CASE REPORT

Conjunctival metastatic adenocarcinoma of unknown origin

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SUMMARY

We describe the case of a presumed metastatic adenocarcinoma discovered in the conjunctival limbus of a 75-year-old male with a history of prostate adenocarcinoma. After an initial clinical diagnosis of pinguecula and unsuccessful topical steroid therapy, the lesion was excised and sent for pathological evaluation and special staining. The histopathological evaluation was consistent with a diagnosis of adenocarcinoma, without evidence of lacrimal tissue. Surprisingly, results from special staining were most consistent with lung adenocarcinoma rather than that from a prostate origin. Systemic radiographic evaluation did not locate the primary tumour, and the patient did not present with any symptoms consistent with malignancy. Watchful waiting was chosen as the therapeutic strategy to manage the patient. This is the first report of an adenocarcinoma, likely metastatic, at the conjunctival limbus.

BACKGROUND

Adenocarcinomas of the conjunctiva are rare among ocular tumours. A Taiwanese study found that adenocarcinomas account for 4.47% of all tumours among the Chinese population of Taiwan. The most common cancers of the conjunctiva was squamous cell carcinoma (SCC) (43.5%), melanoma (23.5%) and lymphoma (23%).¹ A study in Singapore found that conjunctival tumours represented 13% of eye cancers, <2% of which were adenocarcinomas.² In the USA, squamous cell carcinomas and melanomas account for most ocular surface tumours, and no instances of adenocarcinomas were reported.³ Mahoney *et al* found that adenocarcinomas account for 1.1% of primary conjunctival cancers in the USA.⁴

The limbus as the anatomical location of a metastatic lesion is also rare. One case of limbal metastasis is described by Kiratli *et al*.⁵ The patient, however, had a known previous diagnosis of cancer and died of metastasis within 2 months of ocular metastasis. A large retrospective case series conducted at Wills Eye Hospital with 1643 cases of conjunctival tumour found that premalignant or malignant epithelial tumours comprised 11% of the sample. Metastatic tumours to the conjunctiva comprised <1% of the sample. No metastatic tumour to the limbal bulbar conjunctiva was found.⁶

CASE PRESENTATION

A 75-year-old man presented with a 9-month history of an irritating growth on his right eye, and

reported of mild pain and stinging sensation. The growth was pink, raised, mobile and measured 0.5 cm; it was located at the 3 o'clock position of the nasal conjunctiva limbus of the right eye. His corrected vision was 20/20 OU. Intraocular pressure measured 21 mm Hg OD and 20 mm Hg OS while slit-lamp examination revealed mild blepharitis and dry eye in both eyes. The dry eye was symptomatically managed with preservative-free artificial tears. The patient had a history of primary open angle glaucoma in the left eye requiring intraocular pressure-lowering treatment. He had had previous cataract and LASIK surgery in both his eyes. He had a history of prostate adenocarcinoma diagnosed 10 years prior to the development of the conjunctival mass. His prostate cancer was treated with local radiation and brachytherapy about 9 years ago. No symptoms of disease recurrence were reported by the patient. There was also no history of smoking, drinking or use of recreational drugs.

INVESTIGATIONS

The patient was initially managed with topical steroid for symptom relief. The hope was that steroid therapy would lead to decreased irritation and shrinking of the lesion. After two courses of steroid therapy and only mild symptomatic relief, excisional biopsy with cryotherapy to the free margins and a conjunctival graft was performed. The specimen (0.6×0.5×0.2 cm) was submitted for histopathological examination as per institutional protocol. The initial surgery was for symptomatic relief. Since all specimens are submitted for pathological analysis, the surgeons decided to obtain free margins because a malignant process was on the differential. Initial pathological assessment revealed a neoplasm in the substantia propria that was composed of hyperchromatic epithelial cells arranged in glandular structures (figure 1A). Conspicuous mitotic activity was noted. The neoplastic cells demonstrated positive cytokeratin 7 staining and negative cytokeratin 20 staining (figure 2A, B). Additional evaluation revealed multiple cords of tumour cells underlying the epithelium and substantia propria. The glandular/cord-like appearance of the cells was again observed (figure 1B). Areas of nucleoli formation and small pleomorphism along with mild fibrotic reaction between cords of tumour cells were noted (figure 1C). No signs of lacrimal gland tissue were found, which is significant because the lacrimal gland is the most likely source of a primary adenocarcinoma on the ocular surface. While a large

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Figure 1 (A) Low magnification, H&E stain of the lesion. Tumour cells (blue arrows) underlying the substantia propia (red arrows) are noted ($\times 4$). (B) Cord-like structure of the tumour can be observed underlying the substantia propia, and also the fibrotic reaction (green arrows) in between the cords of tumour cells can be noted ($\times 20$). (C) Pleomorphism with prominent nucleoli can be seen in many cells ($\times 40$).

tumour at the site could obscure benign lacrimal tissue, we did not identify any to the best of our assessment.

