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Case Studies

Cellular Neurothekeoma in a Female with Guillain-Barré Syndrome: A Case Report and Review of the Literature

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Key Words

Neurothekeoma · Guillain-Barré syndrome · Dermatology

Abstract

Cellular neurothekeoma is a rare cutaneous tumor that occurs more frequently in women. A 68-year-old female with a history of left nasal alar basal cell carcinoma and Guillain-Barré syndrome presented to the clinic with a 3-mm firm skin-colored papule with scattered telangiectasias. Histopathologic examination with immunohistochemistry of the lesion was consistent with cellular neurothekeoma. It stained positive for microphthalmia transcription factor and NKI-C3 and negative for HMB-45 and S-100. The lesion was excised with 3-mm margins, and no recurrence was noted within 1 year of follow-up. We present a case of cellular neurothekeoma in a patient with a history of Guillain-Barré syndrome as well as a review of the literature. Our case report is unique in that no prior association has been found in the literature between cellular neurothekeoma and Guillain-Barré syndrome.

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Introduction

Cellular neurothekeoma is a rare and almost universally benign cutaneous tumor. Neurothekeomas are divided into myxoid, intermediate, or cellular types based on the amount of the myxoid matrix present [1]. Although the myxoid variants of neurothekeomas are likely of neural sheath origin, cellular neurothekeoma is thought to be of different origin. We present this case of cellular neurothekeoma in a patient with a history of Guillain-Barré syndrome and

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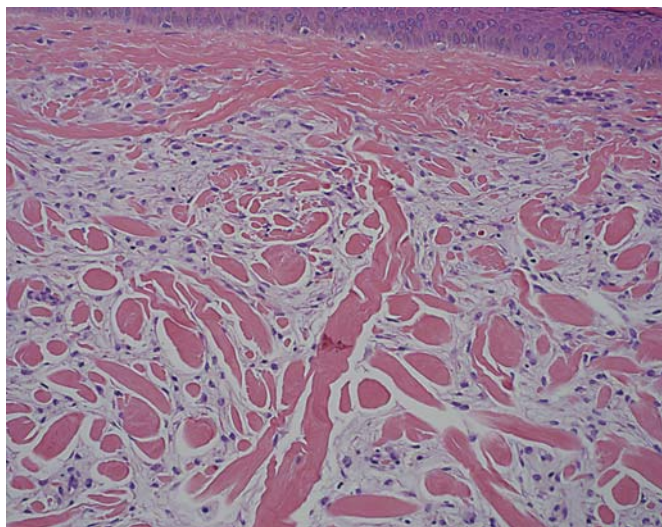


Fig. 1. Histopathology of cellular neurothekeoma. There are fascicles of plump spindle cells in the dermis containing abundant pale cytoplasm with well-defined cellular membranes. $\times 20$.

suggest that when a cellular neurothekeoma is found in a patient, the existence of concurrent or preceding Guillain-Barré syndrome should be ascertained from the history or medical records. We could find no prior association in the literature between neurothekeoma and Guillain-Barré syndrome.

Case Presentation

A 68-year-old female with a history of left nasal alar basal cell carcinoma (BCC) presented to the clinic for her yearly skin examination. She complained of a persistent bump on the left shoulder that she felt had been slowly growing over the preceding 3 months. She denied any pain, pruritus, or other symptoms from the skin lesion. Her past medical history included hypertension, hyperlipidemia, and monoclonal gammopathy of undetermined significance; she had a history of BCC and, most notably, a history of Guillain-Barré syndrome that was treated with intravenous immunoglobulin about 2 years prior to the presentation to our clinic. Her family history was significant for melanoma in her mother. Her medications included hydrochlorothiazide, benazepril, simvastatin, multivitamin, and calcium.

On physical examination, the skin lesion was a 3-mm firm skin-colored papule with scattered telangiectasias. A shave biopsy of the lesion was performed to rule out BCC. Histopathologic examination along with immunochemistry of the lesion was consistent with cellular neurothekeoma with fascicles of plump spindle cells in the dermis, containing abundant pale cytoplasm with well-defined cellular membranes (fig. 1). The lesion exhibited positive staining for microphthalmia transcription factor (MITF) and NKI-C3 (fig. 2) and negative staining for HMB-45 and S-100 (fig. 3). The lesion was then excised with 3-mm margins, and at follow-up 1 year later, there was no recurrence of the tumor.

