CASE REPORT

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

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ABSTRACT

Neurothekeomas are very rare, benign, soft-tissue tumours that originate from the 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 69-year-old woman, who presented to 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 S-100 (−)/CD68 (+) myxoid hypocellular neurothekeoma. The case was presented due to the unusual clinicopathological features.

Keywords: Leg, myxoma, nerve sheath tumours, neurothekeoma, painful.

INTRODUCTION

Neurothekeoma is an uncommon, benign, soft-tissue tumour that 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 tumours are mainly classified into three groups according to cellularity of the tumour, 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 tumour, and also differentiate it from other nervous tissue tumours and melanocytic tumours (1–3). Due to the rarity of neurothekeomas, lack of specific clinical and histological features, and non-standardised immunohistochemical markers for identification, there is no consensus about certain diagnostic criteria, and they are increasingly subjected to conceptual changes in classification (1, 2, 4).

CASE REPORT

A 69-year-old woman was admitted to our dermatology clinic with a tender protrusion located on her left leg which was present for 6 years without any 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, semi-translucent, moderately hard, elastic in consistency, 4.5 × 2.5 cm in size, solid and fusiform soft-tissue tumour on the upper inner surface of the left leg (Fig. 1A, 1B). The patient stated that she did not sleep and walk easily due to the pricking pain, especially with lateral pressure on the lesion.

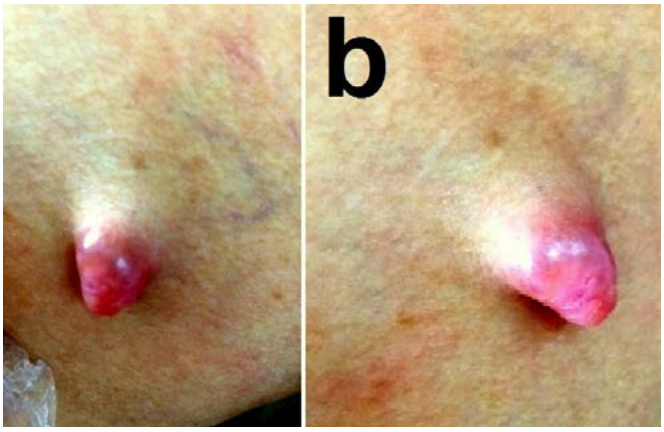

Fig. 1: Clinical views of the lesion: (A) distant, (B) closer.

Routine laboratory examinations of the patient including a red blood cell count, haemoglobin, haematocrit, erythrocyte sedimentation rate, serum biochemistry and urinalysis were within normal limits. Physical examination did not reveal signs of regional or systemic

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lymphadenopathy or hepatosplenomegaly. Neurological examination was normal. Requested soft-tissue ultrasonography showed a well-vascularised, semi-hypoechoic, well-circumscribed dermal tumoural mass. Subsequently, the lesion was totally excised and the defect was closed primarily. Histopathological examination revealed an encapsulated, concentric, dermal tumour 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 tumour was considered to be very low (Fig. 2A–2C). 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 were found. Histochemical staining demonstrated that the tumour cells were strongly positive for alcian blue (> 90%) (Fig. 2D). Immunohistochemical analyses of the cells were negative for S-100 (Fig. 2E, 2F) and glial fibrillary acidic protein (GFAP) (Fig. 2G), and were positive for CD68 (Fig. 2H) and vimentin (Fig. 2I). Additionally, there was focal and non-specific positivity for CD57 (Fig. 2J). Based on the histopathological and immunohistochemical findings, the lesion was diagnosed as S-100 (−)/CD68 (+) myxoid-hypocellular neurothekeoma. The patient was followed up for 15 months without evidence of recurrence.

DISCUSSION

Neurothekeoma was first 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 tumours has not been elucidated and their aetiology has been debated (2). However, they were considered to be derived from nerve cells or Schwann cells (1). The tumour is commonly presents as small, solitary, erythematous nodules on the face and the upper limb.