The glandular appearance of the tumour sample, along with staining characteristics showing CK 20 negativity and CK 7 positivity raised the suspicion for metastatic adenocarcinoma of the lung. Importantly, prostate-specific antigen (PSA) stain, highly specific for prostatic metastasis, was negative in this patient with a history of prostatic adenocarcinoma. α -methyl CoA racemase stain, synaptophysin stain, and napsin-A stain were all negative. Thyroid-transcription factor 1 (TTF-1) stain showed minimal focal staining. Final consensus in pathology is that the tumour was likely a metastatic adenocarcinoma from an unknown primary tumour. The pathological evaluation prompted a work up to find the primary source of the cancer. Whole-body positron emission topography (PET) scan did not reveal a definite primary tumour. Physical examination and medical evaluation also did not elicit symptoms consistent with cancer. CT scan, performed after 3 months, confirmed the lack of a detectable primary tumour.

DIFFERENTIAL DIAGNOSIS

Early differential diagnosis included pyogenic granuloma and pinguecula. However, we could not rule out a malignant process. The most likely ocular surface malignancy would have been a squamous cell carcinoma.⁷ We did not expect pathological analysis to reveal an adenocarcinoma, especially one without evidence of lacrimal tissue, the closest adenomatous tissue.

TREATMENT

The anatomical location of this patient's lesion at the limbus is also unique. In the case of the patient reported here, his limbal

metastasis was likely the first manifestation of an occult primary tumour. We come to this conclusion for several reasons. First, ocular surface adenocarcinomas would most likely originate from the lacrimal gland. However, our microscopic examination did not reveal lacrimal tissue or tissue consistent with ocular origin. Second, the special staining pattern was consistent with a systemic tumour. A metastatic tumour to the limbal conjunctival from an occult source is a unique combination of rare clinical events that also calls into question the next step in management. The lesion on his eye has been excised (figure 3A, B) and imaging has not revealed a primary tumour. However, while our clinical reasoning and pathological analysis indicate a metastatic tumour, it is possible that the lesion was a rare, primary ocular tumour.

Management could include a conservative approach (watchful waiting) or an aggressive approach (irradiation). Radiation was brought up as an option because of the mysterious origin of the lesion. Had the lesion been a primary tumour (eg, a SCC), then a complete excision would have been performed and this would have been curative. Since the histological features and staining characteristics suggested an extraocular origin of the lesion, there exists the possibility of other sites of metastasis (choroid, uveal apparatus). While dilated eye examinations did not reveal a secondary lesion, there is the possibility of early tumour seeds that are not visible. Therefore, out of an abundance of caution, radiation of the eye was considered. However, radiation could lead to decreased or loss of vision in an otherwise functioning eye.

The current care team has elected to wait and see whether the primary cancer manifests or other metastatic lesions occur. The therapeutic strategy selected was watchful waiting since the patient was strongly supportive of conservative management.

Figure 2 Cytokeratin 7 (C) and cytokeratin 20 (D) special staining of the lesion. Lesion is CK7⁺/CK20⁻. (A) CK 7 positive staining of the lesion (CK7 special stain $\times 4$). (B) CK20 absence of staining of the lesion (CK20 special stain $\times 4$).

Figure 3 (A and B) Slit-lamp photos of the patient after the surgery.

OUTCOME AND FOLLOW-UP

Approximately 1 year after discovering the metastatic lesion, no sign of recurrence of the lesion has appeared. Further, no sign of the primary lesion has appeared either. The patient does not manifest signs of cancer. He feels well and has returned to his regular routine. Imaging studies at 1 year included repeat of whole body PET scan, and CT scan of chest and abdomen. Still, no primary lesions have been identified. The patient sees his ophthalmologist regularly (every 2–4 months) for follow-up for glaucoma, at which time the follow-up for his unique adenocarcinoma will also be addressed. Further, follow-up with oncology will be scheduled on a yearly basis, or if there is recurrence of the lesion. At the next follow-up appointment with oncology (~1 year from now), the oncology team will decide whether additional scans are indicated.

