

Review Article

Drug Induced Ectropion: a Systematic Review

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Abstract

Background: To review etiologies, risk factors, management and prognosis of drug induced ectropion as a rare entity.

Material and Methods: In this systematic review, we reviewed all related published articles in English literature until April 2019 by searching Pubmed resources using the keywords ‘drug induced ectropion’.

Results: We found 26 relevant articles describing 48 patients with drug induced ectropion. The patient mean age was 67.4 years (range 15-93 years). Different topical and systemic drugs were reported as the causing agents including chemotherapeutic (45.8 %) drugs as the most frequent cause (22 patients, including 5 patients using topical fluorouracil, 9 patients using systemic fluorouracil, 7 patients using epidermal growth factor receptor inhibitors, and 1 patient using docetaxel), followed by topical anti-glaucoma (39.5 %) drugs (19 patients). The mean interval between starting the drug usage and emergence of ectropion was 9.74 months (range 1 day-72 months). Cessation of the causing drug and conservative treatments including topical lubricants, antibiotics and steroids were the most common management method. Surgery was required only in 10 patients (20.8 %).

Conclusion: Drug induced ectropion can develop following the administration of various topical and systemic drugs. Discontinuation of the causing drug and conservative treatments including topical steroids are often successful in managing the ectropion. Surgical treatment is scarcely needed among patients with drug induced ectropion.

Keywords: Drug Induced; Ectropion; Systematic review.

Article Notes: Received: Apr. 6, 2019; Received in revised form: May. 8, 2019; Accepted: May. 29, 2019; Available Online: Jul. 2, 2019.

How to cite this article: Mehrpour M, Soleimani M. Drug Induced Ectropion: a Systematic Review. Journal of Ophthalmic and Optometric Sciences. 2019;3(3): 61-72.



Introduction

Ectropion is considered the most common eyelid malposition and most frequently involves the lower eyelid^{1,2}. It is generally classified to congenital and acquired subcategories. Acquired types include involutional, cicatricial, paralytic and mechanical types³. Drug induced ectropion is a rare condition which has been reported following the use of various topical and systemic medications⁴⁻²⁹. Generally, it is a cicatricial type of ectropion caused by contracture and shortening of anterior lamella of tars due to periorbital inflammation induced by drugs^{4,5}. This inflammation may be the result of hypersensitivity to the causing drug⁴, cytotoxic effect of drug as seen in chemotherapeutic agents¹⁷, or the effect of drug on modulation of immune system^{26,27}. The mechanical effect of edema at the beginning of inflammation especially in elderly patients with lid laxity and some degrees of involutional ectropion has an important role in initial phase of drug induced ectropion⁴. Drug induced ectropion usually shows a spontaneous reversible nature after withdrawal of the causing drug^{4-6, 10, 13, 14, 16, 19-21, 24-27, 29}. The natural history, risk factors, prognosis and appropriate management of drug induced ectropion have rarely been described in the literature. Hence, in this review article, we reviewed published studies reporting patients with drug induced ectropion to achieve a more comprehensive view on the characteristics of this rare entity and its management.

Material and Methods

This systematic review was performed in Farabi Eye Research Center, Tehran, Iran, and included related articles in English literature up to April 2019. We searched all articles published related to drug induced ectropion

by searching the Pubmed using the keywords 'drug induced ectropion'. We did not have a specific filter rather than being in English language in our search strategy. The first fast screening of articles was performed according to their titles. Then the relevant articles after first screening underwent a second screening using their abstracts. Two reviewers did the screening separately and in case of discrepancy in their results, they reevaluated the results to reach a common decision. The full text of the final relevant articles was reviewed and the related data were extracted.

