American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Case Report

A Case Report Study of Signet Ring Cell Histiocytoid Carcinoma of the Eyelid

Farahnaz Noei*, Hamidreza Faraji, Jinesa Moodley and John Harvey

Department of Pathology and Molecular Medicine, McMaster University Medical Centre, Canada

***Corresponding author:** Farahnaz Noei, Department of Pathology and Molecular Medicine, McMaster University Medical Centre, Canada.

To Cite This Article: *Farahnaz Noei, Hamidreza Faraji, Jinesa Moodley, John Harvey. A Case Report Study of Signet Ring Cell Histiocytoid Carcinoma of the Eyelid. Am J Biomed Sci & Res. 2022 - 16(3). AJBSR.MS.ID.002230.* DOI: 10.34297/AJBSR.2022.16.002230

Received: May 13, 2022; **Published:** June 01, 2022

Introduction

Primary Histiocytoid/Signet-Ring Cell Carcinoma of the Eyelid (PHCE) is rare and locally aggressive tumors [1], reported in over 30 cases in the English literature. There is debate as to whether the tumor is derived from apocrine or eccrine glands [2], thus there are numerous names for the tumor, such as eccrine sweat gland tumor of clear cell origin [3], adenocarcinoma of eccrine sweat glands [4], primary mucinous sweat gland carcinoma [5], primary infiltrating signet-ring cell carcinoma [6], and primary histiocytoid carcinoma of the eyelid [7,8]. When initially described, the tumors were classified as one of three subtypes, including 1. Infiltrating ductal (syringoid) carcinoma, 2. Mucinous carcinoma and 3. Poorly differentiated carcinoma [9].

Clinically, the demographic most affected are elderly males, with a mean age of 67 years [1-16]. Patients often present with clinical symptoms of an inflammatory process such as orbital cellulitis, blepharon conjunctivitis and chalazion and cutaneous metastases of systemic/visceral tumors to the eyelid [17]. Metastasis to the eyelid must be excluded from sites such as breast cancer (especially lobular carcinoma), prostatic adenocarcinoma and signet-ring cell carcinoma of the gastrointestinal tract [18]. Given the clinical differential of benign and malignant entities, biopsy is imperative for diagnosis of PHCE. On biopsy, the tumor infiltrates the dermis while the epidermis is usually unremarkable, with a diffuse infiltrate of small homogeneous cells with histiocytoid and/or signet ring cell appearance. Immunohistochemical studies are imperative to prove both the epithelial origin of the tumor and help exclude metastases from other sites, which is further supported through thorough clinical and radiologic examination. The following case adds to the existing literature of Primary histiocytoid/signet-ring cell carcinoma of the eyelid.

Case Presentation

A 66-year-old man presented with an one year history of left upper eyelid ptosis, swelling and induration. Visual acuity at the time was 20/25+ with -1 elevation deficit in the left eye. His past medical history and clinical review of symptoms were non-contributory. Blood work performed at the time included tumor serum markers and acetylcholine receptor antibodies, all of which were negative. An ill-defined enhancing soft tissue mass on the left upper eyelid without underlying bony abnormality or extension into the orbit was appreciated in magnetic resonance imaging. Biopsy of the lesion was performed and diagnosed as an infiltrative carcinoma, histiocytoid type. The patient was lost to follow up and represented six months later with worsening of symptoms. Magnetic resonance imaging of the orbit showed an ill-defined mass involving both the upper and lower left eyelid with orbital extension involving intraconal and extraconal spaces with subtotal encasement of the globe without intracranial or nodal spread.

