Case report

Primary mucinous adenocarcinoma of the eyelid: A case with initial clinical misdiagnosis requiring surgical re-excision of the tumor

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ARTICLE INFO

Keywords:
Adenocarcinoma
Eyelid tumor
Frozen section
Histopathology
Immunohistochemistry
Epidermal cyst
Sweat gland

ABSTRACT

Introduction and importance: Primary mucinous adenocarcinoma (PMA) of the skin is a rare condition that is usually seen in elderly patients, most commonly involves the periorbital region as a slow growing mass. Histopathological and immunohistochemical (IHC) stains are of paramount importance for the diagnosis of these lesions, which are usually misdiagnosed either as benign or metastatic mucinous adenocarcinomas.

Case presentation: We herein report a rare presentation of PMA in a 70-year-old male patient who presented with an upper eyelid residual lesion after being incompletely excised elsewhere as an epidermal cyst and was successfully managed by complete surgical excision with frozen section control of the margins and no evidence of recurrence.

Discussion: PMA is a rare sweat gland malignancy that involves the eyelid in 41.9% in the head and neck area and is a disease of the elderly with median age of 60 years and variable reported racial and gender predilection. Diagnosis of PMA is challenging both clinically and histopathologically, which was the case in our patient's initial incomplete excision with the presumed diagnosis of a benign epidermal cyst. Proper final tissue diagnosis and surgical management in our patient ensured his favorable outcome.

Conclusion: Accurate diagnosis of PMA requires a high index of clinical suspicion and accurate histopathological diagnosis aided by proper IHC markers.

1. Introduction

Primary mucinous adenocarcinoma (PMA) is considered a rare clinical entity with an incidence of 0.04 cases per 100,000-person years [1]. It most commonly involves the periorbital region, presenting as an asymptomatic, slow-growing, well-circumscribed mass that is often misdiagnosed as a benign lesion [2]. Thus, rapid, and accurate diagnosis of PMA requires a high index of suspicion. In addition, these tumors are often mistaken for the more common metastatic mucinous adenocarcinomas; hence, immunohistochemical (IHC) markers are essential to aid in establishing a definitive diagnosis [3]. We report herein a case of eyelid mucinous adenocarcinoma that was clinically misdiagnosed as a benign epidermal cyst thus incompletely excised elsewhere. He was subsequently managed with complete excision and reconstruction. This case report was prepared in accordance with the ethical standards and the Helsinki Declaration. No trial of new drugs or therapy is applicable in this case. Case reports do not require Ethical approval in our institution. However, a general written informed consent was taken from the patient, which includes permission for anonymous use of information and photos for reporting. This case report has been prepared and reported in accordance with the SCARE 2020 criteria [4].

