

SCIENTIFIC REPORT

Patterns of regional head and neck lymph node metastasis in primary conjunctival malignant melanoma

M Lim, T Tatla, D Hersh, J Hungerford



Br J Ophthalmol 2006;90:1468–1471. doi: 10.1136/bjo.2006.099754

See end of article for authors' affiliations

Correspondence to:
M Lim, Department of Otolaryngology, Royal National Throat, Nose and Ear Hospital, 330–336 Grays Inn Road, London WC1X 8EE, UK; mingyannl@yahoo.com

Accepted 27 July 2006
Published online First 23 August 2006

Objective: To correlate patterns of regional lymph node metastasis with the site of origin in primary conjunctival malignant melanoma.

Design: Retrospective analysis (1990–2003) of clinical data.

Setting: Two London tertiary referral centres.

Participants: 12 patients presenting with regional metastases after failed local treatment for conjunctival malignant melanoma.

Results: 6 cases predominantly involving the temporal conjunctiva metastasised to the pre-auricular lymph nodes. Two cases predominantly involving the nasal conjunctiva metastasised to the submandibular nodes. Of the two cases with purely multifocal disease, one metastasised to the pre-auricular nodes and another to both submandibular and parotid nodes. One primary conjunctival malignant melanoma had its origin in temporal conjunctiva but metastasised to submandibular nodes, and another case originating from nasal conjunctiva metastasised to pre-auricular nodes.

Conclusions: Temporal conjunctival melanotic lesions tend to metastasise clinically to pre-auricular lymph nodes and nasal conjunctival melanotic lesions metastasise to the submandibular lymph nodes. Patterns appear consistent with laboratory-based anatomically mapped lymphatic drainage basins of the conjunctiva.

Current understanding of the lymphatic drainage of the eyelid and conjunctiva is based on light microscopy and vital dye histochemical analysis carried out almost 100 years ago.¹ On the basis of these studies, it has been proposed that the medial eyelid and conjunctiva preferentially drain to the submandibular lymph nodes and the lateral eyelid and conjunctiva to the pre-auricular lymph nodes.² More recently, the use of lymphoscintigraphy in the cynomolgus monkey has shown more complex drainage of the eyelids.¹ In the monkey, the entire lymphatic system in the upper eyelid drains to the pre-auricular lymph nodes, except for the central upper eyelid which also drains to the submandibular lymph nodes. The medial and central portions of the lower eyelid drain to the submandibular lymph nodes, whereas the lower lateral eyelid drains to the pre-auricular lymph nodes.

Clinical data for lymphatic drainage patterns of conjunctival and eyelid malignant tumours have been limited by their rarity. Conjunctival malignant melanoma is a rare malignancy, having an incidence of 0.2–0.8 per million in white populations^{3–6} and contributing to only 2% of all ocular malignancies.⁷ It occurs in three clinical settings: in conjunction with a naevus, de novo and in primary acquired melanosis with atypia, which are determined in many cases by histopathological findings. Although a rare tumour, it is reported to involve metastatic spread to regional lymph nodes in the pre-auricular and submandibular regions in up to one third of these patients,^{8–10} thus increasing its suitability in studying patterns of conjunctival lymphatic drainage. The 5-year mortality is between 18% and 32%,^{8–11} with a poor prognosis once disseminated disease is clinically detectable.

Our study aimed to examine the relationship between primary tumour and regional lymph node metastatic site in conjunctival malignant melanomas, thus determining whether clinically observed patterns of metastasis correlate

with those expected from conventional laboratory-based mapping studies.

PATIENTS AND METHODS

The clinical records of 12 patients presenting to JH at St Bartholomew's Hospital and Moorfields Eye Hospital in London, UK (1990–2003) with primary conjunctival malignant melanoma and regional lymph node metastasis were reviewed retrospectively. Most patients had failed local treatment to the conjunctival malignant melanoma in a secondary care setting before entering our study. The data of these 12 patients have been the subject of a separate paper considering the role of conservative surgery and radiotherapy in regional metastatic disease from conjunctival melanoma.¹²

Data

The following information was obtained from clinical notes: sex, age at onset, laterality, anatomical location of primary, initial diagnosis and management of primary site, location of regional metastasis and time (date) to regional metastasis after diagnosis (table 1).

The primary study outcome measurement was location of regional lymph node metastasis: pre-auricular or submandibular. Median follow-up time was 48 (range 17–147) months.

Statistical analysis

The purely observational nature of the study and the limited patient numbers precluded formal statistical analysis.