Discussion

Cellular neurothekeoma is a rare benign cutaneous tumor that was described by Rosati et al. [2] in 1986 as well as by Barnhill and Mihm [3] in 1990. This tumor is more prominent in females, affecting twice as many women as men [1, 4]. Cellular neurothekeoma is present

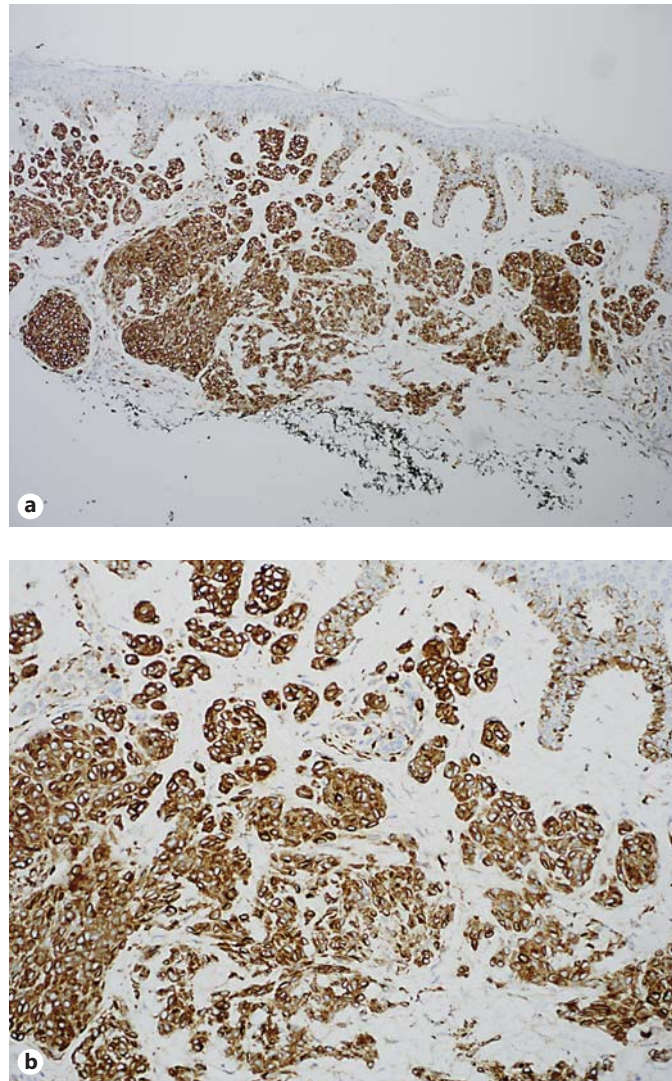


Fig. 2. Positive immunostaining for NKI-C3 in cellular neurothekeoma. ×10 (a). ×20 (b).

in a wide age group of individuals but strongly affects those in the second decade of life [1], which is another reason why this patient's case was quite unique. Most of the lesions typically present as asymptomatic single slow-growing flesh-colored dome-shaped nodules or papules [1], as in our patient. The tumors range in size, with a mean size of 1.1 cm, and with the majority of tumors being <2 cm [4]. The majority of the tumors occur in the upper extremities or in the head and neck area [4, 5]. Histologically, most cellular neurothekeomas have a poorly defined micronodular architecture with nests of epithelioid to spindle cells that are often separated by collagen [4, 5]. The cells exhibit abundant eosinophilic or pale cytoplasm, with many cells having well-defined cellular membranes [3, 6]. Some cellular neurothekeomas exhibit atypical histological features such as a high mitotic rate, pleomorphism, and fat infiltration. These atypical characteristics do not appear to correlate with increased recurrence or have any clinical importance, and thus, cellular neurothekeomas are considered benign [4]. Cellular neurothekeomas occasionally recur and are mainly seen to recur in the case of incompletely excised facial lesions [4].

