Human Pathology (2017) **66**, 183–187

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Case study

Intranodal meningothelial proliferation in a patient with Cowden syndrome: a case report☆

Andrea Olofson MD, Jonathan Marotti MD, Laura J. Tafe MD, Konstantinos Linos MD*

Department of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, 1 Medical Center Dr, Lebanon, NH 03756, USA

Received 17 November 2016; revised 26 January 2017; accepted 3 March 2017

Keywords:
Cowden;
Meningothelial;
Lymph node;
Perineurioma;
Ectopic meningioma

Summary Ectopic meningothelial proliferations are rare and can occur in a multitude of extracranial/spinal anatomic locations. Perineurioma is another uncommon entity that shares similar histological characteristics to those found in meningothelial proliferations. These include bland spindle cells with thin, bipolar nuclei; eosinophilic cytoplasm; and indistinct cell borders, arranged in short fascicles with whorl formation. Given their uncommon occurrence and shared histological and immunohistochemical features, their distinction can present a diagnostic challenge. Immunohistochemical studies can provide guidance when attempting to distinguish between these 2 lesions. Here, we present an unusual case of a patient with Cowden syndrome who was discovered to have a meningothelial proliferation within an axillary lymph node. To the best of our knowledge, this is the first case in which a meningothelial proliferation has been identified in a lymph node. Furthermore, the occurrence in a patient with Cowden syndrome is intriguing and raises the possibility of a pathogenetic link.

1. Introduction

Ectopic meningothelial proliferations are rarely encountered entities that are histologically and genetically similar to their intracranial/spinal counterparts, meningiomas [1]. Although the vast majority of these lesions occur within the head and neck region, other sites of involvement include the lung [2], skin [3], mediastinum [4], and foot [5]. They are believed to arise from arachnoid cell rests, which are neural crest cell derivatives that were displaced during migration in early embryogenesis, or from undifferentiated or multipotential mesenchymal cells [6]. The diagnosis of ectopic meningothelial proliferations may be difficult because of their rarity and potential for unusual locations. Additionally, given the close embryonic relationship between meningiomas and perineuriomas, there is considerable histologic and immunohistochemical overlap between these 2 entities.

Cowden syndrome is an autosomal dominant disease affecting multiple organ systems and is associated with an increased risk for the development of malignancies and benign hamartomatous neoplasms [7]. It results from mutations in the tumor suppressor gene phosphatase and tensin homolog (*PTEN*) on chromosome 10 [8]. A multitude of somatic mutations have been reported in connection with Cowden syndrome resulting in loss of *PTEN* heterozygosity and subsequent tumor proliferation [9]. Common benign lesions include trichilemmomas, oral papillomas, mucocutaneous neuromas, acral keratosis, lipomas, vascular anomalies, and gastrointestinal hamartomas [7].

Meningiomas and other brain tumors are not currently included in the clinical diagnostic criteria for Cowden syndrome

☆ Funding/Support: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
* Corresponding author.
E-mail address: Konstantinos.linos@hitchcock.org (K. Linos).

http://dx.doi.org/10.1016/j.humpath.2017.03.002
0046-8177/

because of a historical lack of data supporting a direct association [10]. Recent studies, however, have provided a growing body of evidence that suggests a link between meningiomas and Cowden syndrome [10,11].

Here we present, to the best of our knowledge, the first case of a meningothelial proliferation within a lymph node from a patient with Cowden syndrome. This case raises the possibility of a pathogenetic association. The challenging distinction between meningothelial proliferations, perineuriomas, and briefly myopericytomas is also discussed.

2. Case report

2.1. Clinical history

A 55-year-old white woman with a clinical diagnosis of Cowden syndrome was admitted to our institution for a left axillary sentinel node excision. Two months prior, a core needle biopsy of her left breast revealed high-grade ductal carcinoma in situ. She subsequently underwent a partial mastectomy of the left breast, which revealed a single area of microinvasion. Magnetic resonance imaging of the left axilla prior to surgery did not demonstrate any suspicious lymph nodes. Two sentinel lymph nodes and 2 nonsentinel nodes were removed during surgery. Her medical history was significant for macrocephaly, lipomas of the breast and palm, gangliocytoma of the posterior fossa, endometrial adenocarcinoma, neurofibroma, and papillary sclerosing lesion with atypical ductal hyperplasia of her right breast. Result of brain magnetic resonance imaging was negative for lesions suggestive of meningioma. Genetic testing performed by a reference laboratory identified a *PTEN* c.209+5G>A alteration, confirming the clinical impression of Cowden syndrome. Her family history is significant for breast cancer in 1 of 4 siblings.