Results

Fifty four articles were found in our primary search, which were reduced to 26 after removing irrelevant articles in our two steps screening. The final 26 reviewed articles consisted of 1 cohort study, 4 case series and 21 case reports describing 48 patients with drug induced ectropion. The mean age of patients was 67.4 years (range 15-93 years). Thirty three patients were male (68.7 %) and 15 patients were female (31.3 %). Thirty six cases (75 %) had bilateral involvement and lower eyelid was involved in 46 cases (95.8 %). Different topical (Table 1) and systemic drugs (Table 2) were reported as the causing agents including chemotherapeutic (45.8 %) drugs as the most frequent cause (22 patients, including 5 patients using topical fluorouracil, 9 patients using systemic fluorouracil, 7 patients using epidermal growth factor receptor inhibitors, and 1 patient using docetaxel), followed by topical anti-glaucoma (39.5 %) drugs (19 patients). The mean interval between starting the drug usage and emergence of ectropion was 9.74 months (range 1 day-72 months). The cessation of the causing agent and conservative treatment consisting of topical

Table 1: Topical medications reported as etiology of drug induced ectropion

Medication	Study	Number of cases with ectropion	Age/Gender	Management
Anti-glaucoma	Bartley et al., ⁶ , 1991 (Dipivefrin)	1	75/ M	Drug cessation
	Aristodemou et al., ⁵ , 2008 (Brimonidine)	1	66/ M	Drug cessation
	Hegde et al., ⁴ , 2007 (Dorzolamide, Brimonidine, Timolol, Latanoprost, Betaxolol)	13	Mean age:78.2 11 M, 2 F	Drug cessation Hydrocortisone cream Surgery for 3 cases
	Custer et al., ⁷ , 2016 (Prostaglandin)	3	Not mentioned	Not mentioned
	Britt et al., ⁸ , 1999 (Apraclonidine)	1	64/ M	Topical lubricants Topical antibiotics Drug cessation Prednisolone eye drop Surgical correction
	Lewis ⁹ , 2008	3	Case 1: 88/ M Case 2: 75/ M Case 3 79/ F	drug cessation in one patient
Topical Fluorouracil	Nikkhah et al., ¹⁰ , 2012	1	83/ M	Drug cessation
	Tsui et al., ¹¹ , 2016	1	85/ M	Drug cessation Surgery
	Wojno et al., ¹² , 1984	1	72/ F	Surgery
Chemical face peeling	Kaiserman et al., ¹³ , 2005 (Trichloroacetic Acid)	1	32/ F	Topical lubricants Dexamethasone eye drop
	Brodell et al., ¹⁴ , 1992	2	Case 1: 68/ F Case 2: 58/ F	Drug cessation

lubricants, antibiotics and steroids were the most common management methods used among patients. Surgery was required only in 10 patients (20.8 %).

Topical Medications

Anti-Glaucoma Drugs

There were 2 case series and 3 case reports describing 19 patients with anti-glaucoma

Table 2: Systemic medications reported as the etiology of drug induced ectropion

Causing Medication	Study	Number of cases	Age/Gender	Management
Systemic 5-fluorouracil	Tatar et al., ¹⁵ , 2018 (Capecitabine)	1	72/ M	Topical lubricants Topical antibiotics Clobetasol propionate cream Drug cessation Surgical correction
	Obi et al., ¹⁶ , 2011 (Capecitabine)	1	80/ M	Topical lubricants Topical antibiotics Moist chamber Drug cessation
	Eiseman et al., ¹⁷ , 2003	1	Not mentioned	Not mentioned
	Straus et al., ¹⁸ , 1977	4	Case 1: 47/ F Case 2: 66/ M Case 3: 61/ M Case 4: 61/ M	Case 1,2: triamcinolone cream and drug cessation Case 3,4: surgical correction in addition to above
	Hurwitz et al. ⁽¹⁹⁾ 1993	2	Case 1: 92/ F Case 2: 72/ M	Dexamethasone ointment Drug cessation
EGFR inhibitors	Saint-Jean et al., ¹⁹ , 2012 (Erlotinib)	1	74/ F	Topical lubricants Topical antibiotics Drug cessation Surgical correction
	Garibaldi et al., ²¹ , 2007 (Cetuximab)	1	49/ M	Topical lubricants Topical antibiotics Desonide ointment Drug cessation
	Methvin et al., ²⁹ , 2007 (Erlotinib)	1	85/ M	Topical lubricants Topical antibiotics Steroid ointment Drug cessation
	Frankfort et al. ⁽²⁰⁾ 2007 (Erlotinib)	1	81/ F	Topical lubricants Topical antibiotics Topical Fluorometholone Drug cessation
	Scofield-Kaplan et al., ²² , 2018 (Panitumumab, Cetuximab)	2	Case 1: 90/ M Case 2: 90/ F	Topical lubricants Oral doxycycline Topical ophthalmic steroid Antibiotic ointment Drug cessation