RESULTS

Patient demographics and primary conjunctival characteristics

There were six men and six women in the study group. The median age was 51 (range 38–86) years. The left eye was

Table 1 Summary of case reports and management of local conjunctival malignant melanoma

Patient	Sex	Age at onset	Laterality	Anatomical location of primary metastasis	Initial diagnosis and management of primary site	Location of regional metastasis	Time (date) to regional metastasis after diagnosis
1	F	52	L	Nasal conjunctiva and caruncle	Jan 1990 WLE large pedunculated MM; background PAM inferior fornix	Pre-auricular	46 months (Nov 1993)
2	F	50	R	Multifocal with nasal nodule	1983-9 \times4 WLE MM; background PAM (initially diagnosed 1973)	Submandibular	96 months (Oct 1991)
3	F	66	L	Temporal limbus	Sept 1998 WLE and cryotherapy MM; background PAM	Precaricular	15 months (Dec 1999)
4	F	42	L	Original lesion temporal limbus, recurrences in lower temporal and nasal fornices	1990-1998 repeated WLE recurrent MM	Pre-auricular	108 months (Jun 1999)
5	F	73	L	Multifocal upper and lower palpebral conjunctiva and eyelid skin	Aug 1998 to Mar 1999 repeated cryotherapy recurrent MM; background PAM (PMH of myeloid dysplasia, IHD, CVD and amblyopic R eye since childhood)	Pre-auricular	13 months (Sep 1999)
6	F	86	L	Multifocal disease with recurrence temporally	1999 multiple WLE; background PAM	Pre-auricular	20 months (Oct 2000)
7	M	54	R	Upper temporal palpebral conjunctiva	Jun 1991 WLE and cryotherapy; cryotherapy for subsequent recurrences; background PAM since 1964	Submandibular	20 months (Feb 1993)
8	M	28	R	Temporal limbus	May 1999 WLE amelanotic MM; subsequent adjuvant cryotherapy for incomplete excision; background PAM	Pre-auricular	18 months (Oct 2000)
9	M	41	L	Inferotemporal limbus	Aug 1998 WLE and cryotherapy of MM; WLE, cryotherapy and surface radiotherapy for recurrences over next 2 years; background PAM	Pre-auricular	26 months (Oct 2000)
10	M	42	L	Multifocal disease	May 2000 WLE amelanotic MM; multiple WLE, cryotherapy and surface radiotherapy for recurrences over next 6 months; background amelanotic PAM	Pre-auricular/submandibular	12 months pre-auricular and 20 months submandibular (May 2001 and Jan 2002)
11	M	44	L	Nasal limbus and caruncle	Apr 1999 WLE and cryotherapy MM; multiple WLE, cryotherapy and surface radiotherapy for recurrences over next 2 years; background PAM	Submandibular	40 months (Aug 2002)
12	M	46	R	Temporal limbus	Dec 1999 WLE and cryotherapy amelanotic MM; Nov 2001 WLE and adjuvant surface radiotherapy for recurrence; background amelanotic PAM	Pre-auricular	32 months (Aug 2002)

CVD, cardiovascular disease; F, female; IHD, ischaemic heart disease; L, left; M, male; MM, malignant melanoma; PAM, primary acquired melanosis; PMH, Princess Margaret Hospital; R, right; WLE, wide local excision.

involved in 8 of 12 patients, the right eye in 4 of 12 patients, with no cases of bilateral disease. The nasal conjunctiva was predominantly involved in three patients (patients 1, 2 and 11), the temporal conjunctiva predominantly in seven patients (patients 3, 4, 6, 7, 8, 9 and 12) and two patients were multifocal (patients 5 and 10). In all, 11 of 12 patients had pre-existing primary acquired melanosis (all except subject 4), two of which were amelanotic (all except subject 8 and 12). Epithelioid tumour cells were noted in seven of the eight histopathological reports in which the melanoma cell type could be determined.

Features of regional lymph node spread

The pre-auricular lymph nodes were affected in eight patients (patients 1, 3, 4, 5, 6, 8, 9 and 12) and the submandibular lymph nodes in three patients (patients 2, 7 and 11). In one patient, both the preauricular and submandibular lymph nodes, were involved (patient 10). These regional metastases occurred at a median of 23 (range 12–108) months after diagnosis of primary conjunctival malignant melanoma.

Relationship between primary conjunctival position and regional metastasis

Of the seven cases (patients 3, 4, 6, 7, 8, 9 and 12) predominantly originating from temporal conjunctiva, six cases (patients 3, 4, 6, 8, 9 and 12) metastasised to the pre-auricular lymph nodes. One of these seven (patient 7) metastasised to submandibular lymph nodes. Four of the six cases (patients 3, 8, 9 and 12) metastasising to pre-auricular lymph nodes were purely temporal lesions. In one (patient 4) the original lesion was temporal with recurrence in the lower temporal and nasal fornices; in another (patient 6) the primary disease was multifocal with conjunctival recurrence temporally.