2. Case presentation

A 70-year-old Syrian healthy gentleman presented to the oculoplastic clinic as a referred case from a private eye care center with a history of gradual, progressive, painless, localized left upper lid swelling over 2 years. The patient had controlled systemic diabetes mellitus and hypertension. His medical, drug, and past ocular history were unremarkable. The family history was not relevant.
On examination, the visual acuity measured 20/20 in both eyes. The intraocular pressure was within normal limits for both eyes. On external inspection, there was no proptosis, and the extra-ocular motility was full, with no pain or limitation in all fields of gaze. Left upper eyelid notched lesion adjacent to the lid margin was noted. It was involving the lateral 1/3 of the left upper eyelid. On palpation it was firm, non-pigmented, irregular depressed lesion and measured 0.5 × 0.7 cm. There was no ulceration, telangiectatic blood vessels, loss of lashes or signs of infection. The palpebral conjunctiva and tarsus were smooth and were not invaded by the lesion. Lymph nodes examination revealed no enlargement. Anterior and posterior segment examinations were within normal limit. The patient gave history of recent surgical excision of what has been described as a pale, raised, rounded lesion measuring around 0.3–0.4 cm outside our facility with the initial clinical misdiagnosis as an epidermal cyst. However, the histopathology report brought by the patient revealed incomplete excision of a mucinous adenocarcinoma. Upon the review of the previous histopathological slides by the 2 experienced pathologists involved in this case report, the diagnosis of adenocarcinoma was confirmed, and the decision was to plan for excisional biopsy with frozen section control of the margins of excision by the oculoplastic surgeon in our tertiary eye care center (Fig. 1A). The patient agreed on the procedure after full explanation, and he successfully underwent complete excision of the lesion via a full-thickness pentagonal eyelid resection and the surgical margins were clear of any tumor involvement (Fig. 1B). The excised mass was firm, round, tan-colored measuring 1.6 × 1 × 0.5 cm. Histopathologically, a well-differentiated dermal malignant tumor composed of multilobulated solid areas and cystic spaces was seen with high resemblance to the appearance of previously excised tumor (Fig. 1C). The solid areas showed cribriform architecture punctuated by mucin filled cystic spaces. The cells showed mild pleomorphism, scattered mitotic activity, and Periodic acid Schiff (PAS)-stained mucinous secretions (Fig. 1D). IHC staining of cells showed positive reactivity for Cytokeratin-7 (CK7) and Carcinoembryonic antigen (CEA) (Fig. 2A and B). The tumor cells also showed strong GATA-3, Estrogen receptor (ER), and Progesterone receptor (PR) expression (Fig. 2C and D), with less reactivity for P63 (Fig. 2E). The findings were consistent with mucinous adenocarcinoma. The patient was advised to undergo initial systemic workup to rule out metastatic mucinous carcinoma. The metastatic workup all yielded unremarkable results. Moreover, clinical history, examination and diagnostic imaging confirmed the exclusion of metastatic mucinous carcinoma. The patient had an uneventful post-operative course with finally excellent cosmetic result at the excision site and no evidence of recurrence in his last follow up 9-months post-excision (Fig. 2F).

3. Discussion

PMAs are considered a rare group of sweat gland malignancies. In an analysis involving 289 cases of head and neck PMA, these tumors were reported to predominantly involve the eyelid in 41.9% followed by the scalp and neck in 25.3% [5]. It is a disease of the elderly with a reported median age of onset of 60 years [3]. Gender predilection varies between reports with some reporting a male to female ratio of 2:1 [6] while Behbahani et al. reported that females were more commonly affected (58.8%; P < 0.05) [5]. Thus, larger series are required to accurately establish the gender relationship. Regarding ethnicity, most cases reported were of Caucasian race [7] while Rismiller in a large series of 411 cutaneous PMA cases demonstrated equal occurrence in both sexes with more predilection among African Americans [1]. A thorough search of the relevant literature yielded only two reported cases from the Middle East [8]. Our patient was an elderly male with Syrian origin.

The clinical manifestations of PMA are quite variable. In this case, the patient presented with a slowly growing mass over two years. Upon review of the literature, most reported cases were less than 2.5 cm in size and have been present for over a year or more prior to the initial presentation like our case [9]. Lesions have been described as either papillomatous, pedunculated, or fungating. The lesion in our patient at initial presentation was small and resembled a benign epidermal cyst. Moreover, the color can vary from flesh to tan, grey, red or blue. The surface may be smooth, bumpy, or crusted and texture varies from firm to cystic.

As the clinical presentation varies widely, establishing a firm clinical diagnosis is usually difficult and may often be mistaken for one of the differential diagnoses, including basal cell carcinoma, squamous cell carcinoma, chalazion, sebaceous carcinoma, malignant melanoma, papilloma, myxoma, hemangioma, Kaposis sarcoma, pyogenic granuloma, and keratoacanthoma [3,9].