2.2. Materials and methods

Immunohistochemistry was performed on 4-μm sections taken from formalin-fixed, paraffin-embedded tissue using the Leica Bond III automated immunostainer (Leica Biosystems Inc, Buffalo Grove, IL). The following antibodies were used: smooth muscle actin (SMA) (Leica Bond, Newcastle, UK, predilute), CD34 (Cell Marque, 1:100), cytokeratin AE1/AE3 (BioGenex, Fremont, CA, 1:140), claudin-1 (Cell Marque, Rocklin, CA, 1:50), desmin (Leica Bond predilute), epithelial membrane antigen (EMA) (Leica Bond predilute), glucose transporter 1 (GLUT-1) (Abcam, Cambridge, UK, 1:2000), progesterone receptor (PR) (Novocastra, Newcastle, UK, 1:150), and S-100 (Dako, Santa Clara, CA, 1:4000).

2.3. Pathology findings

All 4 lymph nodes were negative for any discernible pathological changes on gross examination. Microscopic evaluation of formalin-fixed, paraffin-embedded sections revealed a single 0.2-cm focus of bland, monomorphic spindle cells within the hilar region of 1 sentinel node. The spindle cells possessed ovoid nuclei, abundant eosinophilic cytoplasm, and indistinct cells borders. Cells were arranged in short fascicles with the formation of concentric whorls (Fig. 1). Rare microcalcifications were present. Mitotic figures, pseudoinclusions, and necrosis were not identified. The histologic differential diagnosis included perineurioma, ectopic meningothelial proliferation, and myopericytoma. Immunohistochemistry studies were used to better characterize the spindle cell proliferation. The lesional cells stained positive for EMA, claudin-1, and GLUT-1 and focally positive for PR (Fig. 2), whereas they were negative for cytokeratin AE1/AE3, S100, CD34, desmin, and SMA. Electron microscopy was not performed because of insufficient tissue availability. Based on the morphological and immunohistochemical features of the tumor cells, the primary differential diagnosis included meningothelial proliferation and perineurioma. Although both entities can express positivity for EMA, claudin-1, and GLUT-1, the presence of microcalcifications and focal PR positivity was most consistent with a meningothelial proliferation. All axillary lymph nodes examined were negative for metastatic carcinoma.

3. Discussion

Ectopic meningothelial proliferations have been reported in a multitude of anatomical sites. The morphological features of these lesions are similar to those seen in intracranial meningiomas, including whorl formation, psammoma bodies, nuclear clearing, and pseudoinclusions [12]. The lesion in this case revealed ovoid spindle cells with abundant eosinophilic cytoplasm and indistinct cell borders arranged in short fascicles with whorl formation. Given its location in a lymph node, other spindle cell soft tissue lesions were considered in the differential, the foremost being perineurioma.

Perineuriomas are benign tumors that can histologically mimic meningothelial proliferations. Normal perineurial and arachnoid cells form a close relationship during the embryological development of the peripheral nervous system. As the spinal nerve roots exit the intervertebral lamina, the arachnoid cells underlying the dura slowly give way to the perineurial cells that will sheathe the peripheral nerve fascicles [13]. Perineuriomas are composed solely of uniform perineurial cells that are organized into 2 broad categories: intraneural and extraneural soft tissue variants [14]. Tumors are typically not encapsulated but well circumscribed and uniform in appearance with a thin spindled shape, wavy nuclei, and elongated bipolar cytoplasmic processes. Psammoma bodies are not commonly seen with perineuriomas. These tumors most frequently occur in the subcutis of the upper and lower limbs, although they may be seen in a variety of anatomical sites [15].