



Hybrid Granular Cell Tumor/Perineurioma

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Hybrid peripheral nerve sheath tumors (PNSTs), which show hybrid features of more than one cell type normally found in a peripheral nerve sheath, are recently recognized clinical entities. Various composite tumors have been reported; however, granular cell tumor/perineurioma is a rare combination.¹⁻⁴ Since perineurial cells may be found in other types of PNSTs, it is important to determine if those are reactive, remnantal, or true neoplastic when a perineurial component of the PNST is identified. Main differential diagnoses include granular perineurioma and granular cell tumor with reactive perineurial cell hyperplasia, which show a lack of immunopositivity for S-100 in the granular cells and prominent perineurial cell proliferation throughout the tumor, respectively.

CASE REPORT

A 54-year-old man presented with a 2-year history of a well-circumscribed movable mass in the posterior aspect of the right axilla. He did not complain of tenderness or neuropathic pain. He had no specific familial or medical history of neurogenic tumors, including neurofibromatosis. Laboratory test results, including electrolyte levels and blood cell counts, were all within the normal ranges. The magnetic resonance imaging revealed a well-circumscribed mass in the subcutaneous fat layer of the right posterior axilla (Fig. 1A). The patient underwent an excisional biopsy of the mass.

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Received: December 1, 2013 Revised: March 4, 2014

Accepted: March 24, 2014

Macroscopically, the lesion was a well-circumscribed nodular mass measuring 5.5×5 cm in the greatest dimension. It was tan to gray in color and rubbery to firm in consistency (Fig. 1B). No hemorrhage or necrosis was evident. There were no macroscopic associations with a nerve.

Microscopically, the neoplasm was a well-circumscribed but nonencapsulated deep soft tissue mass. At first glance, there were nests or rounded aggregations of granular cells and prominent encircling spindle cells. Because the spindle cells showed a whorled and storiform growth pattern, the overall appearance of the lesion looked like whorls or eddies (Fig. 1C, D). Although the proportion of granular cells and spindle cells was variable depending on the location of the tumor, the overall proportion was similar (Fig. 1C-E). Two components of the lesion had no transition area and were intimately admixed throughout the lesion. Occasionally, mature adipose tissue was admixed with the lesion, which may have constituted a third component of the lesion (Fig. 1F). Although it occupied a small area, it was distributed widely and not restricted to the periphery. Cytologically, granular cells had a round to polygonal shape and conspicuous eosinophilic granular cytoplasm. The nuclei were small, centrally located, and mildly pleomorphic. Spindle cells were fusiform to spindle-shaped with indistinct cell borders. They had inconspicuous pale eosinophilic cytoplasm and bipolar cytoplasmic processes. No mitotic figures were seen.

Immunohistochemically, granular cells were positive for S-100 (1:1,000, polyclonal, Dako, Glostrup, Denmark) and CD68 (1:3,000, KP1, NeoMarkers, Fremont, CA, USA) but not for epithelial membrane antigen (EMA; 1:100, E29, Dako), glucose transporter 1 (GLUT-1; 1:100, polyclonal, Millipore, CA, USA), or claudin-1 (1:200, polyclonal, Biocare Medical, Concord, CA, USA). However, the spindle cells were immunoreactive for EMA, GLUT-1, and claudin-1 and did not stain for S-100

