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EDITORIAL

Excision and cryosurgery of conjunctival malignant epithelial tumours

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The conjunctival surface is lined by nonkeratinised squamous epithelium and, therefore, malignant epithelial tumours of the conjunctiva are squamous in nature. These tumours represent a spectrum ranging from mild dysplasia to invasive squamous cell carcinoma involving the conjunctiva as well as the cornea, and are grouped as ocular surface squamous neoplasia (OSSN).[1,2] OSSN is an uncommon ocular tumour, with an incidence of 0.03 per 100 000 population in the United States,[3] and is more frequent in Australia with an incidence of 1.9 per 100 000 population.[4] A rise in the incidence of OSSN in recent years has been reported from parts of the African continent.[5] OSSN is predominantly seen in older male Caucasians, although other races or age groups can also be affected.[1,3] Important risk factors include excessive UV light exposure,[3,6] HIV infection,[7] and genetic susceptibility in conditions such as xeroderma pigmentosa.[8] The role of human papillomavirus infection in causation of OSSN is not clearly established.[6,9,10]

The presence of a perilimbal circumscribed fleshy growth is typical of OSSN. Associated prominent feeder vessels and surface leukoplakia are characteristic findings. However, the clinical features are not helpful in differentiating conjunctival intraepithelial neoplasia (CIN) from invasive squamous cell carcinoma (SCC). The differentiation is made by careful histopathologic evaluation to determine extension of the tumour beyond the basement membrane in SCC.

Almost 20 years ago, Fraunfelder and Wingfield[11] reported improved tumour control when excision was combined with cryotherapy as compared to excision or cryotherapy performed alone. This was attributed to eradication of microscopic residual tumour beyond the clinically visible margin by the cryotherapy. Involvement of the margins at the initial excision is the most important risk factor for recurrence.[12] Although recurrence rates of over 50% have been reported in the past, at present a recurrence rate of only 5–10% is generally accepted.[1]

In addition to cryotherapy, other modalities of adjunctive therapy include radiotherapy, which is reported to offer excellent tumour control rates.[13,14] Currently, there is great interest in the use of topical chemotherapy (interferon,[15] mitomycin C (MMC)[16] and 5-fluorouracil[17]). Topical chemotherapy is generally advocated where tumour excision is not feasible or incomplete; such treatment has also been used as primary treatment or as secondary treatment for recurrent tumours.[18] It appears that topical MMC is effective in the treatment of OSSN that lack invasion beyond the basement membrane. Further studies are necessary to establish clearly the role of topical chemotherapy in the management of OSSN.

In an article published in this issue, Peksayar *et al*[19] report on the efficacy of excision and cryotherapy in the treatment of malignant epithelial tumours of the conjuntiva. The study includes 55 subjects (57 eyes) treated in a large teaching hospital. Despite the fact that the study includes cases treated over a period of 20 years, all eyes were treated similarly (excision and double freeze–thaw cryotherapy) by the same surgeon. By excluding the eyes that were treated by other methods, the authors have attempted to increase the validity of their results by minimising variables that could have influenced the outcome. Nevertheless, not all cases were similar. The age ranged from 15 to 82 years, about 80% involved the corneoscleral limbus, some tumours were small (5 mm × 5 mm) and some were large (15 mm × 20 mm), and about 14% of cases were treated for recurrent tumour whereas others were undergoing primary treatment.

The eyes were approximately equally divided between CIN (49%) and SCC (51%) by

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histopathology. During the follow-up period of a minimum of 6 months and ranging up to 15 years (mean 31.7 months), recurrence was observed in seven (12.3%) eyes. The median time to recurrence was 18 months and was independent of the original diagnosis (CIN or SCC). However, the median time to recurrence was shorter (12 months) in SCC as compared to those with CIN (36 months).

Although limited by the retrospective nature of the study, their findings demonstrate excellent tumour control with excision and cryosurgery. The data also imply that even with microscopic evidence of invasive carcinoma, careful dissection and cryotherapy offers an equally good result. Unfortunately, the authors do not comment on the status of resection margins. Because of the small number of cases in their series, information regarding the risk factors predictive of recurrence could not be ascertained. The risk factors should not be limited to the clinical or histopathologic findings and should include molecular genetic markers such as immunostaining for proliferating cell nuclear antigen and p53 gene expression.[20] Perhaps in the future, we will have the ability to identify accurately high-risk patients with OSSN and treat such patients with prophylactic topical chemotherapy.