Computed tomography of the chest, abdomen and pelvis were all non-contributory, demonstrating no clear primary lesion. The patient then went on to have exenteration of the left eye with

wide surgical resection and post-operative radiation. The lesion was consistent with histiocytoid carcinoma, which extensively involved the eyelid, conjunctiva, orbit, muscles of the eyelid, extraocular muscles, periorbital adipose tissue and lacrimal gland. On light microscopic examination the lesion consisted of homomorphous histiocytoid cells with indistinct cell borders arranged between collagen fibers, occasionally forming short files with mild atypia. The tumor diffusely infiltrated the dermis without epidermal involvement. The nuclei were round/oval with finely granular chromatin with occasional nucleoli. Mild to moderate pleomorphism was observed focally. Very rare signet-ring cells and mitoses were observed. Perineural invasion was present and positive skin and soft tissue margins. The lesion showed positive immunohistochemical staining for CAM 5.2, CK AE1/AE3, CK 7, BRST-2 (GCDFP-15), E-cadherin, and BER-EP4. The lesion was negative for ER, PR, CK 5, CK6, CK 20, CD68, TTF-1, p63, S100, HMB-45, PSA and CDX2.

Discussion

Histological features of PHCE are fairly consistent among cases, showing sparing of the epidermis, but full dermis involvement by singly scattered cells, small strands, or solid aggregates of neoplastic epithelial cells, interstitially arranged between the collagen bundles of the dermis. The lesion does not demonstrate connection to the dermal adnexa or any other dermal structure. At low power, the lesion mimics an inflammatory fibrotic process. On high power microscopic examination, the individual cells with eccentric nuclei and ample cytoplasm infiltrate between collagen bundles [2].

There is no specific immunohistochemical panel exclusively for PHCE. It has been showing that PHCE is consistently positive for AE1AE3, CAM5.2, CK7, gross cystic disease fluid protein-15, BER-Ep4 and EMA. It is negative for CK20, CK5/6 and S100. Some authors reported that P63, Estrogen and Progesterone receptors can be positive [2], however, these markers are negative in most of the cases. Recently, three cases have been reported to be positive for GATA-3, adding to the diagnostic complexity of PHCE [19]. Important primary sites of malignancy include the invasive lobular carcinoma of the breast, signet ring cell carcinoma of the gastrointestinal tract and prostate. An expanded immunohistochemical panel including PSA and NKX3.1 to rule out prostatic malignancy should be considered. In this case, the CK7 positivity and CK20 negativity, helped exclude lower gastrointestinal tract origin. A gastrointestinal marker such as CDX2 could also be added to the upfront immunohistochemical panel. The positivity of BRST-2 (GCDFP-15) in the context of CK7 positivity and broad cytokeratins ultimately aids in supporting the diagnosis of primary histiocytoid carcinoma of the eyelid, in the absence of a clinical breast lesion. Given the histiocytoid morphology, it is pertinent to exclude a histiocytoid infiltration, which was excluded through negativity for CD68. Another panel of stains which can be useful in distinguishing primary cutaneous adenocarcinoma from metastatic visceral adenocarcinomas, includes P63, D2-40 and P40 [20-22]. Although not all three stains were performed in this case, the positivity can help further support the tumor being of primary cutaneous origin.

Furthermore, when faced with the histologic features of PHCE, as described above, immunohistochemical stains are imperative to prove the epithelial nature of the lesion. Due to the small number of cases of this entity, no specific immunohistochemical panel can prove the diagnosis. Simply, the immunohistochemical stains are helpful in ruling out pertinent differential diagnoses, such as a histiocytoid infiltration and melanoma, and guiding exclusion of other visceral primary sites. Discussion with the clinical team with regards to thorough clinical, endoscopic and radiologic findings in conjunction with histologic and immunohistochemical studies, ultimately support the diagnosis of PHCE. Treatment for PHCE includes wide local excision or orbital exenteration with or without radiotherapy [1-16]. Prognosis is poor, as PHCE is known to have a considerable rate of recurrence and metastases. From a study of 28 cases, 5 patients presented with recurrence and 7 patients presented with metastases, 5 of them to the lymph nodes [18]. Metastases to skin, bone marrow, parotid gland and thoracic spine are described, but as single cases. In one case, an aggressive PHCE metastasized to skull, mandible and other bones of the face and vertebrae [16].

Conclusion

Primary histiocytoid/signet-ring cell carcinoma of the eyelid is both a clinical and pathologic diagnostic challenge. The combination of thorough immunohistochemical, clinical and radiologic studies are imperative to rule out metastatic signet ring cell histiocytoid carcinomas from other sites.

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