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Comparative Case Reports of Nerve Sheath Myxoma and Neurothekeoma

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Abstract

Nerve sheath myxoma has been confused with neurothekeoma due to similarities in their histopathological findings. Here we describe the clinical, histopathological, and immunohistochemical features in one case of nerve sheath myxoma and two cases of neurothekeoma. Case 1 was a 49-year-old woman who presented with a 10-year history of a non-tender, rubbery, firm, highly mobile, 5-mm subcutaneous tumor on the left third finger. Case 2 was a 24-year-old woman who presented with a 2-year history of a 17 × 10-mm non-tender, reddish-brown nodule, with a rough surface on the right shoulder. Case 3 was a 12-year-old boy who presented with a 1-year history of an approximately 10-mm non-tender, red papule, with a glossy surface on the lower right portion of his back. In all cases, microscopic examination demonstrated multiple, closely aggregated nodules that were separated by a band of fibrous connective tissue in the dermis. Each nodule was composed of spindle and large epithelioid cells, with various amounts of mucin. S-100 protein was positive in Case 1, with a diagnosis of nerve sheath myxoma. In contrast, S-100 protein was negative in Cases 2 and 3, with a diagnosis of neurothekeoma. Nerve sheath myxoma and neurothekeoma can be differentiated based on S-100 protein expression, and this was supported by microarray analysis findings in recent reports. It is important to recognize these two tumors as separate entities.

Keywords

Comparative study; Immunohistochemistry, nerve sheath myxoma; Neurothekeoma; S-100 protein

Introduction

Ever since it was initially described by Harkin and Reed in 1969 in the Atlas of Tumor Pathology series of the Armed Forces Institute of Pathology [1], nerve sheath myxoma has been a controversial topic phylogenetically. Neurothekeoma was introduced by Gallager and Helwig in 1980 as a superficial tumor of purported nerve sheath derivation, similar to nerve sheath myxoma [2]. Subsequently, in 1986, Rosati et al. proposed a subgroup of cellular neurothekeoma, which had an abundant cellular component and a scant amount of myxoid matrix [3]. Recently, neurothekeoma has been divided morphologically into three subtypes based on the amount of myxoid matrix, namely myxoid, mixed, and cellular [4-6].

Although Fetsch et al. reported in 2005 that nerve sheath myxoma and neurothekeoma were

morphologically, immunohistochemically, and clinically distinct [7], there still exist some reports confusing these two entities [8-10].In Particular, nerve sheath myxoma has been regarded as a myxoid variant of neurothekeoma; therefore, these two terms have been used synonymously.

To highlight the difference between these 2 diseases, we report one case of nerve sheath myxoma and two cases of neurothekeoma.

Case Reports

Case 1: A 49-year-old woman presented with an approximately 10-year history of an asymptomatic subcutaneous tumor on the finger, which gradually increased in size. Physical examination revealed a non-tender, rubbery, firm, highly mobile, 5-mm subcutaneous tumor on the left third finger (Fig. 1a,b; Table 1). Microscopic examination demonstrated a multilobular configuration in the dermis and subcutis, which was typically separated by a band of fibrous connective tissue. The lobules had abundant myxoid matrix and consisted of spindled and epithelioid cells (Fig. 1c–e).

Case 2: A 24-year-old woman presented with a 2-year history of an asymptomatic small nodule on the shoulder. Physical examination revealed a 17 × 10-mm non-tender, reddish-brown nodule with a rough surface on the right shoulder (Fig. 2a,b; Table 1). Microscopic examination demonstrated multiple, closely situated nodules, separated by a band of fibrous connective tissue in the dermis. Each nodule was composed of spindle and large epithelioid cells with a scant amount of myxoid matrix, and partially contained osteoclast-like giant cells and syncytial-like cells (Fig. 2c–e).

Case 3: A 12-year-old boy presented with a 1-year history of an asymptomatic small nodule on the back, which gradually increased in size. Physical examination revealed an approximately 10-mm, non-tender, red papule with a glossy surface on the lower right portion of the back (Fig. 3a,b) (Table 1). Microscopic examination revealed multiple small nodules separated by a band of fibrous connective tissue in the dermis and subcutis. Each nodule was composed of spindle and epithelioid cells, with focal myxoid matrix, and it partially contained atypical cells (Fig. 3c–e).