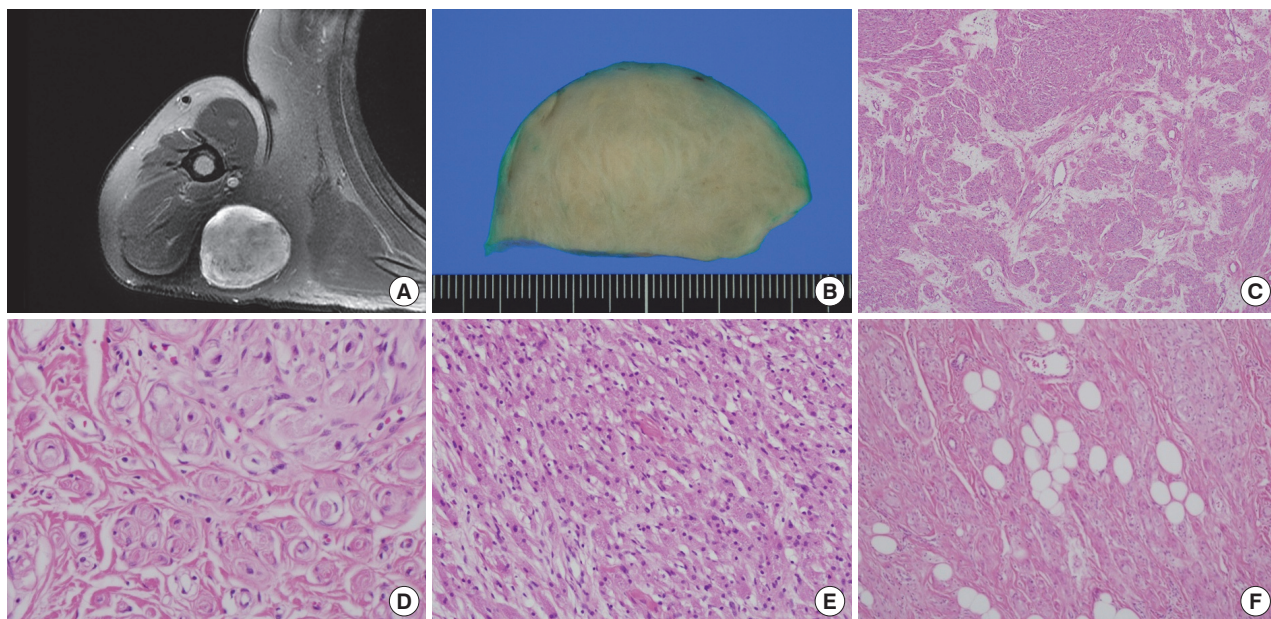


Fig. 1. Right shoulder magnetic resonance imaging reveals a well-circumscribed mass in the right posterior axilla (A). Grossly, it is tan to gray in color (B). At low power, the tumor reveals a whorled and storiform growth pattern (C) and rounded aggregations of granular cells with encircling spindle cells (D). (E) Predominant aggregation of granular cells is also observed. (F) Mature adipose tissue is occasionally admixed with main components of the tumor.

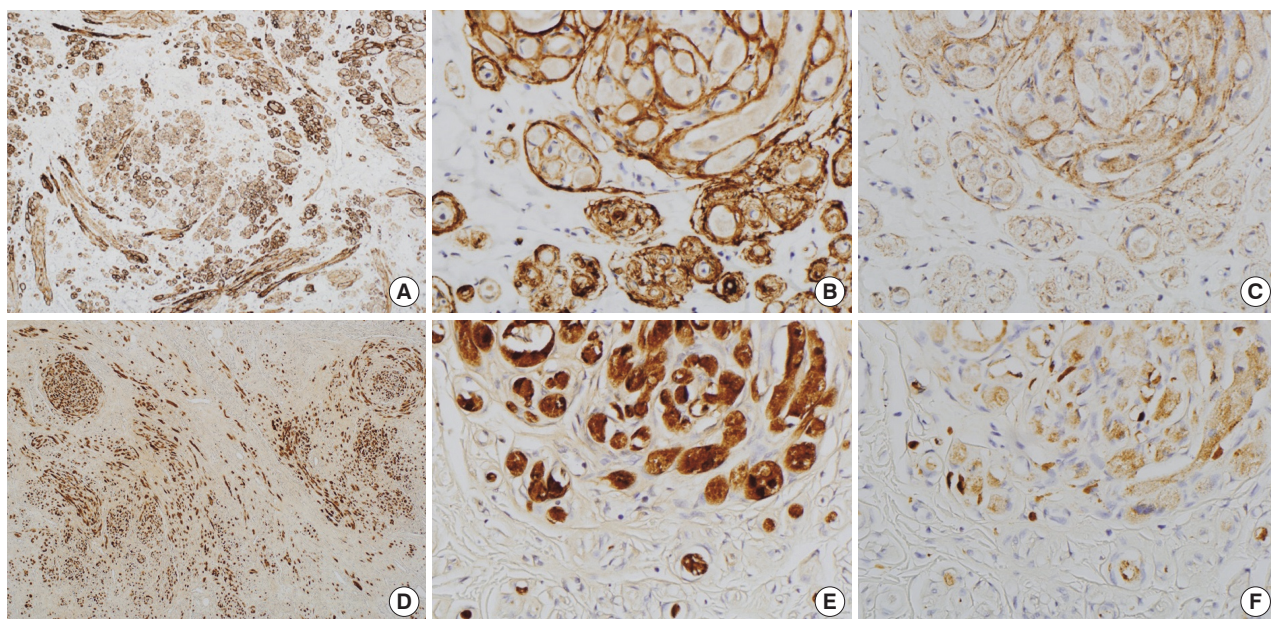


Fig. 2. Immunohistochemical findings of the area in Fig. 1D. Spindle cells are immunopositive for glucose transporter 1 (A, B) and epithelial membrane antigen (C). Granular cells are immunoreactive for S-100 (D, E) and CD68 (F).