Three cases (patients 1, 2 and 11) predominantly involved the nasal conjunctiva. Two of these metastasised to the submandibular lymph nodes (patients 2 and 11) and one metastasised to the pre-auricular lymph nodes (patient 1). Both patients 1 and 11 had purely nasal lesions, whereas patient 2 had multifocal disease, although the main nodule was located in the nasal conjunctiva.

Patient 5, with multifocal disease, metastasised to the pre-auricular lymph nodes. Patient 10, also with multifocal disease, metastasised to both pre-auricular and submandibular lymph nodes.

DISCUSSION

Laboratory-based research has contributed much to evidence-based medicine in clinical practice. The goal of this article is to corroborate laboratory-based findings with clinical practice.

The main clinical findings are that melanomas involving the nasal conjunctiva tend to metastasise to the submandibular lymph nodes and melanomas involving the temporal conjunctiva tend to metastasise to the pre-auricular lymph nodes. There was a single case (patient 1) in which the nasal conjunctiva was involved, with unexpected metastasis to the pre-auricular lymph nodes, and another case (patient 7) in which the temporal conjunctiva was involved with metastasis to the submandibular lymph node.

The clinical findings support current understanding of lymphatic drainage patterns of the conjunctiva as proposed by conventional laboratory-based studies. The published laboratory techniques date mainly from the first half of the 20th century and include injection methods,¹³ with the slit lamp,¹⁴ by vital staining,¹⁵ by hydrogen peroxide injection¹⁶ and by the injection of radio-opaque fluid.¹⁷

These studies show that within the conjunctiva itself there is a superficial lymphatic network in the conjunctiva proper

and a deeper system in the fibrous layer of the conjunctival submucosa. These drain towards the lateral and medial canthi. From the lateral canthus, the lymphatics drain to superficial parotid intraglandular and paraglandular lymph nodes and from the medial canthus to facial and submandibular lymph nodes.¹⁸

The study of Most¹³ is one of the more comprehensive. He showed that the lymph vessels of the conjunctiva are intimately connected to the lymph vessels of the eyelid. The lymph vessels from these two networks are divided into superficial and deep vessels, mainly according to whether they arise from the outer skin of the lid or from the conjunctiva. The superficial lateral vessels originate in the skin of nearly the entire upper lid and the outer half of the lower lid. These drain into a typical lymph node situated superficially in the parotid gland at the level of the external auditory canal. From this node, vessels go to other deeper parotid lymph nodes. The deep lateral vessels arise in the conjunctiva of the upper lid and the outer third of the lower lid. These drain into the superficial and deep parotid nodes. The superficial median vessels arise mainly in the skin of the inner half of the lower lid and in that of the inner corner of the eye. Their regional gland is one of the submaxillary lymph nodes. The deep median vessels arise chiefly from the conjunctiva of the inner two thirds and from the region of the caruncle. They drain to the submaxillary nodes.

This study was limited by the small size of the series analysed, which in turn was dependent on the rarity of conjunctival melanoma with regional lymph node metastases. In addition, it was not possible to “divide the conjunctiva/eyelids into thirds” as described by Most¹³ or as performed in lymphoscintigraphy with the cynomolgus monkey,¹ because the melanomas were not necessarily limited to a particular third of the eyelids or conjunctiva. In addition, the position of most of the conjunctival lesions did not allow for analysis of lymphatic drainage based on superior–inferior positions of the conjunctival lesions. Only two of the patients had lid involvement, and hence lymphatic drainage of the lids could not be commented on.

Clinically, the importance of a thorough understanding of the lymphatic drainage of the eyelids is that it directs the clinician specifically to seek and detect regional metastatic spread of the primary disease. Furthermore, inadequate appreciation of the lymphatic anatomy may result in disruption of lymphatic channels during surgery and trauma, reducing lymphatic drainage and resulting in avoidable, prolonged eyelid and conjunctival oedema.¹⁹

Although lymphatic metastasis may be predictable based on the primary position of the tumour it is not always failsafe, especially in watershed areas. In 1990, intraoperative lymphatic mapping and selective lymph node dissection were introduced as an alternative to cervical lymph node dissection in patients with clinical stage I cutaneous melanoma.²⁰ Selective lymph node dissection is based on the theory that a primary melanoma will involve the sentinel node before spreading to other nodes further along the lymphatic chain. The tumour status of the sentinel node excised during selective lymph node dissection thus determines the tumour status of the regional lymph nodes and affects surgical planning of lymph node dissection.