Immunohistochemistry

Using formalin-fixed paraffin-embedded tissue, all cases were immunohistochemically stained with the following antibodies: S-100 protein (1:6; Dako, Glostrup, Denmark), HMB-45 (prediluted; Dako), glial fibrillary acidic protein (GFAP) (1:12; Dako), CD10 (56C6, 1:2; NICHIREI, Tokyo, Japan), CD34 (QBEnd10, 1:100; Dako), CD68 (PG-M1, 1:100; Dako), Factor XIIIa (E980.1, 1:40; Leica Biosystems Newcastle, Newcastle Upon Tyne, United Kingdom), neuron specific enolase (NSE) (BBS/NC/VI-H14, prediluted; Dako), smooth muscle actin (SMA) (1A4, 1:400; Dako), and epithelial membrane antigen (EMA) (E29, 1:100; Dako).

Immunohistochemical analysis revealed that S-100 protein and GFAP were positive in Case 1, but negative in Cases 2 and 3 (Fig. 4a–f). HMB-45, CD34, and EMA were negative in all cases. SMA was negative in Case 1, positive in Case 2, and partially positive in Case 3 (Fig. 4g–i). CD68 was negative in Cases 1 and 2, but was partially positive in Case 3. CD10 was negative in Case 1, partially positive in Case 2, and strongly positive in Case 3 (Fig. 4j–l). Factor XIIIa was negative in Cases 1 and 2, but was partially positive in Case 3. NSE was negative in Case 1, but was focally, weakly positive in Cases 2 and 3 (Table 2).

Diagnosis

Based on these findings, Case 1 was diagnosed with nerve sheath myxoma, and Cases 2 and 3 were diagnosed with a cellular type of neurothekeoma.

Discussion

Case 1, with a diagnosisof nerve sheath myxoma, had many spindle cells with abundant myxoid matrix. The tumor was positive for S100 protein and GFAP and was negative for NSE, EMA, and CD10. We considered that the origin of this tumor was not perineurial cells, but rather Schwann cells.

Case 2, with a diagnosis of cellular-type neurothekeoma, reacted with SMA fairly and with CD10 partially, but did not react with CD34, CD68, or Factor XIIIa. These results implied that this tumor was derived from either a fibroblast-like cell or a myofibroblast. Case 3, also with a diagnosis of cellular-type neurothekeoma, exhibited partial positivity for SMA, CD68, and Factor XIIIa, strong positivity for CD10, and was negative for CD34. We speculated that this tumor was derived from a fibroblast-like cell, myofibroblast, or fibrohistiocyte. Cases 2 and 3 had cell-rich tumors, which were composed of spindle and epithelioid cells, and lacked S100 protein and GFAP expression, suggesting that these tumors were not derived from the peripheral nerve sheath or melanocytes.

Based on immunophenotypic and ultrastructural findings, nerve sheath myxoma is considered to be derived from Schwann cells [4-6, 10-13]. In 2005, Fetsch et al. suggested that nerve sheath myxoma was a special type of schwannoma or, less likely, neurofibroma. This was due to the low number of intralesional CD34-positive fibroblasts and EMA-positive perineurial cells, a rarity of intralesional axons, and the infrequent presence of foci that suggest nuclear palisading or loose Verocay body formation [7].Sheth et al. also suggested that nerve sheath myxoma demonstrated very similar molecular genetic signatures to those of schwannomas on microarray analysis [14].

Given the absence of S-100 protein in the tumor, there has been some doubt as to whether cellular neurothekeoma (cellular type) is neurosustentacular in origin [4-6, 15-16]. In 2007, Fetsch et al. suggested that neurothekeoma was derived from fibroblast-like cells with the capacity to produce myxoid matrix and differentiate into myofibroblasts; this was based on the morphology of the tumor cells, the population of non-lesional cells, the occasional presence of neoplastic cells with actin, CD99, and CD10 expression, and an occasional resemblance to plexiform fibrohistiocytic tumor [17]. Sheth et al. also suggested that all subtypes of neurothekeoma more closely resembled cellular fibrous histiocytomas on microarray analysis [14].