(Fig. 2). In particular, EMA and GLUT-1 highlighted the cytoplasmic processes of the spindle cells. The tumor cells were not immunoreactive for CD34 (1:300, QBEnd10, Dako), cytokeratin (1:200, AE1/AE3, Dako), desmin (1:100, D33, Dako), neurofilament protein (1:2,000, 2F11, Dako), or smooth muscle

actin (1:200, 1A4, Dako).

Ultrastructurally, two populations of the lesion were easily identified. Granular cells exhibited abundant cytoplasm filled with phagolysosomes with electron-dense debris. Spindle cells revealed discontinuous and irregular basal lamina, rudimentary

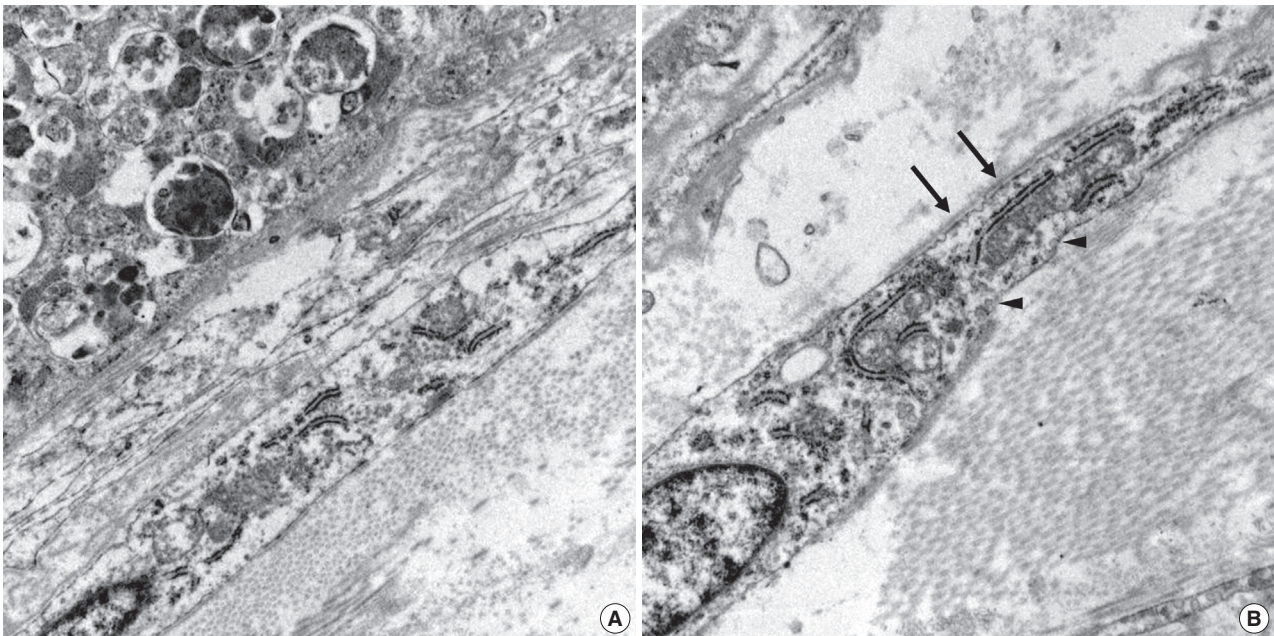


Fig. 3. Electron microscopy of the granular cells and perineurial cells derived from formalin-fixed tissue. Granular cells reveal abundant cytoplasm filled with phagolysosomes (A, $\times 8,000$), and spindle cells show irregular basal lamina (arrows) and pinocytotic vesicles (arrowheads) (B, $\times 15,000$).

intercellular junction, thin cytoplasmic processes, and pinocytotic vesicles (Fig. 3).