Causing Medication	Study	Number of cases with ectropion	Age/Gender	Management
EGFR inhibitors	Salman et al., ²³ , 2015 (Erlotinib)	1	79/ M	Topical lubricants Hydrocortisone cream No drug cessation
Docetaxel	Kaya et al., ²⁴ , 2008	1	56/ M	Topical lubricants Topical antibiotics Oral methylprednisolone Drug cessation
Etretinate	Brenner et al., ²⁵ , 1990	1	75/ M	Drug cessation
TNF α inhibitors	Teo et al., ²⁶ , 2019 (Adalimumab)	1	15/ M	Topical steroids Oral antibiotics Antihistamines High-dose oral prednisone Drug cessation
Dupilumab	Barnes et al., ²⁷ , 2017	1	61/ M	Oral prednisone Drug cessation

drug induced ectropion. The mean age of patients was 64.3 years (range 60-93 years). Fourteen patients were male (73.7 %) and 5 patients were female (26.3 %). The mean interval between starting the drug usage and emergence of the ectropion was 18.2 months (range 2-72 months).

Hegde et al.,⁴ in their retrospective observational case series reported 13 patients presenting with topical drug induced ectropion. Dorzolamide was the most common causing medication (53 %), followed by brimonidine (23 %) ⁴. All patients improved completely or partially with cessation of causing medication and only two patients needed surgical management ⁴. None of patients managed with drug discontinuation and a short course of topical corticosteroids needed surgery. The authors introduced a step-wised algorithm for management of suspected drug induced

ectropion ⁴. The first and the cornerstone step of this management model was cessation of the suspected drug which was both diagnostic and therapeutic ⁴. They emphasized that delaying the drug discontinuation results in a decrease in the rate of spontaneous reversal of the ectropion ⁴. For the second step of treatment in patients not responding to drug cessation, they suggested topical steroids ⁴. Surgery was only suggested for patients unresponsive to all conservative managements ⁴.

Bartley et al.,⁶ reported a 75-year-old man with left lower eyelid ectropion after using topical dipivalyl epinephrine (dipivefrin) due to open angle glaucoma, which was resolved after drug discontinuation.

Aristodemou et al.,⁵ reported a case of bilateral cicatricial ectropion due to the use of topical brimonidine, which was resolved with cessation of the eye drop. Both authors

suggested that surgery should not be considered as the primary management in drug induced ectropion.

Custer et al., ⁷ evaluated the orbital soft tissue changes caused by using topical prostaglandins in 35 patients with prostaglandin orbitopathy and observed cicatricial ectropion in 3 patients. One patient's ectropion was improved with drug cessation, but they did not describe the clinical course of the two other patients ⁷.

Britt et al., ⁸ reported a 64-year-old man with non-resolving left eye conjunctivitis for 6-8 months resulting in the lower lid ectropion. The patient's symptoms began two months after starting apraclonidine hydrochloride 1 % (Iopidine) eye drops. They managed the patient with drug cessation, topical steroid, and antibiotic eye drops ⁸. Although patient's signs and symptoms resolved considerably, the ectropion progressed to cicatricial entropion and corrective surgery was necessary ⁸. The pathology of patient's eyelid revealed reactive lymphocytic infiltration ⁸.

Topical Fluorouracil

Fluorouracil (5-FU), one of the most common chemotherapeutic medications in management of malignant neoplasms in topical and systemic forms, is a DNA synthesis inhibitor which works by blocking the thymidylate synthetase as a pyrimidine analogue ¹⁷. 5-FU affects rapidly proliferating cancer cells, so the inflammation in tissues with rapid proliferation such as the corneal epithelium, conjunctiva and lacrimal duct could be a complication of this drug, which may explain its reported ocular adverse effects like ectropion.