Nerve sheath myxoma and neurothekeoma have similar findings, namely a multilobulated mass consisting of spindle and epithelioid cells with a myxoid matrix that is separated by a band of fibrous connective tissue. Therefore, differentiation between these 2 diseases is difficult. Particularly, nerve sheath myxoma has been confused with myxoid neurothekeoma (myxoid type), and these terms have often been used synonymously. However, Fetsch et al. reported that immunoreactivity of S-100 protein was useful in differentiating nerve sheath myxoma from myxoid neurothekeoma, i.e., S-100 protein was positive in nerve sheath myxoma, but negative in (myxoid) neurothekeoma [17].

There are also clinical differences between nerve sheath myxoma and neurothekeoma. Nerve sheath myxoma has a peak incidence in the fourth decade of life, has a strong predilection for the fingers,

and has a male-to-female ratio of almost 1:1. Neurothekeoma has a peak incidence in the second decade of life, has a strong predilection for the head and upper extremities, and has a male-to-female ratio of 1:2 [7,17].

In the present report, Case 1 represented nerve sheath myxoma in terms of clinical manifestations, such as age and the site of the tumor. Cases 2 and 3, on the other hand, corresponded well to the clinical characteristics of neurothekeoma.

In summary, nerve sheath myxoma and neurothekeoma can be differentiated based on S-100 protein expression, which was supported by the microarray analysis findings of recent reports. They also have different clinical features; it is important to understand the differences between these 2 diseases.

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Figures

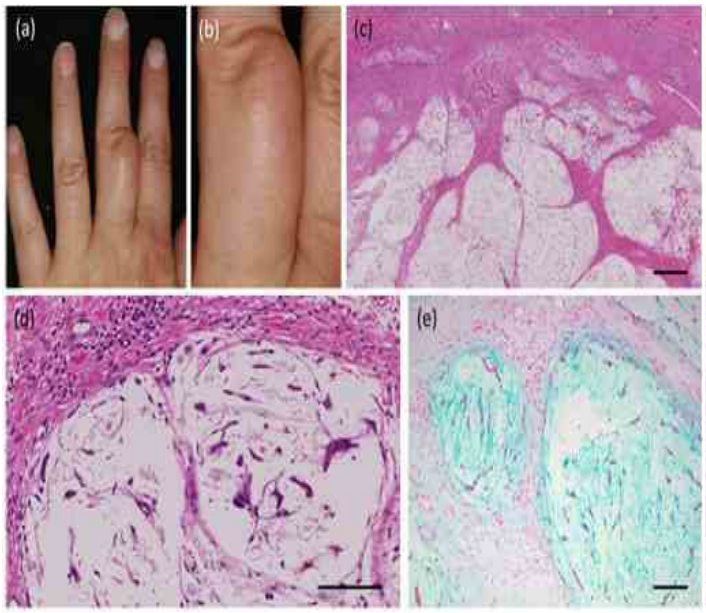

Figure 1: (a, b) A 5-mm subcutaneous tumor on the left third finger. (c–e) Histopathology revealed a nerve sheath myxoma on the finger. (c) The multilobular configuration was typically separated by a band of fibrous connective tissue [Hematoxylin and eosin (HE), original magnification ×25, index bar indicates 0.5mm]. (d) Lobules included abundant myxoid matrix, spindle, and epithelioid cells (HE, original magnification ×200, index bar indicates 100μm). (e) Myxoid matrix is evident on Alcian blue staining (Alcian blue pH2.5, original magnification ×100, index bar indicates 100 μm).

