

**A Painful S-100 (-) /CD68 (+) Myxoid-hypocellular Neurothekeoma: A Case Review
through an Unusual Nerve Sheath Tumor**
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ABSTRACT

Neurothekeomas are very rare benign soft tissue tumors which originate from sheath of the peripheral nerves. They are commonly located on the upper extremities or the head and the neck. Pain is an unusual clinical symptom. We report a case of a sixty-nine year-old woman, who presented us with a painful nodule on the upper inner surface of the left leg. With the histopathological, histochemical and immunostaining features the lesion was diagnosed as S100 (-) / CD68 (+) myxoid hypocellular neurothekeoma. The case was presented due to the unusual clinicopathological features.

Keywords: Leg, myxoma, nerve sheath tumors, neurothekeoma, painful

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INTRODUCTION

Neurothekeoma is an uncommon benign soft tissue tumor which originates from the sheath of the peripheral nerves with fairly distinctive histological features (1). It is commonly located on the head, neck and upper extremities of young females in the second or third decades of life (2, 3). The tumors are mainly classified into three groups according to cellularity of the tumor, growth pattern, and amount of stromal mucin as myxoid, cellular, and mixed type (2, 4). Immunohistochemical staining features can help to distinguish the histological variants of the tumor, and also differentiate it from other nervous tissue tumors and melanocytic tumors (1-3). Due to the rarity of neurothekeomas, lack of their specific clinical and histological features, and non standardized immunohistochemicals for identification, there is no consensus about the certain diagnostic criteria, and they are increasingly subjected to conceptual changes in classification (1, 2, 4).

CASE REPORT

A sixty-nine year-old woman was admitted to our dermatology clinic with a tender protrusion located on her left leg which was present for six years without history of trauma and precursor lesion. There was no additional complaint or other significant medical or family history. The dermatological examination showed a pinkish-purple, semitranslucent, moderately hard, elastic in consistency, 4.5x2.5 cm in size, solid and fusiform soft tissue tumor on the upper inner surface of left leg (Fig. 1a,b). The patient stated that she did not sleep and walk easily due to the pricking pain, especially with lateral pressure onto the lesion. Routine laboratory examinations of the patient including a red blood cell count, hemoglobin, hematocrit, erythrocyte sedimentation rate, serum biochemistry and urinalysis were within the normal limits. Physical examination did not reveal signs of regional or

systemic lymphadenopathy or hepatosplenomegaly. Neurological examination was normal. Requested soft tissue ultrasonography showed a well-vascularized, semi-hypoechoic, well-circumscribed dermal tumoral mass. Subsequently, the lesion was totally excised and the defect was closed primarily. Histopathological examination revealed an encapsulated concentric dermal tumor composed of a single large nodule with scattered stellate and spindle-shaped cells on a background of myxoid-rich eosinophilic stroma, and prominent angioplasia of the dermal vessels. Cellularity of the tumor was considered to be very low. (Fig. 2a,b,c). It was filling the dermis and extended to subcutaneous fatty tissue, but did not invade it. No vascular or perineural invasion, high mitosis or cytological pleomorphism was found. Histochemical staining demonstrated that the tumor cells were strong positive for alcian blue (>90 %) (Fig. 2d). Immunohistochemical analyses of the cells were negative for S-100 (Fig. 2e,f) and glial fibrillary acidic protein (GFAP) (Fig. 2g), and were positive for CD68 (Fig. 2h) and vimentin (Figure 2i). Additionally, there was focal and nonspecific positivity for CD57 (Fig. 2j). Based on the histopathological and immunohistochemical findings, the lesion was diagnosed as S100 (-) / CD68 (+) myxoid-hypocellular neurothekeoma. The patient was followed up for fifteen months without evidence of recurrence.

DISCUSSION

Neurothekeoma was firstly described by Hakin and Reed in 1969, as nerve sheath myxoma, but the name 'neurothekeoma' was given by Gallager and Helwing in 1980 (5). The origin of these tumors has not been elucidated and their etiology has been debated upon (2). However, they were considered to be derived from nerve cells or Schwann cells (1). The tumor is commonly present as small solitary erythematous nodules on the face and the upper limb. Other locations such as oral cavity, cauda equina, lower limb, shoulder, and neck have been