In our literature review, we found 3 studies reporting 5 patients with topical 5-FU induced ectropion. The patients mean age was 82 ± 5.09 years (range 75- 88 years) and all

patients were male. The mean interval between starting the drug usage and the ectropion emergence was 18.2 ± 7.6 days (range 10-30 days).

Lewis ⁹ reported 3 patients developing eyelid ectropion following the use of 5-FU cream 5 % for treatment of multiple actinic keratoses. Ectropion was bilateral in two of them and unilateral in the last patient. Two patients resolved completely after the termination of treatment without interruption of their regimen ⁹. One other patient needed the discontinuation of the drug to achieve complete cure of the ectropion ⁹.

Nikkhah et al., ¹⁰ presented a case of bilateral lower lid cicatricial ectropion following the use of topical 5-FU. After two weeks of drug cessation, patient's ectropion in both eyes were resolved completely ¹⁰. They suggested an algorithm for management of similar patients with ectropion induced by topical 5-FU, which included discontinuation of the medication and close observation ¹⁰. They suggested surgical procedures should be considered only in presence of secondary changes due to ectropion including blepharitis, palpebral conjunctival hypertrophy, keratinization and conjunctival scarring ¹⁰.

Tsui et al., ¹¹ reported a case with bilateral cicatricial lower eyelid ectropion after using topical 5 % 5-FU cream. The patient was first managed with drug cessation, erythromycin eye ointment and steroid drops, but 5 months of conservative management was fruitless and the patient underwent surgery to correct ectropion ¹¹.

Chemical Face Peeling

Chemical face peeling is a cosmetic procedure used for skin rejuvenation. Chemical solutions such as alpha-hydroxy acids, trichloroacetic

acid and carbolic acid (phenol) are used for inducing a limited burn to stimulate reproduction of collagen, elastin and re-epithelization of the skin. These medications might lead to extensive scar formation and result in contracture and ectropion³⁰.

Wojno et al.,¹² described a case of lower eyelid cicatricial ectropion following the use of a chemical face peel. The patient was managed surgically with successful results¹².

Kaiserman et al.,¹³ reported a 32-year-old woman developing severe left eye blepharoconjunctivitis and ectropion due to the use of a peeling mask containing trichloroacetic acid. They managed her with steroid eye drop and lubrications and her symptoms improved after 3-4 days¹³.

Tretinoin

Brodell et al.,¹⁴ reported two patients developing ectropion following treatment with topical tretinoin. Both cases were completely cured with discontinuation of the tretinoin and the use of lubrications. Shortening of the lid margin because of tightening of the skin due to long term use of tretinoin was described as possible explanation¹⁴.

Systemic Medications

Systemic Fluorouracil

There were 5 studies including a cohort study, one case series and 3 case reports describing 9 patients with systemic 5 FU induced ectropion. The patients mean age was 68.8 ± 13.5 years (range 47- 92 years). Six patients were male (66.7 %) and three patients were female (33.3 %). The mean interval between starting the drug usage and emergence of the ectropion was 5.2 months (range 9 days to 14 months).

Eiseman et al.,¹⁷ in their cohort study on 52 patients treated with systemic 5-fluorouracil only found one patient with bilateral cicatricial ectropion (prevalence rate of 1.9 %). The detailed management of patient was not reported, but they mentioned that the surgical correction of patient was delayed until completion of his 5-FU treatment¹⁷. They suggested some possible mechanisms for 5-FU induced ectropion including shortening of the anterior lamella as a result of the chronic inflammation of the eyelid skin and preexisting contributing factors such as eyelid laxity due to senile changes¹⁷.

Tatar et al.,¹⁵ introduced a case of bilateral progressive ectropion following the use of oral capecitabine, 500 mg daily for three months. Capecitabine is a prodrug of 5-fluorouracil considered to have more tolerable side effects. Their case was a 72-year-old man diagnosed with cholangiocellular carcinoma¹⁵. The patient's lid biopsy which was planned because of his refractory progressive ectropion showed interstitial granulomatous dermatitis accompanied by elastophagocytosis¹⁵. Since the ectropion was not resolved by drug cessation and topical conservative treatments such as topical steroids and lubrications, surgical procedure was performed for its correction¹⁵.