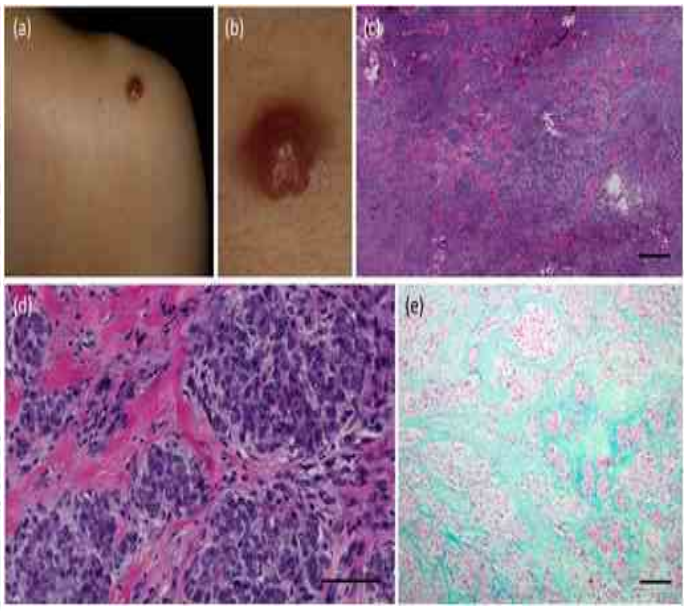

Figure 2: (a, b) A 17 × 10-mm small nodule on the right shoulder. (c–e) Histopathology revealed cellular-type neurothekeoma on the shoulder. (c) Multiple nodules were separated by a band of fibrous connective tissue in the dermis (HE, original magnification ×25, index bar indicates 0.5mm). (d) They were composed of spindle and large epithelioid cells with occasional osteoclast-like giant cells and syncytial-like cells (HE, original magnification, ×200, index bar indicates 100 μm). (e) Myxoid matrix is evident on Alcian blue staining (Alcian blue pH2.5, original magnification ×100, index bar indicates 100 μm).

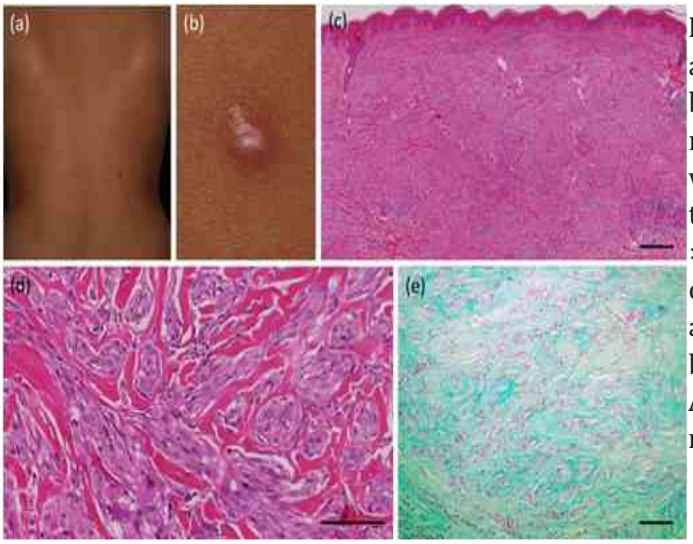

Figure 3: (a, b) A small nodule with a size of approximately 10 mm on the lower right portion of the back. (c–e) Histopathology showed cellular-type neurothekeoma on the back. (c) Multiple small nodules were separated by a band of fibrous connective tissue in the dermis and subcutis (H-E, original magnification ×25, index bar indicates 0.5mm). (d) They were composed of spindle and epithelioid cells, and partially atypical cells. (HE, original magnification, ×200, index bar indicates 100 μm). (e) Myxoid matrix is evident on Alcian blue staining (Alcian blue pH2.5, original magnification ×100, index bar indicates 100 μm).