References

1 Lee GA, Hirst LW. Ocular surface squamous neoplasia. *Surv Ophthalmol* 1995; **39**: 429–450.
2 Grossniklaus HE, Green WR, Lukenback M, Chan CC. Conjunctival lesions in adults: a clinical and histopathologic review. *Cornea* 1987; **6**: 78–116.
3 Sun EC, Fears TR, Goedert JJ. Epidemiology of squamous cell conjunctival cancer. *Cancer Epidemiol Bio Prevent* 1997; **6**: 73–77.
4 Lee GA, Hirst LW. Incidence of ocular surface epithelial dysplasia in metropolitan Brisbane. A 10-year survey. *Arch Ophthalmol* 1992; **110**: 525–527.
5 Poole TR. Conjunctival squamous cell carcinoma in Tanzania. *Br J Ophthalmol* 1999; **83**: 177–179.
6 Newton R. A review of the aetiology of squamous cell carcinoma of the conjunctiva. *Br J Cancer* 1996; **74**: 1511–1513.
7 Waddell KM, Lewallen S, Lucas SB, Atenyi-Agaba C, Herrington CS, Liomba G. Carcinoma of the conjunctiva and HIV infection in Uganda and Malawi. *Br J Ophthalmol* 1996; **80**: 503–508.
8 Hertle RW, Durso F, Metzler JP, Varsa EW. Epibulbar squamous cell carcinomas in brothers with xeroderma pigmentosa. *J Pediatr Ophthalmol Strabismus* 1991; **28**: 350–353.
9 McDonnell JM, Mayr AJ, Martin WJ. DNA of human papillomavirus type 16 in dysplastic and malignant lesions of the conjunctiva and cornea. *N Engl J Med* 1989; **320**: 1442–1446.
10 Karcioglu ZA, Issa TM. Human papilloma virus in neoplastic and non-neoplastic conditions of the external eye. *Br J Ophthalmol* 1997; **81**: 595–598.
11 Fraunfelder FT, Wingfield D. Management of intraepithelial conjunctival tumors and squamous cell carcinomas. *Am J Ophthalmol* 1983; **95**: 359–363.
12 Erie JC, Campbell RJ, Liesegang TJ. Conjunctival and corneal intraepithelial and invasive neoplasia. *Ophthalmology* 1986; **93**: 176–183.
13 Lommatzsch P. Beta-ray treatment of malignant epithelial tumors and squamous cell carcinoma. *Am J Ophthalmol* 1976; **81**: 198–206.
14 Kearsley JH, Fitchew RS, Taylor RG. Adjunctive radiotherapy with strontium-90 in the treatment of conjunctival squamous cell carcinoma. *Int J Radiant Oncol Biol Phys* 1988; **14**: 435–443.
15 Vann RR, Karp CL. Perilesional and topical interferon alfa-2b for conjunctival and corneal neoplasia. *Ophthalmology* 1999; **106**: 91–97.
16 Frucht-Pery J, Sugar J, Baum J, Sutphin JE, Pe'er J, Savir H *et al*. Mitomycin C treatment for conjunctival–corneal intraepithelial neoplasia: a multicenter experience. *Ophthalmology* 1997; **104**: 2085–2093.
17 Midena E, Angeli CD, Valenti M, de Belvis V, Boccato P. Treatment of conjunctival squamous cell carcinoma with topical 5-fluorouracil. *Br J Ophthalmol* 2000; **84**: 268–272.
18 Frucht-Pery J, Rozenman Y, Pe'er J. Topical mitomycin-C for partially excised conjunctival squamous cell carcinoma. *Ophthalmology* 2002; **109**: 548–552.
19 Peksayar G, Altan-Yaycioglu R, Onal S. Excision and cryosurgery in the treatment of conjunctival malignant epithelial tumours. *Eye* 2002; **17**: 226–230.
20 Aoki S, Kubo E, Nakamura S, Tsuzuki A, Tsuzuki S, Takahashi Y *et al*. Possible prognostic markers in conjunctival dysplasia and squamous cell carcinoma. *Jpn J Ophthalmol* 1998; **42**: 256–261.