DISCUSSION

Benign PNSTs include schwannomas, neurofibromas, and perineuriomas, which have distinct histomorphological and immunohistochemical profiles. They originate from the connective tissue sheath of peripheral nerves, such as Schwann cells, perineurial cells, and fibroblasts. PNSTs comprising more than one distinct histologic cell type, called “hybrid PNSTs,” have recently been described. After Feany *et al.*⁵ first described a hybrid PNST in 1998, these tumors have been increasingly identified, likely due to the aid of ancillary tests, such as immunohistochemical staining. Among these tumors, hybrid schwannoma/perineurioma and hybrid neurofibroma/perineurioma are the most common combinations.⁶ Hybrid granular cell tumor/perineurioma is a somewhat rare combination, and there have been only a few reports in the English literature.¹⁻⁴

Perineuriomas are uncommon benign peripheral nerve sheath neoplasms composed exclusively of well-differentiated perineurial cells. Perineurial cells are neurosustentacular cells that surround nerve fascicles and constitute a blood-nerve barrier that acts to preserve the nerve tract by creating tight junctions with endothelial cells.¹ These cells are also involved in other tumors

of the peripheral nerve sheath, such as neurofibromas, schwannomas, and malignant PNSTs. Perineurial cells are immunoreactive for EMA, CD34, GLUT-1, and claudin-1, which are used as diagnostic markers.⁷

When granular cells and perineurial cells are seen as predominant tumor components, granular cell changes of perineurioma and reactive hyperplastic changes of perineurial cells in a granular cell tumor must be excluded before a final diagnosis of hybrid granular cell tumor/perineurioma can be made.^{8,9} Since perineurial cells can be observed as an additional minor component in PNSTs, such as neurofibromas and granular cell tumors, it is important to determine if they are hyperplastic or neoplastic. Reactive hyperplastic or remnant perineurial cells in neoplasms of neurosustentacular cells are usually located in the periphery or perivascular area. They are usually related to nerve fascicles and arranged in a concentric pattern.⁸ In our case, perineurial and granular cells are major tumor components that are intimately admixed with each other in most areas of the lesion and are not associated with nerves. On the basis of these findings, a hybrid granular cell tumor/perineurioma was diagnosed rather than a single PNST.

Granular cell changes can be seen in various non-neoplastic or neoplastic lesions, including granular cell traumatic neuroma, dermatofibrosarcoma protuberans, leiomyoma, leiomyosarcoma, basal cell carcinoma, and perineurioma.^{9,10} These changes

may be nonspecific morphologic changes due to lysosomal accumulation as a result of metabolic alterations. Recently, there was a reported case of granular perineurioma based on granular cells negative for S-100 and perineurial cells positive for EMA, claudin-1, and GLUT-1.⁷ Immunoreactivity for S-100, which represents the neurogenic origin of granular cell components, was a main differentiation point between granular perineurioma and hybrid granular cell tumor/perineurioma. That study stated that granular cell changes were nonspecific findings resulting from lysosomal defects, and the granular components were not neoplastic.

The origin of hybrid PNSTs is unclear; however, there are a few suggestions. It has been proposed that, because both components of hybrid PNST are of schwannian origin, any combination of individual PNSTs is possible by a hypothetically divergent differentiation,¹ which is supported by reports of various combinations of PNSTs. Others have indicated that cellular dimorphism is a result of metaplastic processes based on transition cells with immunohistochemical dual-lineage expression.⁴ In the present case, there were multiple foci of intralesional adipose tissue proliferation that were thought to be minor tumor components rather than entrapped tissue. Although one case cannot represent all tumors, this feature suggests that this composite tumor is a type of hamartomatous lesion or originates from pluripotent mesenchymal cells.

With improvement in ancillary studies, such as immunohistochemistry, hybrid PNSTs will be more readily recognized and diagnosed. In the present case, granular cell and perineurial components were easily detected due to distinct histomorphologies. Granular perineurioma and granular cell tumor with reactive perineurial cell hyperplasia should be excluded during diagnosis. A careful histomorphologic examination of perineurial cell location within the tumor and immunohistochemical stains for S-100, EMA, GLUT-1, and claudin-1 are needed to make a definitive diagnosis. We reported herein a rare case of hybrid granular cell tumor/perineurioma.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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