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## **Punctal and canalicular stenosis associated with systemic fluorouracil therapy**

*Report of five cases and review of the literature*

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**Abstract.** Ocular side effects of systemic fluorouracil include excessive lacrimation, due to punctal and canalicular stenosis and fibrosis. Obstruction of the tear ducts after systemic therapy with fluorouracil is more frequent than is assumed. Five patients with breast cancer and punctal or canalicular stenosis are presented. Although complaints of epiphora usually resolve two weeks after cessation of systemic therapy, local antibiotics and steroids may be indicated. In patients with persisting complaints, and patients treated with fluorouracil for a prolonged period of time, prophylactic intubation of the tear ducts with silastic tubes has been advocated. (Conjunctivo)dacryocystorhinostomy may be unavoidable.

### **Introduction**

Fluorouracil is a pyrimidine analogue inhibiting DNA synthesis and is commonly used in the treatment of carcinomas of the breast, and of the gastrointestinal and genitourinary tract. Systemic therapy with fluorouracil may lead to a variety of ocular complications. Ocular toxicity includes blurred vision, accommodation disorders, oculomotor disturbances, nystagmus, photophobia, keratoconjunctivitis, optic neuropathy, ocular pain, periorbital edema, blepharitis, blepharospasm, ankyloblepharon, hyperemia and hyperpigmentation of the eyelids, cicatricial ectropion, epiphora, chronic canaliculitis, and dacryofibrosis and stenosis [1-23].

In the literature, only seven cases of excessive lacrimation associated with systemic therapy with fluorouracil have been reported [4, 9, 17, 19]. We present five additional patients with complaints of epiphora after systemic therapy with fluorouracil.

### **Patients**

*Case 1.* In April 1990, a 61-year-old female patient was referred because of excessive lacrimation of both eyes. Complaints had started in may 1989,

when systemic administration of fluorouracil and tamoxifen was commenced because of breast cancer. Examination disclosed complete occlusion of all lacrimal puncta. A membrane overlying the puncta was surgically removed and local treatment with antibiotics and steroids was administered for two weeks. However, complaints did not resolve. Conjunctivodacryocystorhinostomy was refused by the patient.

*Case 2.* A 62-year-old woman with breast cancer had been referred in September 1992 because of tearing eyes. Until January 1992 she had been treated with tamoxifen, which therapy was changed to a combination of cyclophosphamide, methotrexate and fluorouracil (CMF) because of bone metastases. Complaints of epiphora started directly after first administration of systemic chemotherapy. On ocular examination, stenosis of all puncta was identified. Probing of the tear duct revealed partial stenosis of the lower canaliculi in both eyes. Irrigation of the lacrimal sac to the nasopharynx was positive. Local treatment with steroids was started. However, complete obstruction of the right lower canaliculus was found two weeks later. After gentle probing of the lacrimal duct irrigation was positive. Therapy with local steroids was continued. After repeated probing and completion of systemic therapy with CMF after 11 months, local steroids could be discontinued and ocular complaints resolved.

*Case 3.* A 49-year-old female patient had primary breast cancer for five months and was treated with fluorouracil and tamoxifen for two months when she was referred in January 1993 because of epiphora for four weeks. Examination revealed severe stenosis of all puncta. Local therapy with steroids was initiated and the complaints resolved three weeks after cessation of fluorouracil therapy in April 1993.

*Case 4.* In June 1993 a 70-year-old woman with breast cancer was referred because of ocular pain for two years, which complaint started four weeks after systemic treatment with fluorouracil and tamoxifen. On examination stenosis of all puncta was diagnosed. Probing the lower canaliculi of both eyes, a resistance was found. After piercing a membrane-like structure, irrigation of both lacrimal sacs to the nose was positive. Artificial tears were prescribed and complaints diminished.

*Case 5.* In September 1993 a 70-year-old female patient treated with fluorouracil and tamoxifen since January 1993 because of breast cancer had complaints of epiphora of both eyes for seven months. At examination severe stenosis of the lower punctum of the right eye was diagnosed with com-

plete occlusion of the canaliculus. On the left complete stenosis of the lower punctum was found. Conjunctivodacryocystorhinostomy on the right was performed in January 1994 with favorable results.

## Discussion

Chronic tearing eyes are tedious, the more so when excessive lacrimation is iatrogenic.

Fluorouracil inhibits DNA synthesis in rapidly proliferating tissues as the cornea epithelium, conjunctiva and tear duct, and may lead to inflammation. It has been proved that fluorouracil has severe toxic effects to the ocular surface epithelium [18]. This may give rise to increased reflex lacrimal secretion due to irritation to cornea and conjunctiva or reduced basal tear secretion [12]. Inflammation may lead to scarring and stenosis of the tear ducts resulting in obstruction of the lacrimal system and complaints of excessive lacrimation [4, 5, 9, 10, 17]. Cicatricial ectropion, due to skin changes in the eyelids, may also cause epiphora [19].

