Squamous Metaplasia of the Conjunctiva: A Previously Unrecognized Adverse Effect of Risedronate Sodium

A previously unrecognized adverse effect of the osteoporosis drug risedronate sodium (Actonel; Warner Chilcott Co, LLC) was observed in 2 unrelated patients who developed squamous metaplasia (epidermidalization) of their conjunctival epithelium, a vision-threatening condition, which resolved after discontinuation of the drug.

Report of Cases. Case 1. An 80-year-old white woman from Philadelphia, Pennsylvania presented with conjunctival plaques (Figure 1A and B). Both eyes were affected with white plaques or deposits in the inferior fornix, without symblepharon. Her medication history showed the current use of the osteoporosis drug risedronate sodium for osteopenia. Additional medications included diuretics. A biopsy disclosed an acanthotic conjunctival epithelium, resembling epidermis with a thick layer of surface keratin, a prominent granular cell layer, and the absence of goblet cells with subepithelial chronic inflammation (Figure 1C and D). The results of an immunofluorescence study were negative for IgA, IgG, and C3. This, together with the results of a histopathologic examination, eliminated ocular cicatricial pemphigoid as a diagnosis. The histopathologic diagnosis was conjunctival epidermidalization, which resolved completely after 1 month following discontinuation of risedronate sodium.

Case 2. A 62-year-old African American woman from Syracuse, New York, presented with a conjunctival mass in the inferior cul-de-sac of both eyes (Figure 2A and B). The lesion rapidly increased in size, was not in a sun-exposed area, and was pearly gray in color. Other mucosal surfaces were not in-
involved. The woman’s medical history revealed that she used Actonel (150 mg per month) for osteopenia for 6 years. Additional medications included vitamins, aspirin, and preservative-free tears. A biopsy of the left inferior fornical conjunctiva disclosed a thick layer of a benign stratified squamous epithelium devoid of goblet cells and covered by a prominent layer of keratin and parakeratin (Figure 2C and D). Dyskeratotic cells were not evident within the acanthotic epithelium. The underlying substantia propria showed minimal chronic inflammation. The Ki-67 immunostain disclosed a significant number of proliferating cells in the lower layers of the abnormal epithelium. The pattern of immunoreactivity resembled skin and differed from normal conjunctival tissue in which proliferation usually is confined to the basal layer. The histopathologic diagnosis was conjunctival epidermidalization. The conjunctival keratinization improved within 1 month and completely resolved at 8 months following discontinuation of Actonel.

Comment. Bilateral conjunctival epidermidalization, a true metaplasia, is very rare. Yet, histopathology supported this diagnosis and prompted us to look for a potential inducer of this squamous metaplasia. Given the clinical evidence and medication history, we propose that the conjunctival epidermidalization observed in both patients was caused by risedronate sodium, a drug used for the prevention and treatment of osteoporosis. Risedronate belongs to the family of drugs called bisphosphonates, was approved by the US Food and Drug Administration in 2000, and is administered orally to inhibit osteoclast–induced bone resorption and to increase bone mineral density turnover. Recently, the US Food and Drug Administration has raised concerns about the risk-benefit ratio of bisphosphonates, including risedronate specifically, as it relates to the time of initiation, their long-term use, and additional newly reported complications, including atypical femoral fractures. Our cases are significant because conjunctival epidermidalization has never been reported as an ocular adverse effect of Actonel. Previously reported ocular adverse effects of bisphosphonates include uveitis, nonspecific conjunctivitis, dry eye, episcleritis, or scleritis. For scleritis to resolve, the bisphosphonates must be discontinued.

Known systemic adverse effects include esophageal irritation and inflammation, heartburn, abdominal pain, and diarrhea, all of which are linked to increased local acidity. Inflammatory responses to bisphosphonates include skin rash and osteonecrosis of the jaw.