reported in literature (3). It can originate in mucosa or submucosa (6). The tumors are difficult to diagnose prior to performing a biopsy due to the lack of specific clinical manifestations or imaging characteristics (2). However, they are usually slow-growing nontender lesions which are either dermal or subdermal (3,4). Myxoid type is primarily found in adults, with a predilection for the head and neck region in women. The cellular variant was first described in 1986 by Rosati et al. stating that they were frequently observed in the face of young persons (1). In our case, the lesion was painful and located on an unusual anatomic location of upper-leg and these unusual clinical features were not consistent with the common literature. Neurothekeomas show three histological variants: Myxoid (classical or hypocellular), cellular, and mixed (4) primarily on the basis of the amount of myxoid matrix (1,4), cellularity, growth pattern (4), and S-100 positivity (7). Fetsch et al. classified that, tumors with >50% myxoid matrix as myxoid type, tumors with >10% but ≤50% myxoid matrix as mixed-type, and those with ≤10% myxoid matrix as cellular type (1). The histopathological findings of myxoid neurothekeomas are lobular to plexiform dermal tumor masses composed of spindle-to stellate-shaped cells, with a striking myxoid stroma. The cellular variants have an ill-defined fascicular growth pattern consisting of plump epitheloid spindle cells (8), and the mucinous matrix is sparse or absent (1). They can show variable cytological atypia and mitotic activity (2,7). The mixed type has shares features of both (4). Additionally, atypical cellular subtype of cellular neurothekeoma is characterised by some features such as large size of up to 6 cm, penetration into subcutaneous fat and/or muscle, diffusely infiltrating borders, vascular invasion, a high mitotic rate and marked cytological pleomorphism (8). Our lesion did not show prominent cellularity, which was then considered as hypocellular (myxoid) type. It stained positively >90 % for alcian blue, which is a characteristic for myxoid type. Additionally, the tumor was composed of a big single nodule with delicate, concentric layers, and therefore it matched

the lobular growth pattern that is attributed to the myxoid (hypocellular) type. For these reasons, we first thought that our lesion could be a classical myxoid hypocellular neurothecoma. On the other hand, it has been stated that the subtypes of neurothecoma could be distinguished with some immunohistochemical markers such as S100 protein, glial fibrillary acidic protein (GFAP), nerve growth factor receptor (NGFR), CD57, NKI/C3, Ki-M1p, and CD68 (1). Myxoid types are typically positive for markers of nerve-origin cells, such as S100 protein, GFAP, and NGFR, but not for macrophage markers including Ki-M1p and CD68. Therefore, myxoid subtypes are considered to be derived from nerve cells or Schwann cells (1). However, our lesion was negatively stained for S-100 and GFAP, but positive for CD68 which did not comply with the literature regarding the myxoid type. On the other hand, cellular type is usually negative for S-100, GFAP, NGFR, and CD57, but positive for NKI/C3, Ki-M1p and CD68. For this reason, it has been postulated that cellular variant shows a fibrohistiocytic differentiation. Although S-100 negativity is known to be useful in differentiating the myxoid variants from the cellular ones, firstly Strumia et al. reported S-100 (-) myxoid neurothecoma in 2001 (1,9). Some authors suggested that myxoid neurothecoma can lose the strong S-100B expression when cells are less differentiated (4). Only four S-100 (-) myxoid neurothecomas have been reported in literature. However, in only one case, the fibrohistiocytic staining such as CD68 was performed. In addition, the staining for vimentin is usually positive in both type (1) as seen in our case. However, it has been stated that fibrohistiocytic markers such as vimentin, EMA, factor XIIIa or SMA, and neuroectodermal antigens including neuron-specific enolase, NKI/C3, PGP 9.5 have restricted diagnostic value in determining the histological types. On the other hand, mixed types can have both types of features, but the immunostainings often exhibit non-regular features with an irregular or absent reactivity to S100 protein and smooth muscle actin. Moreover, in 2002 Rudolph and Schubert first reported a “myxoid cellular neurothecoma” which has the typical histological features of

the myxoid type, but was negative for S100 protein or NGFR, and positive for NKI/C3 and Ki-M1p (1). In our case, although the lesion had high degree staining with alcian blue, low cellularity and lobular growth pattern which are specific for myxoid types, because of the negative staining for S 100 and GFAP and the positive staining for CD68 and vimentin, it was diagnosed as lobular, S100 (-) / CD68 (+) myxoid-hypocellular neurothekeoma. The cases of Rudolph and Schubert, and Yun et al. (1) were similar to our lesion. However, although their lesions did not exhibit prominent cellularity, they named their lesions as “myxoid cellular” according to only immunohistochemical staining features. However, we think that the term “cellular” must only describe a histological feature rather than a immunohistochemical staining characteristic, and, describing these complicated lesions according to only one diagnostic criterion can lead to diagnostic shortcomings. Therefore, we suggest that in the naming and classification of these tumors, the mucin content, growth pattern, cellularity and immunohistochemical staining features must be defined and evaluated separately to avoid diagnostic confusion. In the main differential diagnoses of neurothekeomas, fibroma, dermatofibroma, leiomyoma, neurilemmoma, neurofibroma (7), melanocytic tumors (5), skin cysts, or adnexal neoplasms (1) should be considered. The neurothekeomas are usually slow growing benign tumors, and if totally excised do not recur. No metastasis has been reported (2,4,5). We think that elaborated clinical, histological, immunohistochemical and also electronmicroscopic descriptions with the finest details of new cases will help us to better to understand, and accurately diagnose these unusual and very rare tumors more easily. Therefore, reporting each different finding about new cases in the future is very important to avoid misdiagnosis, to make differential diagnosis easier, and to provide a diagnostic consensus. Our case was presented in order to emphasize the rarity, diagnostic difficulties and correct naming of neurothekeomas.

Conflict of interest: The authors declare that they have no conflict of interests.