DISCUSSION

Metastasis to the conjunctiva is rare among ocular lesions. Grossniklaus *et al*⁷ evaluated 2455 conjunctival lesions in adults and found only 1 case of metastatic carcinoma. The detection of ocular metastasis prior to the primary tumour discovery is a documented phenomenon. A study of 182 uveal metastases found 44% from the lung were discovered prior to the discovery of primary lung cancer.⁸ A survey of 520 eyes found that 34% of uveal metastasis had no history of cancer. In 51% of cases, a primary cancer could not be found.⁹

The identification of metastatic tumours of unknown origin is a challenge for pathologists and oncologists. The immunohistochemical profile of the specimen could be helpful in identifying the primary source of a metastatic lesion. The sample found in the patient reported here demonstrated CK7⁺/CK20⁻. A survey of 435 epithelial neoplasms found CK7 to be positive in majority of lung neoplasms, and infrequently in prostate neoplasms. CK20 is mostly likely to be positive in cases of colon, skin or pancreas neoplasm. A combination of CK7⁺/CK20⁻ was most probable in breast, ovarian adenocarcinoma, endometrial, thyroid and lung adenocarcinoma. Su *et al*¹⁰ reviewed the TTF-1, Ck20, and CK7 staining pattern of 66 cases of lung adenocarcinoma and found that 60% of adenocarcinomas of lung origin had the profile of TTF-1⁺/CK7⁺/CK20⁻. Our patient did have a history of prostate cancer, although the PSA negativity makes a prostate metastasis less likely. PSA is 97% sensitive in identifying metastasis of prostate origin. A negative PSA makes a metastasis of prostate origin unlikely.¹¹ A primary sebaceous carcinoma of the conjunctiva is another possible diagnosis in this case. Primary sebaceous carcinoma can present at the limbus, and present with pain, diplopia, proptosis and extraocular motility disturbances. CK 7 stain positivity has also been noted.¹² While we did not observe sebaceous differentiation nor evidence of lacrimal tissue, we cannot exclude a primary

sebaceous carcinoma as a possibility. However, based on our pathological assessment, we believe an obscure metastatic adenocarcinoma to be of higher probability.

Patient's perspective

- ▶ Written on follow-up after imaging modality failed to reveal a primary tumour.
- ▶ "The CT didn't show a cancer which makes me very happy. I've had cancer in my prostate before, but that was many years ago. I was scared that I might have something again. I really did not think that this thing in my eye was more than a nuisance. But doctors are telling me that they are not going to give me drugs and surgeries. This is great because at my age I don't want any more things done. Still, grateful so many folks were concerned and wanted to make sure I'm alright."

Learning points

- ▶ This case highlights the role that pathologists have in diagnosing tumours, in addition to retrospectively confirming diagnoses. With diligent follow-up after pathological diagnosis, patient management can be optimised.
- ▶ Even benign-appearing lesions of the eye may harbour a more sinister illness. Diligent follow-up and referral to pathology can help discover systemic illness.
- ▶ Conservative management of illness may be the best option in a patient who is otherwise healthy. It is difficult to improve on a healthy patient.

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Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 Cheng CY, Hsu WM. Incidence of eye cancer in Taiwan: an 18-year review. *Eye (Lond)* 2004;18:152–8.
- 2 Lee SB, Au Eong KG, Saw SM, *et al*. Eye cancer incidence in Singapore. *Br J Ophthalmol* 2000;84:767–70.
- 3 Lee GA, Hirst LW. Ocular surface squamous neoplasia. *Surv Ophthalmol* 1995;40:429–50.

- 4 Mahoney MC, Burnett WS, Majerovics A, *et al.* The epidemiology of ophthalmic malignancies in New York State. *Ophthalmology* 1990;97:1143–7.
- 5 Kiratli H, Shields CL, Shields JA, *et al.* Metastatic tumours to the conjunctiva: report of 10 cases. *Br J Ophthalmol* 1996;80:5–8.
- 6 Shields CL, Demirci H, Karatza E, *et al.* Clinical survey of 1643 melanocytic and nonmelanocytic conjunctival tumors. *Ophthalmology* 2004;111:1747–54.
- 7 Grossniklaus HE, Green WR, Luckenbach M, *et al.* Conjunctival lesions in adults: a clinical and histopathologic review. *Cornea* 1987;6:78–116.
- 8 Shah SU, Mashayekhi A, Shields CL, *et al.* Uveal metastasis from lung cancer: clinical features, treatment, and outcome in 194 patients. *Ophthalmology* 2014;121:352–7.
- 9 Shields CL, Shields JA, Gross NE, *et al.* Survey of 520 eyes with uveal metastases. *Ophthalmology* 1997;104:1265–76.
- 10 Su YC, Hsu YC, Chai CY. Role of TTF-1, CK20, and CK7 immunohistochemistry for diagnosis of primary and secondary lung adenocarcinoma. *Kaohsiung J Med Sci* 2006;22:14–19.
- 11 Queisser A, Hagedorn SA, Braun M, *et al.* Comparison of different prostatic markers in lymph node and distant metastases of prostate cancer. *Modern Pathology* 2015;28:138–45.
- 12 Kiratli H, Tarlan B, Firat P. Primary sebaceous carcinoma of the lacrimal gland. *Orbit* 2012;35:352–4.

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