With respect to the conjunctival epithelium’s metaplastic potential, epidermidalization has been reported in the literature with sus-

![Figure 2](https://example.com/figure2.jpg)
risedronate sodium. The potentially dangerous adverse effect of conjunctival epidermidalization is a pro-
duction of Actonel-induced epidermidalization, which may resolve over the course of a few months, after the
drug is discontinued. Persistent or recurrent inflammation of the conjunctiva, as was observed in case 1, can
call itself lead to epidermidalization. It has been proposed that the mechanism probably involves a region-specific cellular immune re-
sponse to the topical application, rather than a drug mechanism–specific reaction, because the com-
pharmacology and pathology (Ms Geneva and Drs Barker-Griffith and Weisenthal), Pathology (Dr Barker-Griffith), and
Biochemistry and Molecular Biology (Ms Geneva), State University of New York, Upstate Medical Uni-
versity, Syracuse; and Wills Eye Institute, Thomas Jefferson University, Philadelphia, Pennsylvania (Drs
Eagle and Stefanyiszyn).

Correspondence: Dr Barker-Griffith, Departments of Ophthal-

mology and Pathology, 766 Irving Ave, Weiskotten Hall, Room 2137A,
State University of New York, Upstate Medical University, Syracuse,
NY 13210 (barkerga@upstate .edu).

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by unrestricted grants from Research to Prevent Blindness and by the Lions District 20-Y1.

Myoclo spiders and nonmiotic antiglau-
coma drugs, mydriatics, preserva-
tives, antiviral compounds, sulfon-
amides, penicillin, hydrocortisone,
epidermal growth factor, prostaglan-
dins, practolol, and thyroid hor-
mone, none of which have been used
by the 2 patients reported herein. In
most instances, the prolonged use of
oral or topical medications is the primary cause of their conjunctival epidermidalization. Although the mechanisms for the development of Actonel-induced epidermidalization are not fully under-
stood, potential mechanisms include conjunctival inflammation and dry eye. Conjunctival epidermidalization constitutes a serious, vision-threatening condition that is likely to resolve after discontinuation of the drug, but it could lead to vision loss if the drug is continued. Therefore, clinicians should be aware that conjunctival epidermidalization is a potentially dangerous adverse effect of risedronate sodium.

Ivayla I. Geneva, BA
Ralph C. Eagle Jr, MD
Ann Barker-Griffith, MD, FRCSC
Mary Stefanyiszyn, MD
Robert Weisenthal, MD

Author Affiliations: Departments of Ophthalmology (Ms Geneva and Drs Barker-Griffith and Weisenthal), Pathology (Dr Barker-Griffith), and Biochemistry and Molecular Biology (Ms Geneva), State University of New York, Upstate Medical University, Syracuse; and Wills Eye Institute, Thomas Jefferson University, Philadelphia, Pennsylvania (Drs Eagle and Stefanyiszyn).

Report of Cases. Case 1. A 20-year-

old man presented with a 1-month

history of blurry vision. Prior to pre-

sentation, he completed a 1-week
course of oral levofloxacin for com-

munity-acquired pneumonia. His vi-

sual acuity was 20/25 in the right eye

and 20/30 in the left eye. The oph-

thalmologic findings were normal, ex-

cept for bilateral optic disc edema (Figure 1 A and B). The results of neuroimaging using magnetic resonance imaging and all the cerebrospinal fluid parameters, including opening pressure level and cell counts, were normal. The results of a laboratory workup for Lyme disease, syphilis, and Bartonella henselae were negative. The results of a chest radiograph were normal, and the levels of angiotensin-converting enzyme and calcium were within normal limits. Because of his recent outpatient treatment for community-acquired pneumonia, serology testing for M pneumoniae was performed, and elevated IgM and IgG antibodies were found. The patient was treated with a 1-week course of oral azithromycin. One month after presentation, the patient’s visual acuity returned to 20/20 in both eyes, and his optic disc edema had resolved.

Case 2. A 14-year-old boy pre-

presented with a 1-month history of bi-

lateral eye pain, blurry vision, head-

ache, and subjective fevers. On phys-

ical examination, he was found to

have an erythematous macular rash on his lower extremities. His vi-
sual acuity was 20/40 and 20/50 in the

right and left eyes, respectively. An ophthalmo-

logic examination revealed bilateral conjunctival injection, with 3+ cell and flare in the an-
terior chambers. A diluted fundus examination showed 2+ cell in the vitreous and bilateral optic disc edema and serous macular detachments (Figure 2 A and B). There