No definite associations have been reported between systemic diseases and cellular neurothekeomas in our literature search. However, cellular neurothekeoma may possibly be

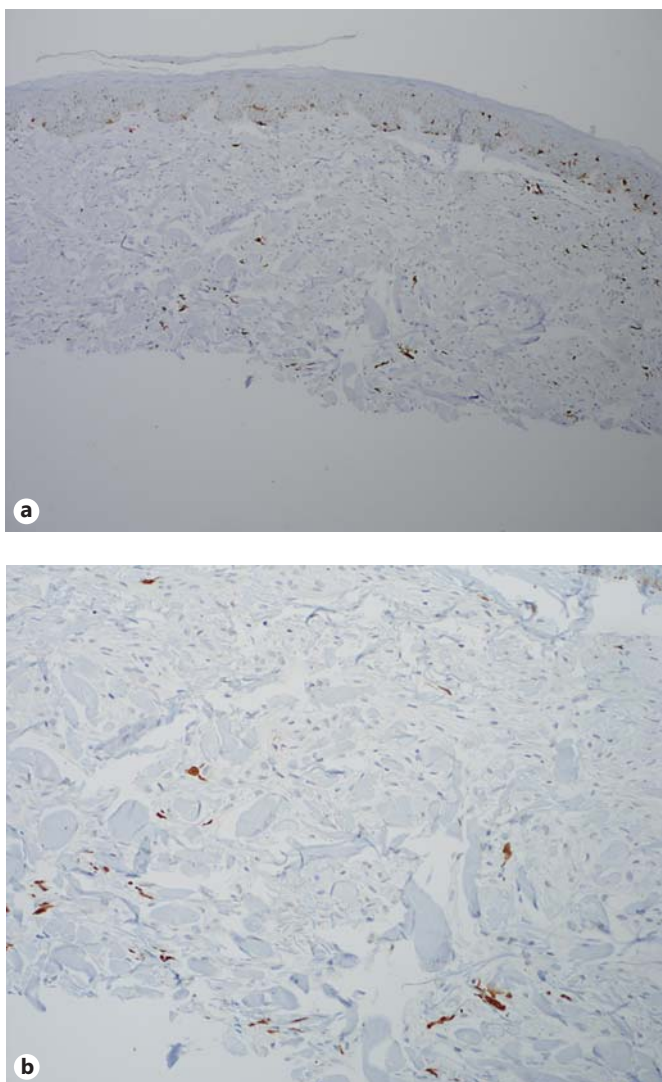


Fig. 3. Negative immunostaining for S-100 in cellular neurothekeoma. $\times 10$ (a). $\times 20$ (b).

associated with estrogen production, as demonstrated by the case of a young female who presented with a nodular erythematous lesion that appeared after menarche and displayed worsening erythema during menstruation; this nodule was histologically diagnosed as a cellular neurothekeoma. Because the tumor appeared a few months after menarche (when estrogen is produced in more substantial amounts) and because there was worsening erythema around the lesion during every menstrual cycle (with the start of the follicular phase), the authors suggested a possible link between estrogen production and neurothekeoma [7]. Thus, cellular neurothekeoma may be associated with other medical conditions that have a high estrogen production.

Guillain-Barré syndrome has been reported to have some cutaneous manifestations. There is a case report of orf, a cutaneous zoonotic viral infection, associated with Guillain-Barré syndrome as it was found to precede the onset of this syndrome by 2 weeks [8]. Guillain-Barré syndrome may be associated with pyogenic granulomas and Beau's lines as both these cutaneous manifestations have been reported to occur at the same time following the onset of this syndrome [9].

A cellular neurothekeoma can be difficult to diagnose clinically as it often appears similar to other common skin lesions, especially BCC. Both frequently present as a papule with overlying telangiectasias. Cellular neurothekeoma has been reported to exhibit overlying blood vessels arranged in a branch-like pattern under dermoscopy, similar to BCC, but these lesions can be differentiated based on histopathologic examination with immunohistochemistry [10].

