

Masquerade syndrome: sebaceous carcinoma presenting as an unknown primary with pagetoid spread to the nasal cavity

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Abstract

Sebaceous carcinoma of the eyelid is an uncommon tumour with unusual modes of presentation. It can remain occult at the primary site, without producing any mass, masquerading as chronic blepharoconjunctivitis, while setting up metastases in the regional lymph nodes especially in the pre-auricular group.

We report here a case that not only masqueraded as chronic blepharoconjunctivitis with nodal metastases from an 'unknown primary' in the neck, but whose tumour spread in a pagetoid manner along the nasolacrimal duct producing a nasal tumour that was believed to be the 'unknown primary'.

This case emphasizes the need for ophthalmologists, ENT surgeons and pathologists to keep sebaceous carcinoma in mind while evaluating patients with chronic blepharoconjunctivitis and cervical node metastases from 'unknown primary'. Histological clues for picking up a sebaceous carcinoma at a metastatic site include a tumour with comedo or ductal growth pattern and intracytoplasmic lipid.

Key words: Carcinoma, Squamous Cell; Eyelid; Nose; Neoplasms, Invasiveness; Neoplasm Metastasis

Introduction

The masquerade syndrome was described in the late sixties,^{1,2} as a chronic blepharoconjunctivitis due to intraepithelial spread of an underlying conjunctival sebaceous carcinoma. Since these tumours do not produce a mass they are invariably misdiagnosed¹ and after a period of time they present as metastases of an unknown primary to the pre-auricular lymph node.^{3,4,5} Even at this stage they go unrecognized and continue being labelled as metastases from an 'unknown primary'.

We report here a case of masquerade syndrome presenting with neck node metastases from an occult sebaceous carcinoma and with pagetoid spread along the nasolacrimal duct producing a nasal mass, which was at first mistaken for the primary tumour.

Case report

A 65-year-old male presented in August 1998 with a 2 × 2 × 1-cm Level II node mass on the left side of his neck of two months duration. Fine needle aspiration cytology (FNAC) reported metastases of a poorly differentiated squamous carcinoma. A search for the primary cancer was instituted. Upper gastrointestinal endoscopy, indirect laryngoscopy, computed tomography (CT) scan of head and neck and X-ray chest examination failed to reveal a primary tumour anywhere. Hence a left side radical neck dissection was performed. Sections from the nodal mass were reported as metastasis of a poorly differentiated squamous carcinoma with perinodal extension. The patient was advised radiation therapy in divided doses. He, however, defaulted after the first dose. He was operated for cataract in the right eye in early 1999. In January 2001

the patient developed epistaxis and symptoms of nasal obstruction. A CT scan revealed a mass occupying the entire right nasal cavity also involving the orbit along the nasal side (Figure 1). A punch biopsy from this mass revealed a poorly differentiated carcinoma and this was believed to be the primary site for the previously treated

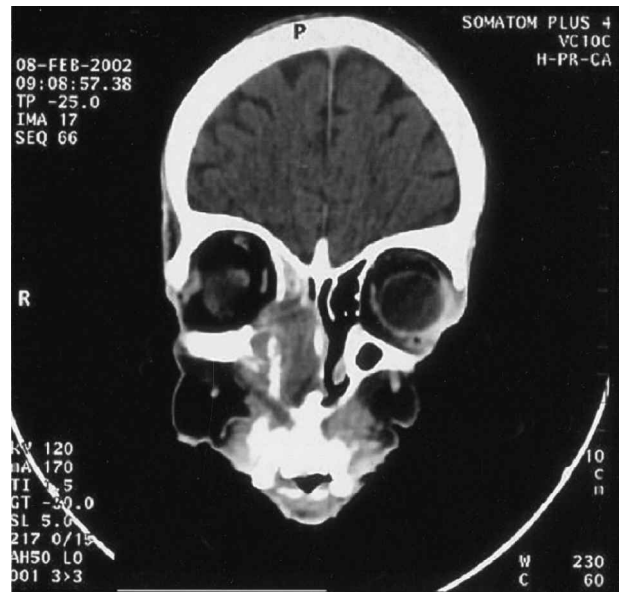


FIG. 1

Computed tomographic scan revealed a nasal mass destroying adjacent bony septa.

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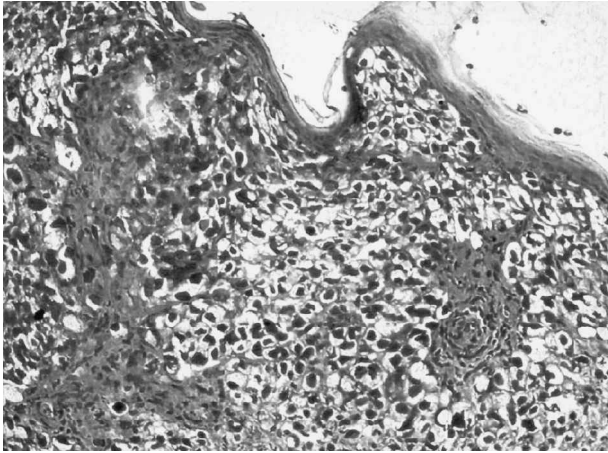