Obi et al.,¹⁶ reported a case of colorectal cancer with dihydropyrimidine dehydrogenase deficiency (a major enzyme in the catabolism of 5-FU) developing bilateral cicatricial ectropion and upper lid shortening following the treatment with capecitabine. In spite of severe ocular signs and symptoms due to eyelid ectropion such as exposure corneal keratopathy, patient was managed conservatively with a moist chamber¹⁶.

Straus et al.,¹⁸ reported 4 patients developing bilateral cicatricial ectropion following

treatment with systemic 5-FU for their advanced cancer. The first case was treated with topical steroid cream and discontinuation of the drug, while the second patient was managed with conservative treatment but died before the resolution of ectropion. The other two cases underwent surgical correction of ectropion without drug cessation.

Hurwitz et al.,¹⁹ reported two cases of bilateral cicatricial lower eyelid ectropion during the course of chemotherapy with systemic 5-FU. They successfully managed their patients with topical steroid ointment and completed their chemotherapy course¹⁹.

Epidermal Growth Factor Receptor (EGFR) Inhibitors

The epidermal growth factor receptor (EGFR) belongs to the ErbB family of receptor tyrosine kinases. According to its important effect on cell growth and differentiation, it has become the target of some anti-cancer drugs classified as EGFR inhibitors such as erlotinib, cetuximab and panitumumab²⁸. We found 6 studies reporting 7 patients developing ectropion following administration of EGFR inhibitors including erlotinib, cetuximab and panitumumab. The mean age of patients was 78.2 ± 14.1 years (range 49- 90 years) years. Four patients were male (57.1 %) and three were female (42.9 %). The mean interval between starting the drug usage and emergence of the ectropion was 20 ± 15.4 days (range 7-42 days).

Saint-Jean et al.,²⁸ in their case series of 5 patients with ocular complications associated with the systemic EGFR inhibitors (panitumumab and erlotinib), reported one patient with bilateral ectropion following one month administration of erlotinib for treatment of lung adenocarcinoma. They initially

managed the patient with intensive lubrication and ciprofloxacin ointment, but because of the persistence of ectropion, patient underwent surgery for ectropion correction²⁸. The authors attributed ocular complications of these drugs to the role of EGFR in proliferation of epithelial cells as EGFR is expressed in basal epithelial cells of the cornea and conjunctiva²⁸. Garibaldi et al.,²¹ reported a 49-year-old man with metastatic colorectal cancer showing periocular toxicity and ectropion of both eyes after adding cetuximab (an EGFR inhibitor) to his baseline chemotherapy regimen. The ectropion was improved completely after discontinuation of the causing drug²⁸.

Methvin et al.,²⁹ reported an 85-year-old man presenting with bilateral lower eyelid ectropion after 6 weeks treatment with erlotinib. The patient's ocular symptoms and ectropion was resolved completely after cessation of the drug, so the authors suggested avoiding surgery as the first step in correcting ectropion due to erlotinib²⁹.

Frankfort et al.,²⁰ reported an 81-year-old woman with history of metastatic small-cell lung cancer developing bilateral cicatricial ectropion after one week of taking oral erlotinib 150 mg daily. She was managed successfully with discontinuation of drug, use of bacitracin ointment, topical fluorometholone and artificial tear.

Scofield-Kaplan et al.,²² reported two cases of bilateral cicatricial ectropion following the use of EGFR inhibitors, panitumumab in one patient and cetuximab in the other one²². Both patients were managed successfully with topical ophthalmic steroid, antibiotic ointment, lubrications, topical facial steroid cream and oral doxycycline. Panitumumab was discontinued, but the case treated with cetuximab continued the drug infusion²². The authors suggested that drug cessation may not be a necessary part

of the treatment for EGFR inhibitors induced ectropion and it is better to try conservative treatment prior to drug cessation ²².

Salman et al., ²³ reported a 79-year-old man with lung adenocarcinoma developing bilateral cicatricial ectropion following erlotinib treatment. He was successfully managed with symptomatic treatment without discontinuation of causing medication ²³. The authors concluded that drug cessation depends on the severity of ectropion and the risk-benefit ratio of discontinuing the treatment ²³.