CONCLUSION

Nasal conjunctival melanomas tend to metastasise to submandibular lymph nodes and temporal conjunctival melanomas metastasise to the pre-auricular or parotid lymph nodes. This study provides clinical evidence for lymphatic drainage patterns of a rare conjunctival tumour and supports drainage patterns described by conventional laboratory-based microscopic methods.

.....

Authors' affiliations

M Lim, T Tatla, Department of Otorhinolaryngology–Head and Neck Surgery, Northwick Park Hospital, Harrow, Middlesex, UK

D Hersh, J Hungerford, Ocular Oncology Service, St Bartholomew's Hospital, West Smithfield, London, UK

Competing interests: None.

REFERENCES

- 1 **Cook E**, Lucarelli J, Lemke N, *et al*. Eyelid lymphatics II: a search for drainage patterns in the monkey and correlations with human lymphatics. *Ophthalm Plast Reconstr Surg* 2002;**18**:99–106.
- 2 **Bron J**, Tripathi C, Tripathi J. The ocular appendages: eyelids, conjunctiva and lacrimal apparatus. In: *Wolffs anatomy of the eye and orbit*. London: Chapman and Hall, 1997:69–70.
- 3 **Seregard S**. Conjunctival melanoma. *Surv Ophthalmol* 1998;**42**:321–59.
- 4 **Jakobiec A**. Conjunctival melanoma. *Arch Ophthalmol* 1980;**98**:1378–84.
- 5 **Yu P**, Hu N, McCormick S, *et al*. Conjunctival melanoma: is it increasing in the United States? *Am J Ophthalmol* 2003;**135**:800–6.
- 6 **Tuomaala S**, Kivela T. Conjunctival melanoma: is it increasing in the United States? *Am J Ophthalmol* 2003;**136**:1189–90.
- 7 **Kanski J**. Disorders of the conjunctiva. In: *Clinical ophthalmology: a systematic approach*. London: Butterworth-Heinemann, 1999:86–90.
- 8 **Anastassiou G**, Heiligenhaus A, Bechrakis N. Prognostic value of clinical and histopathological parameters in conjunctival melanomas: a retrospective study. *Br J Ophthalmol* 2002;**86**:163–7.
- 9 **Shields L**, Shields A, Gunduz K, *et al*. Conjunctival melanoma: risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients. *Arch Ophthalmol* 2000;**118**:1497–507.
- 10 **Esmaili B**, Wang X, Youssef A, *et al*. Patterns of regional and distant metastasis in patients with conjunctival melanoma. Experience of a cancer center over four decades. *Ophthalmology* 2001;**108**:2101–5.
- 11 **Paridaens D**, Minassian C, McCartney C, *et al*. Prognostic factors in primary malignant melanoma of the conjunctiva: a clinicopathological study of 256 cases. *Br J Ophthalmol* 1994;**78**:252–9.
- 12 **Tatla T**, Hungerford J, Plowman N. Conjunctival melanoma: the role of conservative surgery and radiotherapy in regional metastatic disease. *Laryngoscope* 2005;**115**:817–22.
- 13 **Most**. *Arch Anat Physiol* 1905;**96**.
- 14 **Vogt A**. *Lehrbuch und Atlas der Spaltlampenmikroskopie d*, Vol 1. Berlin: Lebenden Auges, 1930.
- 15 **Chinaglia**. *Ann Ottal* 1955;**81**:325.
- 16 **Stübel**. *v. Graefe's Arch Ophthalmol* 1923;**112**:347.
- 17 **Katamaya**. *Acta Soc Ophthalmol Japan* 1951;**55**:880–3.
- 18 **Duke-Elder S**, Wybar C. Anatomy of the visual system. In: *System of ophthalmology*. London: Henry Kimpton, 1965;**2**:551.
- 19 **Levine MR**, Davies R, Ross J. Chemosis following blepharoplasty: an unusual complication. *Ophthalm Surg* 1994;**25**:593–6.
- 20 **Morton DL**, Wen DR, Wong JH, *et al*. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992;**127**:392–9.

International Forum on Quality & Safety in Health Care

18–20 April 2007, Palau de Congressos, Barcelona.

Why attend?

- Join over 1000 healthcare professionals from over 40 countries worldwide
 - Learn from experienced leaders and improvement experts
 - Gain new skills and tools for creating change in your organisation
 - Take home practical solutions for improvement methods
- <http://www.quality.bmj.com>