negative for various cytokeratins and may be positive for S100 protein, thus being a diagnostic challenge [37].

Angiomatoid fibrous histiocytoma is a circumscribed, multinodular or multicystic hemorrhagic tumor, with a thick fibrous pseudocapsule surrounding nodules, sheets, short fascicles or whorls of monomorphic spindle cells with eosinophilic cytoplasm, accompanied by characteristic lymphoplasmacytic infiltrates. The tumor may be highly cellular with bland histiocytoid cells, spaces and myxoid stromal change. A recently reported case of angiomatoid fibrous histiocytoma describes a reticular morphological variant that looks similar to our case, but the immun-expression of desmin and EMA that are typically seen in angiomatoid fibrous histiocytoma are not seen in our case.

Establishing the diagnosis of microcystic/reticular schwannoma by morphology alone is arduous without the help of extensive ancillary studies. When present, areas of classic schwannoma are an important diagnostic clue, thus saving unnecessary work-up.

Most schwannomas are benign and usually cured by surgical resection, although the so-called “malignant schwannoma” does rarely occur [38]. The follow-up

data in the scientific literature emphasizes the fact that microcystic/reticular schwannomas are completely benign. Due to the comorbidities and the treatment procedures that our patient was subjected to, the interpretation of follow-up data in this case is problematic, but supports the information from the scientific literature.

✉ Conclusions

Microcystic/reticular schwannoma poses a challenge to both surgeons and pathologists. A high index of suspicion and awareness of the histological features of this rare and unusual morphological variant is essential for accurate diagnosis, enlarging the catalog of differential diagnoses for soft tissue tumors with a reticular growth pattern. Extensive literature review concerning this very rare tumor uncovered a paucity of case reports on this matter especially with cutaneous layout, and the authors emphasize the importance of further data collection.

Conflict of interests

The authors declare that they have no conflict of interests.

Ethical standards

We undersign, certificate that the procedures and the experiments we have done respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000 (5), as well as the national law.

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