Docetaxel

Docetaxel a semisynthetic taxan is a chemotherapeutic medication effective against the neoplastic cells by inhibiting mitotic spindle ²⁴.

Kaya et al., ²⁴ reported a 56-year-old man with history of non-small cell lung cancer complicated with severe erythematous skin reaction and bilateral ectropion following docetaxel infusion. Biopsy of the skin lesions showed lymphocytic infiltration in the upper dermis and the patient signs were subsided two weeks after management with systemic steroid and antihistamine in addition to topical lubricants and antibiotics ²⁴.

Etretinate

Brenner et al., ²⁵ reported a case of psoriasis developing bilateral ectropion following 6 weeks of treatment with etretinate, a retinoid drug. Their patient did not improve despite drug discontinuation after two years of follow up ²⁵.

TNF α Inhibitors

Teo et al., ²⁶ described a 15-year-old boy with

Crohn disease presenting with conjunctival hyperemia and scaly erythematous eyelids after receiving infliximab, which was not improved with prednisone usage. Switching his drug to adalimumab because of relapse of his Crohn resulted in worsening of his ophthalmic signs and developing bilateral lower eyelid ectropion ²⁶. Their management with topical steroids, antibiotics, antihistamines and high dose oral prednisone was ineffective, so they discontinued adalimumab and replaced it with methotrexate; which dramatically improved the patient's ectropion ²⁶. The authors attributed the ectropion to a new onset or exacerbation of tissue inflammation as a paradoxical reaction during treatment with anti TNF- α drugs, which can be seen in genetic susceptible patients as a result of the dominance of helper T cells types 1 and 17 and extreme immune reaction due to overproduction of interferon α by plasmacytoid dendritic cells ²⁶.

Dupilumab

Dupilumab is a human monoclonal antibody inhibiting interleukin-4 receptor, with promising results in treatment of allergic diseases ³¹. Barnes et al., ²⁷ described a case of bilateral cicatricial ectropion following treatment with dupilumab for atopic dermatitis. Ectropion was subsided after discontinuation of the causing drug and administration of oral prednisone ²⁷. The mechanism of inducing conjunctivitis and cicatricial ectropion by dupilumab is unclear.

Discussion

In this systematic review, we reviewed 26 studies describing 48 patients with drug induced ectropion. This rare entity can develop following administration of various topical

and systemic drugs including anti-glaucoma drugs ⁴⁻⁸, chemotherapeutic agents ^{9-11, 15-24, 28, 29} and immunomodulatory medications ^{26, 27}. Chemotherapeutic drugs were the most reported drugs causing drug induced ectropion followed by topical anti-glaucoma drugs. Although drug induced ectropion is considered cicatricial, bilateral lower eyelid involvement was the most common clinical presentation in reported cases. Additionally, elderly patients (mean age 67.4 years) were more susceptible. These findings confirm that the patients with risk factors associated with involutional ectropion such as lid laxity and old age are more prone to drug induced ectropion. Hence, in case of using medications causing the risk of ectropion, clinicians should pay more attention to periorbital eye exam of vulnerable patients with risk factors for involutional ectropion, especially those who have some degrees of ectropion before beginning of the treatment.

The review of managements employed in this condition, revealed that causing drug cessation is the most recommended and effective intervention. Some studies emphasized the effect of early discontinuation of the causing drug ⁴. However, scarce studies have reported spontaneous resolution of ectropion only with conservative treatments and without drug

cessation ^{9, 22, 23} and have recommended trial of conservative managements before drug discontinuation. Conservative treatments such as topical lubricants, antibiotics and especially topical steroids have an important role in management of drug induced ectropion according to reviewed articles. Surgical correction was needed in only 20.8 % of all reported cases and most studies emphasized on reversible nature of this complication recommending surgery as the last intervention after failure of drug cessation and conservative management.

Conclusion

Drug induced ectropion can develop following the administration of various topical and systemic drugs. Discontinuation of the causing drug and conservative treatments including topical steroids are often successful in managing the ectropion. Surgical treatment is scarcely needed among patients with drug induced ectropion.

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Footnotes and Financial Disclosures

Conflict of interest

The authors have no conflict of interest with the subject matter of the present study.