Other locations such as the oral cavity, *cauda equina*, lower limb, shoulder, and neck have been reported in literature (3). It can originate in mucosa or submucosa (6). The tumours 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, non-tender 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 the upper leg and these unusual clinical features were not consistent with the common literature. Neurotehekeomas 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 as follows: tumours with > 50% myxoid matrix as myxoid type, tumours 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 tumour 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 epithelioid spindle cells (8), and the

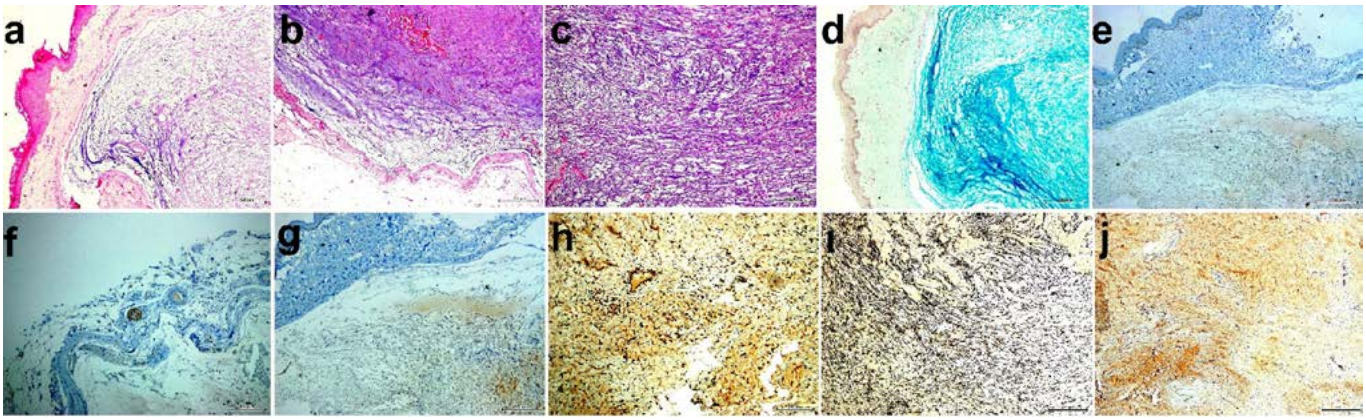

Fig. 2: Histopathological views of the lesion: (A) HE ×40, (B, C) HE ×100, (D) alcian blue ×40, (E) S-100 ×40, (F) S-100 positive control ×100, (G) GFAP ×40, (H) CD68 ×100, (I) Vimentin ×40, (J) CD57 ×40.

mucinous matrix is sparse or absent (1). They can show variable cytological atypia and mitotic activity (2, 7). The mixed type 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 of the myxoid type. Additionally, the tumour 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 neurothekeoma. On the other hand, it has been stated that the subtypes of neurothekeoma could be distinguished with some immunohistochemical markers such as S-100 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 S-100 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 the cellular variant shows a fibrohistiocytic differentiation. Although S-100 negativity is known to be useful in differentiating the myxoid variants from the cellular ones, first Strumia *et al.* reported S-100 (−) myxoid neurothekeoma in 2001 (1,9).

Some authors suggested that myxoid neurothekeoma can lose the strong S-100B expression when cells are less differentiated (4). Only four S-100 (−) myxoid neurothekeomas 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 types (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 S-100 protein and smooth muscle actin. Moreover, in 2002 Rudolph and Schubert first reported a 'myxoid cellular neurothekeoma' which has the typical histological features of the myxoid type, but was negative for S-100 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, S-100 (−)/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 an 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 tumours, 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 tumours (5), skin cysts, or adnexal neoplasms (1) should be considered. The neurothekeomas are usually slow-growing, benign tumours, and if totally excised, do not recur. No metastasis has been reported (2, 4, 5). We think that elaborated clinical, histological, immunohistochemical and also electron-microscopic descriptions with the finest details of new cases will help us to better understand, and accurately diagnose these unusual and very rare tumours 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 emphasise the rarity, diagnostic difficulties and correct naming of neurothekeomas.

AUTHORS' NOTE

The authors declare that they have no conflict of interests.

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