Mycoplasma pneumoniae:
The Other Masquerader

Mycoplasma pneumoniae is a bacte-

rium in the class of Mollicutes and is

a common cause of atypical pneu-

monia, particularly in children and

young adults. A Mycoplasma infec-
tion primarily manifests as a respira-
tory tract disease, but an extrapul-

monary manifestation has occurred in

up to 25% of infected patients. The

organ systems that may be involved

include the skin, the gastrointestinal
tract, and the musculoskeletal, cardiac, renal, hematopoietic, and nervous systems.1 Ocular dis-

ease from M pneumoniae has also

been reported, with conjunctivitis

being the most frequent finding.2

Less common ophthalmologic mani-
festations of M pneumoniae include

cranial neuropathies, optic papilli-
tis, and anterior uveitis.2 We pre-

sent herein 1 case of bilateral optic

papillitis and 2 cases of uveitis sec-
tory to M pneumoniae infection.

The results of neuroimaging using magnetic resonance imaging and all the cerebrospinal fluid parameters, including opening pressure level and cell counts, were normal. The results of a chest radiograph were normal, and the levels of angiotensin-converting enzyme and calcium were within normal limits. Because of his recent outpatient treatment for community-acquired pneumonia, serology testing for M pneumoniae was performed, and elevated IgM and IgG antibodies were found. The patient was treated with a 1-week course of oral azithromycin. One month after presentation, the patient’s visual acuity returned to 20/20 in both eyes, and his optic disc edema had resolved.

Case 2. A 14-year-old boy presented with a 1-month history of bilateral eye pain, blurry vision, headache, and subjective fevers. On physical examination, he was found to have an erythematous macular rash on his lower extremities. His visual acuity was 20/40 and 20/50 in the right and left eyes, respectively. An ophthalmologic examination revealed bilateral conjunctival injection, with 3+ cell and flare in the anterior chambers. A diluted fundus examination showed 2+ cell in the vitreous and bilateral optic disc edema and serous macular detachments (Figure 2 A and B). There

Mycoplasma pneumoniae:
The Other Masquerader

Mycoplasma pneumoniae is a bacte-

rium in the class of Mollicutes and is

a common cause of atypical pneu-

monia, particularly in children and

young adults. A Mycoplasma infec-
tion primarily manifests as a respira-
tory tract disease, but an extrapul-

monary manifestation has occurred in

up to 25% of infected patients. The

organ systems that may be involved

include the skin, the gastrointestinal
tract, and the musculoskeletal, cardiac, renal, hematopoietic, and nervous systems.1 Ocular dis-

ease from M pneumoniae has also

been reported, with conjunctivitis

being the most frequent finding.2

Less common ophthalmologic mani-
festations of M pneumoniae include

cranial neuropathies, optic papilli-
tis, and anterior uveitis.2 We pre-

sent herein 1 case of bilateral optic

papillitis and 2 cases of uveitis sec-
tory to M pneumoniae infection.

Report of Cases. Case 1. A 20-year-

old man presented with a 1-month

history of blurry vision. Prior to pre-

sentation, he completed a 1-week
course of oral levofloxacin for com-

munity-acquired pneumonia. His vi-

sual acuity was 20/25 in the right eye

and 20/30 in the left eye. The oph-

thalmologic findings were normal, ex-

cept for bilateral optic disc edema (Figure 1 A and B). The results of neuroimaging using magnetic resonance imaging and all the cerebrospinal fluid parameters, including opening pressure level and cell counts, were normal. The results of a chest radiograph were normal, and the levels of angiotensin-converting enzyme and calcium were within normal limits. Because of his recent outpatient treatment for community-acquired pneumonia, serology testing for M pneumoniae was performed, and elevated IgM and IgG antibodies were found. The patient was treated with a 1-week course of oral azithromycin. One month after presentation, the patient’s visual acuity returned to 20/20 in both eyes, and his optic disc edema had resolved.

Case 2. A 14-year-old boy presented with a 1-month history of bilateral eye pain, blurry vision, headache, and subjective fevers. On physical examination, he was found to have an erythematous macular rash on his lower extremities. His visual acuity was 20/40 and 20/50 in the right and left eyes, respectively. An ophthalmologic examination revealed bilateral conjunctival injection, with 3+ cell and flare in the anterior chambers. A diluted fundus examination showed 2+ cell in the vitreous and bilateral optic disc edema and serous macular detachments (Figure 2 A and B). There