FIG. 2

Histology from the lid excision reveals intraepithelial pagetoid spread of the sebaceous carcinoma (H&E; ×200)

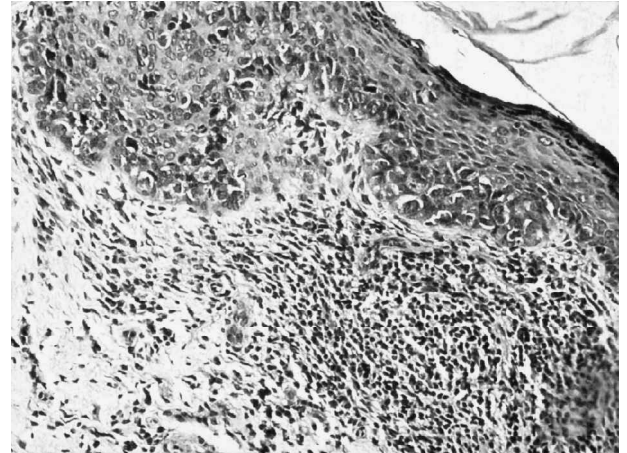


FIG. 3

Biopsy from the nasal mass reveals pagetoid spread to the overlying epithelium with break in the basement membrane blending with the underlying mass (H&E; ×200)

- Sebaceous carcinoma of the eyelid may masquerade as blepharoconjunctivitis
- In this case the patient also had nodal metastases and the primary tumour also spread along the nasolacrimal duct
- This paper is reported to emphasize this association

neck node metastases. The patient received radiotherapy to the primary site and the neck. During the treatment he consulted his ophthalmologist for persistent watering of eyes and unbearable itching of the lower right eyelid. As he did not respond to the usual local treatment and the itching became worse, eyelid stripping was done. These slides were reviewed at our institute. The histopathology showed squamous epithelium with pagetoid infiltration by large cells (Figure 2) extending to involve the sebaceous apparatus and hair follicles intraepithelially. A single nest of meibomian or sebaceous carcinoma was seen beneath this epithelium. A retrospective review of nodal metastases showed a carcinoma with a comedo pattern of growth and intra-cytoplasmic lipid, two features, which are specific for a sebaceous carcinoma. A few squamous morules were also noted. Immunohistochemistry was performed retrospectively on the primary tumour and the neck node metastases showed that the tumour expressed c-erb2, Human milk fat globulin (HMFG), cytokeratin and epithelial membrane antigen (EMA). It was CD15, S-100 and HMB45 negative. The biopsy from the nasal mass also showed pagetoid intra-epithelial spread (Figure 3), with a break in the basement membrane blending with the underlying mass.

Finally on detailed questioning, all the pieces of the puzzle fell in place. The patient gave a history of loss of eyelashes and constant itching of the lower eyelid over the last six years since 1996, two years before the neck swelling appeared. On examination the lower eyelid and palpebral conjunctiva appeared ulcerated scarred and inflamed, no tumour could be seen or felt.

This was a case of a primary sebaceous carcinoma, which did not present as a mass lesion but as blepharitis. Failure to recognize and treat it early led to neck node metastases. The tumour then spread in a pagetoid manner via the nasolacrimal duct to the nasal cavity and produced

a mass there. In view of the extensive lesion the patient received additional radiotherapy and chemotherapy. He subsequently developed an enlarged left side pre-auricular lymph node and upper cervical nodes on the right side, for which a neck node dissection was done. There was metastatic disease in these nodes also. The nasal mass had preceded nodal metastasis on the opposite side. He was advised chemotherapy and radiation but he failed to follow up.

Discussion

Sebaceous carcinoma of the eyelid is a great clinical masquerader. We have documented a case that masqueraded clinically as: (1) chronic blepharoconjunctivitis for six years; (2) metastasis from an 'unknown primary' malignancy; (3) nasal carcinoma.

If the primary treating ophthalmologist had recognized the true nature of the blepharoconjunctivitis the subsequent course of this patient may have been different. The blepharoconjunctivitis-like clinical syndrome is caused by the propensity of this tumour to spread within the epithelium⁶ similar to Paget's disease associated with an underlying breast or sweat gland carcinoma. This same mode of spread was responsible for the appearance of the nasal mass in this case and is a very rare, not well-documented clinical presentation of this tumour. This pagetoid spread in sebaceous carcinomas is associated with poor prognosis and should be recognized⁵ as early as possible.