Fig. 1. A: The histopathological appearance of the previously excised tumor that was misdiagnosed as basosquamous carcinoma (Original magnification ×50 Hematoxylin and eosin). B: The intra-operative appearance of the left upper lid full-thickness pentagonal resection. C: The histopathological appearance of the tumor in the final excision showing solid cribriform architecture with mucin filled cystic spaces (Original magnification ×200 Hematoxylin and eosin). D: The higher power appearance of the pleomorphic tumor cells with Periodic acid Schiff (PAS) stained mucinous secretions (Original magnification ×400 PAS).
In addition, the histopathological appearance of PMA is classically characterized by dermal infiltration, and a lobulated structure in which small islands of epithelial cells are found to be floating in pools of mucin separated by fibrovascular septae giving the appearance of tumor nests that are either solid, or cribriform - as seen in this case-, or tubular [10]. Tumor cells are typically cuboidal or polygonal with scanty homogenous eosinophilic cytoplasm. Nuclear pleomorphism is usually absent [3]. Moreover, mucin produced by tumor cells is Periodic acid Schiff (PAS) positive and can be highlighted using colloidal iron, mucicarmine, and Alcian blue (PH 2.4) stains, which is also consistent with the non-sulfated sialomucin1 that is sialidase labile but hyaluronidase and diastase resistant. The slow growth and low metastatic rate of PMA is thought to be related to the huge amount of mucin secreted which interferes with cellular nutrition, and in turn, retarding the growth of neoplastic cells [3,6,10].

The use of immunohistochemical staining to distinguish primary mucinous adenocarcinoma from metastatic mucinous adenocarcinoma is of great importance. Recent studies support the use of p63 as a marker for differentiating between the two entities. It has been noted that the expression of p63 confirms the presence of myoepithelial cells indicating a primary adnexal origin of mucinous adenocarcinoma, which was found in our case [11]. Additionally, similar to breast cancer; PMA is cytokeratin (CK) 7, (GCDFP-15), epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), estrogen receptor (ER), and progesterone receptor (PR) positive, but CK20 negative. In contrast, gastrointestinal (GI) malignancies are CK7 negative and CK20 positive. Dirty necrosis (necrotic eosinophilic foci with nuclear debris) and epithelial cells with absorptive or goblet cell differentiation are other hints that the cells may have come from an intestinal origin [6,10–15].

Nonetheless, full clinical investigation remains the gold-standard to identify the origin of mucinous adenocarcinoma in the skin [16]. Thus, our patient also underwent initial systemic workup to rule out metastatic causes. All investigations yielded unremarkable results.

Since PMAs are considered locally invasive, the mainstay of treatment has been wide local excision [17]. The use of Mohs micrographic surgery which was first reported by Weber et al. [18] and is suggested as an alternative method by recent studies [10]. Although the metastatic rate of PMA is considered low accounting for approximately 3%, the recurrence rate of these tumors is reported to range between 26 and 40% [3,10]. It is generally thought to be the result of either incomplete resection, or lesions located at the inner canthus which are difficult to excise [17,19]. Our patient did not show any evidence of recurrence after a follow up period of 9 months.

It has been reported in one of the largest series of cutaneous PMA that distant disease was found in 5.8% of cases only and specific mortality was independent of gender, age, race, the primary site, the tumor size, stage, histologic tumor grade, or treatment [1]. The mean overall survival (OS) was reported to be 11.4 years with 5-year and 10-year OS being 85.0% and 78.0%, respectively [5].

4. Conclusion

We are reporting a case of a 70-year-old male with a PMA involving the upper eyelid. These tumors usually present as a slow-growing, well-circumscribed mass that is often misdiagnosed as a benign lesion; thus, ophthalmologists should be familiar with such a lesion to plan proper surgical complete excision. Accurate diagnosis of PMA requires a high index of suspicion and IHC markers are of great importance to aid in establishing a definitive diagnosis by pathologists.

Ethical approval

This case study was performed in accordance with the ethical standards of the institutional and national research Human Ethical Committee (HEC) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. However, IRB/Ethics Committee approval is not needed for Case reports in our institution.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

All authors have read and approved the manuscript. RMA and HMA: did literature search and wrote the manuscript draft. HMA critically revised the manuscript, provided histopathology figures and responsible

Fig. 2. A and B: Tumor cells clearly demonstrating reactivity to Cytokeratin (CK7) 7 in A and Carcinoembryonic antigen (CEA) in B (Original magnification ×400). C and D: The strong expression of tumor cells to GATA3 in C and Estrogen receptor (ER) in D (Original magnification ×400). E: Scattered expression of tumor cells to p63 (Original magnification ×400). F: The cosmetically satisfactory appearance of the left upper eyelid following tumor excision.
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