Histologically, cellular neurothekeomas can be confused with melanocytic tumors like the Spitz nevus, dermal nerve sheath myxoma, pilar leiomyoma, plexiform fibrohistiocytic tumor (PFH), and cellular dermatofibroma. A dermal nerve sheath myxoma can be differentiated from a cellular neurothekeoma as it mostly occurs on distal extremities, has an abundant myxoid matrix on histology, is positive for Schwann cell markers S-100 protein and glial fibrillary acidic protein (GFAP), and has a higher recurrence rate. Spitz nevi can also be differentiated from cellular neurothekeoma as they are positive for S-100 and MART-1, which are negative in cellular neurothekeoma. Spitz nevi also exhibit downward maturation and tend to have a junctional component [4]. Pilar leiomyomas can be differentiated from cellular neurothekeomas as they often have longer nuclei and brighter eosinophilic cytoplasm and are almost always positive for desmin [4]. PFH can be differentiated from cellular neurothekeoma because the cells it contains are less epithelioid and, histologically, it often exhibits a prominent fibroblastic component [4]. Generally, PFH also shows more subcutaneous involvement compared to cellular neurothekeomas [1]. It has been found that the expression of MITF, which is a transcription factor involved in melanocyte development in histiocytoid cells, may help differentiate between histiocyte-predominant PFH and cellular neurothekeoma, as it was found to be diffusely positive in the latter and negative in PFH [5]. In addition, cellular neurothekeomas have been described at times to have a mainly fascicular growth pattern with associated collagen at the periphery, similar to cellular dermatofibroma. However, cellular neurothekeomas can be differentiated from cellular dermatofibromas because they contain a focal area of lobulated/nested architecture, the presence of epithelioid cells with abundant cytoplasm, and a lack of factor XIIIa expression [11].

The origin of cellular neurothekeomas is currently undetermined. In a study involving an analysis of 178 cellular neurothekeomas, they typically stained positive for NKI-C3 and MITF and were negative for S-100 protein, GFAP, and melan-A [1]. The absence of GFAP and S-100 protein supports a lack of peripheral nerve sheath origin (unlike myxoid neurothekeomas). In contrast, it has been shown in a gene expression array study that nerve sheath myxomas likely have a peripheral nerve sheath origin because they mainly had upregulated genes that are involved in the development of the peripheral nerve sheath [12]. This is in direct opposition to cellular neurothekeomas, as noted above. The most statistically significant factor between the two groups was the differential expression of the S100B gene. The main genes that were found to be differentially expressed and upregulated in cellular neurothekeomas in comparison to nerve sheath myxomas and schwannomas included those involved in extracellular matrix remodeling and growth [12]. Therefore, it is currently believed that cellular neurothekeomas are not derived from the neural sheath.

Instead, cellular neurothekeomas have a similar gene expression profile to fibrous histiocytomas, suggesting that these two entities may be related [12]. Cellular neurothekeomas may have a neuroectodermal origin, as supported by positive staining with NKI-C3, MITF, and PGP 9.5 [13]. Although cellular neurothekeomas have been shown to stain positive for the melanocytic markers NKI-C3 and MITF, these markers are not specific for melanocytes. And, because cellular neurothekeomas have been found to be negative for melanocytic markers including S100, HMB-45, tyrosinase, and melan-A, it can be argued that they are not of melanocytic origin [1]. In addition, myofibroblastic differentiation of the tumor cells in cellular neurothekeoma has been suggested because about 60% of the lesions exhibited focal staining for smooth muscle actin in a study involving the detailed characterization of 133 cellular

neurothekeomas [4]. It has also been implied that the tumor cells of cellular neurothekeomas have a neuroendocrine differentiation as they were found to stain positive for neuroendocrine markers including neuron-specific enolase, chromogranin, synaptophysin, and CD56 [14]. Thus, it is possible that cellular neurothekeomas originate from undifferentiated mesenchymal cells that exhibit characteristics of both neuroendocrine and myofibroblastic differentiation [14] or can be derived from either.

The treatment of choice for cellular neurothekeoma is complete surgical excision [1]. Mohs micrographic surgery has also been recommended for cellular neurothekeomas, primarily because of their poorly defined clinical margins, their ability to recur if not completely excised, and their primary location on cosmetically appealing areas such as the head and neck region [15]. Furthermore, no recurrence has been noted for the 4 cases of cellular neurothekeoma that have been treated with Mohs micrographic surgery [15].

This case report is unique because cellular neurothekeoma is a rare tumor, and no prior association could be found between Guillain-Barré syndrome and neurothekeoma in our literature search. Thus, the question arises whether this is in fact truly a rare association or whether clinicians need to be further educated to be aware of this potential relationship.

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Disclosure Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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