REFERENCES

1. Yun SJ, Park HS, Lee JB, Kim SJ, Lee SC, Won YH. Myxoid Cellular Neurothekeoma: A New Entity of S100-Negative, CD68-Positive Myxoid Neurothekeoma. *Ann Dermatol* 2014; **26**: 510–13.
2. Li J, Shi Z, Jing J. Neurothekeomas of the thoracic and lumbar area in an adult man: A case report. *Mol Clin Oncol* 2014; **2**: 156–8.
3. Stratton J, Billings SD. Cellular neurothekeoma: analysis of 37 cases emphasizing atypical histologic features. *Mod Pathol* 2014; **27**: 701–10.
4. Wollina U, Hansel G, Schönlebe J, Haroske G. Myxoid neurothekeoma--a painful case in a less common location. *Dermatol Online J* 2009; **15**: 3.
5. Akhtar K, Zaheer S, Ray PS, Sherwani RK. Myxoid neurothekeoma: a rare soft tissue tumor of hand in a male toddler. *Niger J Surg* 2013; **19**: 32–4.
6. Cribier B1, Baran R, Varini JP. Nerve sheath myxoma of the hyponychium. *Ann Dermatol Venereol* 2013; **140**: 535–39.
7. Avninder S, Ramesh V, Vermani S. Benign nerve sheath myxoma (myxoid neurothekeoma) in the leg. *Dermatol Online J* 2007; **13**: 14.
8. Wilson AD, Rigby H, Orlando A. Atypical cellular neurothekeoma--a diagnosis to be aware of. *J Plast Reconstr Aesthet Surg* 2008; **61**: 186–8.
9. Strumia R, Lombardi AR, Cavazzini L. S-100 negative myxoid neurothekeoma. *Am J Dermatopathol* 2001; **23**: 82–3.

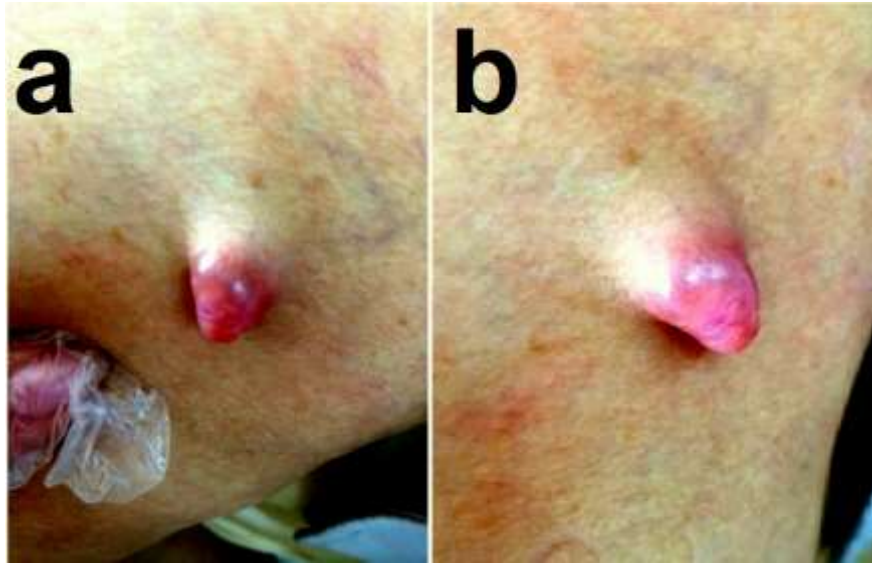


Fig. 1: Clinical views of the lesion (a. distant, b. closer)

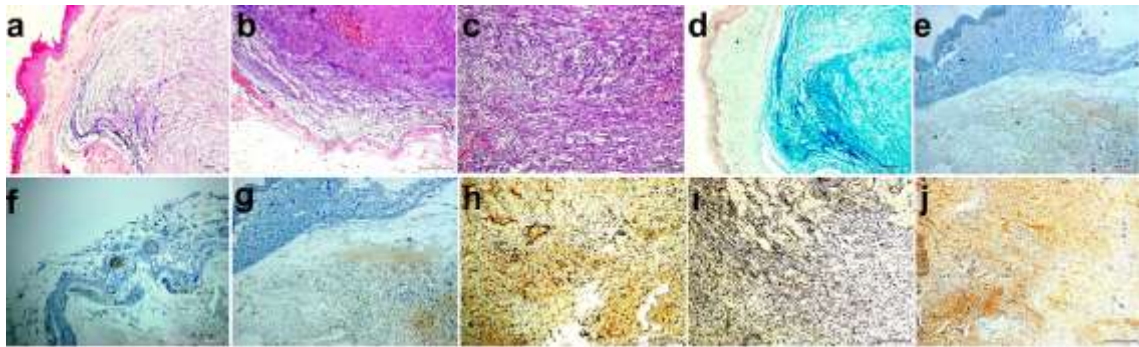


Fig 2: Histopathological views of the lesion (a.HEX40, b,c.HEX100, d. alcian blueX 40, e. S100X 40, f. S100 positive control X100, g.GFAPX40, h. CD68X100, i. VimentinX40, j. CD57X40)