Christophidis *et al.* [5] measured the concentration of fluorouracil in both tears and plasma in eight patients with carcinoma of the colon treated with systemic fluorouracil. In three patients with complaints of excessive lacrimation, fluorouracil could be detected both in tears and in plasma. However in five patients without ocular complaints, no fluorouracil was detectable in tear fluid. The concentration in plasma was comparable to the concentration in patients without complaints. Therefore, excessive lacrimation seemed to be related to penetration of fluorouracil in tear fluid. Loprinzi *et al.* [15] were able to detect fluorouracil in the tear fluid of 12 patients. Contrary to Christophidis *et al.* [5], they did not find a correlation of fluorouracil tear concentration with ocular complaints.

Fluorouracil has been used in patients with glaucoma to inhibit fibrosis and closure of the fistula following filtering procedures. However, in these cases, treatment with topical fluorouracil is limited to a short period of time and in case of local application the area treated is elaborately irrigated afterwards to avoid the toxic effects of fluorouracil to ocular surface epithelium. Furthermore, mitotic rate of conjunctival cells is decreased [6, 14, 18]. In patients with epiphora associated with systemic fluorouracil therapy for a prolonged period of time (months), chronic excretion of fluorouracil in tears may lead to inflammation, scarring and stenosis of the tear ducts and complaints of epiphora.

Epiphora has rarely been mentioned after systemic therapy with adriamycin [3], doxorubicin [8] and methotrexate [7]. From tamoxifen, epiphora as an ocular complication has not been reported.

Tearing eyes are described in one third of patients treated with CMF or with fluorouracil alone appearing gradually after starting fluorouracil therapy [5, 10, 15]. In the literature only seven patients with stenosis of the tear duct associated with systemic fluorouracil therapy have been reported. Straus *et al.* [19] described a 61-year-old male patient with presumed pancreatic carcinoma treated with systemic fluorouracil. Cicatricial ectropion was diagnosed and the lacrimal ducts were obstructed. Surgical correction of the ectropion did not affect the complaints of lacrimation. Haidak *et al.* [9] published the findings in a patient with obstructed canaliculi and scarring of the lacrimal sac. Biopsy revealed fibrosis of the punctum. Caravella *et al.* [4] described four patients with punctal and canalicular stenosis after systemic therapy with fluorouracil. In a 54-year-old female patient with carcinoma of the colon a mucosa-like membrane overlying the stenosed lacrimal puncta was detected. Slight stenosis of the lower canaliculus on the left was identified. Irrigation from the lacrimal sac to the nose was normal. A 58-year-old male patient with carcinoma of the colon presented with complete occlusion of the inferior punctum on the right, due to a mucosa-like membrane. Stenosis of the other three puncta and of the lower left canaliculus was found. Irrigation of the sac to the nasopharynx was normal. A 38-year-old female patient with adenocarcinoma of the small bowel presented with severe stenosis of all four puncta and canaliculi with normal irrigation of the lacrimal sac to the nose. She was treated with intubation of the tear ducts with silastic tubes with favorable results. A 43-year-old female patient treated with a combination of fluorouracil and methotrexate because of breast cancer, was seen because of complaints of epiphora due to stenosis of the lower lacrimal punctum on the right. Finally, Seiff *et al.* [17] described a 69-year-old female patient treated with fluorouracil because of pancreatic carcinoma, presenting with complete punctal and canalicular obstruction of both eyes. Bilateral conjunctivodacryocystorhinostomy was performed with favorable results.

In three of our patients, local therapy with antibiotics and/or steroids, whether or not with removal or piercing of a membrane overlying the punctum or obstructing the canaliculi, resulted in resolution of the complaints of excessive lacrimation. Examination in two patients disclosed complete stenosis. In one patient complaints resolved after conjunctivodacryocystorhinostomy.

Complaints of epiphora usually resolve spontaneously one or two weeks after cessation of systemic fluorouracil therapy. Symptomatic relief of cromolyn and of placing ice packs on the eyes during fluorouracil injection has been reported. However, local therapy consisting of antibiotics and steroids may be indicated to prevent complete punctal or canalicular stenosis. In patients with persisting complaints of excessive lacrimation, prophylactic

intubation of the tear ducts with silicon tubes is advocated. In some patients surgical treatment as (conjunctivo)dacryocystorhinostomy may be necessary [4, 12, 15, 17].

Stenosis and fibrosis of tear ducts are serious complications of systemic fluorouracil and appear to be more common than is assumed. Fluorouracil treated patients should be monitored carefully for ophthalmic complications. Persisting tearing eyes need ophthalmic consultation.

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