Just as clinicians should recognize the varied clinical presentations of sebaceous carcinoma, pathologists must recognize sebaceous carcinoma in lymph node metastases from an unknown primary. Pathologists in general are unfamiliar with the appearance of sebaceous carcinoma even when it occurs in the eyelids. Only 22 to 50 per cent of eyelid sebaceous carcinoma are correctly labelled at initial pathological examination.⁷⁻⁹ Similarly we believe that sebaceous carcinomas are regularly missed in nodal metastases, although no report until now has specifically highlighted this issue. The problem is further complicated by the fact that sebaceous carcinoma often shows frank squamous differentiation with keratinization.^{5,7} Nodal metastases are therefore frequently mislabelled as those of a squamous carcinoma. Histologically sebaceous carcinoma in a nodal metastasis resembles breast carcinoma, with most of the tumour groups showing a ductal growth

pattern and comedo-type central necrosis. Intracellular lipid or abundant clear cytoplasm is always present. Thus when faced with a metastasis of a 'poorly differentiated carcinoma' with comedo necrosis and focal squamous differentiation in an upper cervical node especially the preauricular node, a serious attempt should be made to rule out sebaceous carcinoma of the eyelid.

The ancillary techniques that can aid in the detection of sebaceous carcinoma in nodal metastases are electron microscopy and immunohistochemistry. Sebaceous carcinoma on immunohistochemistry is usually positive for HMFG¹⁰, CD15¹⁰, Thomsen Friedenreich antigen,¹¹ c-erb2¹² and androgen receptors.¹³ Testing for these antigens may aid in the diagnosis of at least some cases. As seen, the immunohistochemistry overlaps with that of breast carcinoma.

Does detection of sebaceous carcinoma in nodal metastases mean a lost case? The incidence of nodal metastases in sebaceous carcinoma is 17–28 per cent.³ Once node metastasis is present, only half of patients with sebaceous carcinoma survive five years.³ However, recent reports have indicated that sebaceous carcinoma is a radiosensitive tumour, so even patients with nodal metastases can be salvaged with radiotherapy and aggressive local surgery.^{14,15} Thus detection of sebaceous carcinoma in a nodal metastasis from an unknown site is not a futile effort. Combined treatment of radical surgery at the primary site, parotidectomy, radical neck dissection and planned post-operative radiation therapy may improve the five-year survival of patients with limited regional lymph node metastasis. Avoiding delay in the diagnosis is the key factor in reducing the high mortality in sebaceous carcinoma.

References

- Theodore FH. Conjunctival carcinoma masquerading as chronic conjunctivitis. *Eye Ear Throat Mon* 1967;**46**:1419–20
- Irvine AR. Diffuse epibulbar squamous cell epithelioma. *Am J Ophthalmol* 1967;**64**:550–4
- Maniglia AJ. Meibomian gland adenocarcinoma of the eyelid with neck metastasis. *Laryngoscope* 1978;**88**:1421–6
- Mashburn MA, Chonkich GD, Chase DR. Meibomian gland adenocarcinoma of the eyelid with preauricular lymph node metastases. *Laryngoscope* 1985;**95**:1441–3
- Rao NA, Hidayat AA, Mclean IW, Zimmerman LE. Sebaceous carcinoma of the ocular adnexa: A clinicopathologic study of 104 cases with five year follow up data. *Hum Pathol* 1982;**13**:113–22
- Margo CE, Lessner A, Stern GA. Intraepithelial sebaceous carcinoma of the conjunctiva and skin of eyelid. *Ophthalmology* 1992;**99**:227–31
- Wolfe JT, Campbell JR, Yeatts PR, Waller RR, Wick MR. Sebaceous carcinoma of the eyelid. Errors in clinical and pathologic diagnosis. *Am J Surg Pathol* 1984;**8**:597–606
- Doxanas MT, Green WR. Sebaceous gland carcinoma. Review of 40 cases. *Arch Ophthalmol* 1984;**102**:245–9
- Khan JA, Doane JR, Grove AS Jr. Sebaceous and meibomian carcinoma of the eyelid. Recognition diagnosis and management. *Ophthalmic Plast Reconstr Surg* 1991;**7**:61–6
- Ansai S, Hashimoto H, Aoki T, Hozumi Y, Aso K. A histochemical and immunohistochemical study of extra-ocular sebaceous carcinoma. *Histopathology* 1993;**22**:127–33
- Hassanein AM, Al-Quran SZ, Kantor GR, Pauporte M, Telang GH, Spielvogel RL. Thomsen-Friedenreich (T) antigen possible tool for differentiating sebaceous carcinoma from its simulators. *Appl Immunohistochem Mol Morphol* 2001;**9**:250–4
- Cho KJ, Khang SK, Koh JS, Chung JH, Lee SS. Sebaceous carcinoma of the eyelids: frequent expression of c-erb2 oncoprotein. *J Korean Med Sci* 2000;**15**:545–50
- Bayer-Garner IB, Givens V, Smoller B. Immunohistochemical staining for androgen receptors; a sensitive marker of sebaceous differentiation. *Am J Dermatopath* 1999;**21**:426–31
- Pardo FS, Wang CC, Albert D, Stracher MA. Sebaceous carcinoma of ocular adnexa: Radiotherapeutic management. *Int J Radiation Oncol Biol Physics* 1989;**17**:643–7
- Wolter JR, Bromley WC. Intraepithelial sebaceous epithelioma of lids, conjunctiva and cornea treated with minimal orbital exenteration. *Ophthalmic Surg* 1991;**22**:341–4

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