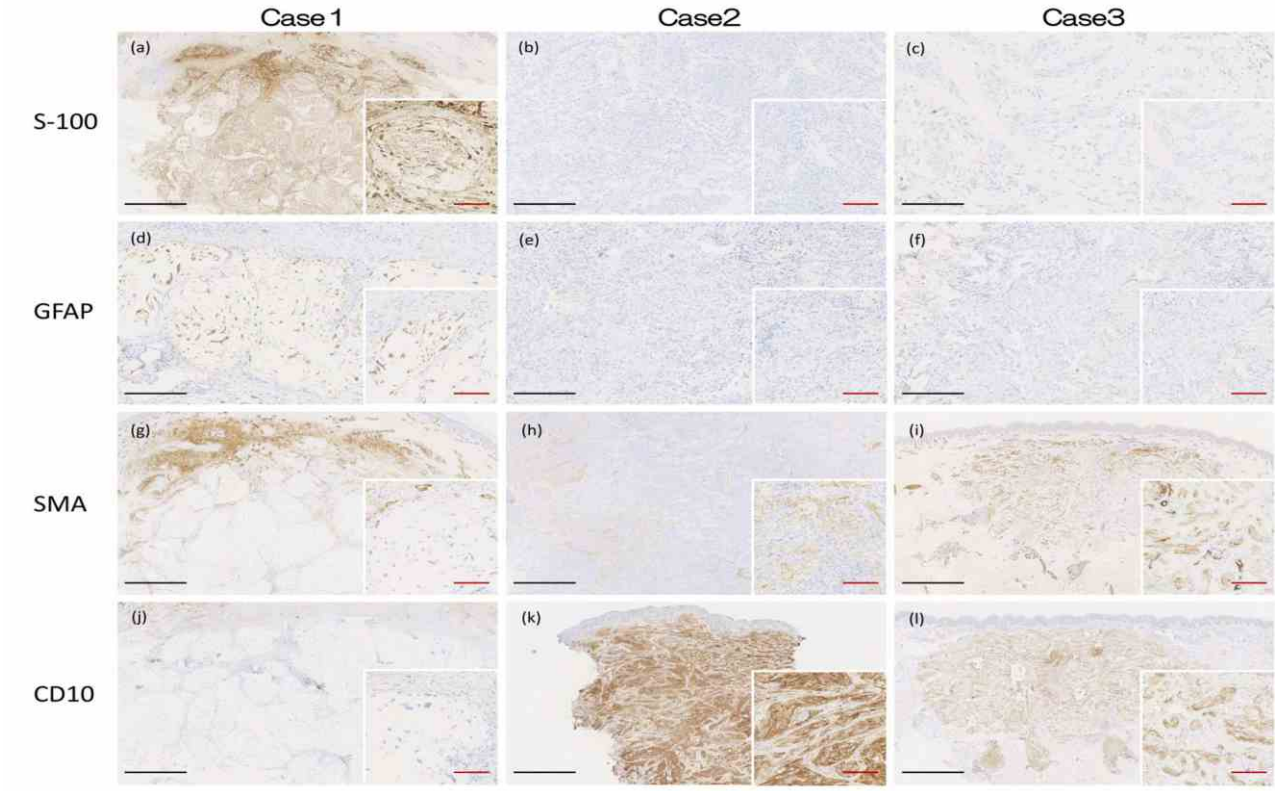

Figure 4: (a–l) Immunohistochemical findings of the three cases. S-100 protein was positive in Case1 (a), but negative in Cases 2 (b) and 3 (c). GFAP was positive in Case 1 (d), but was negative in Cases 2 (e) and 3 (f). SMA was negative in Case 1 (g), positive in Case 2 (h), and partially positive in Case 3 (i). CD10 was negative in Case1 (j), partially positive in Case 2 (k), and strongly positive in Case 3 (l) (original magnification ×25 and ×200 (inset), black bar indicates 1mm, and red bar indicates 100 μm).

Tables

Table 1. Clinical features

Case	Diagnosis	Age	Sex	Site	Clinical manifestations
1	nerve sheath myxoma	49	F	left third finger	5mm, asymptomatic, rubbery firm, well-mobile subcutaneous tumor
2	cellular neurothekeoma	24	F	right shoulder	17mm×10mm, asymptomatic reddish brown nodule with rough surface
3	cellular neurothekeoma	12	M	lower right portion of the back	10mm, asymptomatic, red papule with glossy surface

Table 2. Immunohistochemical findings

case	Diagnosis	S100	HMB-45	SMA	CD68	CD34	CD10	Factor XIIIa	NSE	GFAP	EMA
1	nerve sheath myxoma	+	–	–	–	–	–	–	–	+	–
2	cellular neurothekeoma	–	–	+	–	–	partially +	–	weakly +	–	–
3	cellular neurothekeoma	–	–	partially +	partially +	–	strongly +	partially +	weakly +	–	–

S-100, S-100 protein; SMA, smooth muscle actin; NSE, neuron specific enolase; GFAP, glial fibrillary acidic protein; EMA, epithelial membrane antigen.

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