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-
volved. 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.1 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.1 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.2,3 For scleritis to resolve, the bisphosphonates must be discontinued.4 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.5

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

Figure 2. A 62-year-old African American woman who presented with a conjunctival mass in the inferior cul-de-sac of both eyes (case 2). A and B, External photographs show plaques of conjunctival epidermidalization in the inferior fornical conjunctivae of both eyes. C and D, The results of a conjunctival biopsy disclose a conjunctival epithelium resembling skin (hematoxylin-eosin, original magnification ×100 [C]), with mild chronic inflammation in the substantia propria (hematoxylin-eosin, original magnification ×200 [D]).
pected causative agents including miotic and nonmiotic antiglaucoma drugs, mydriatics, preservatives, antiviral compounds, sulfonamides, penicillin, hydrocortisone, epidermal growth factor, prostaglandins, pronolol, and thyroid hormone, none of which have been used by the 2 patients reported herein. In most instances, the prolonged use of a topical medication seems to induce conjunctival epidermidalization, which may resolve over the course of a few months, after the drug is discontinued. Persistent or recurrent inflammation of the conjunctivae, as was observed in case 1, can itself lead to epidermidalization. It has been proposed that the mechanism probably involves a region-specific cellular immune response to the topical application, rather than a drug mechanism—specific reaction, because the compounds that are responsible vary widely in chemical structure and therapeutic effect.3

 Conjunctival epidermidalization has been associated with ocular drying related to exposure, Stevens-Johnson syndrome, and avitaminosis A with xerophthalmia.4 Because ocular drying was present in case 2, it is a possible mechanism.

 Based on the clinical and histopathologic findings in these 2 unrelated patients, we propose that the administration of risdonate sodium is the primary cause of their conjunctival epidermidalization. Although the mechanisms for the development of Actonel-induced epidermidalization are not fully understood, 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 risdonate sodium.

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 **3.** Wright P. Squamous metaplasia or epidermalization of the conjunctiva as an adverse reaction to topical medication. *Trans Ophthalmol Soc UK.* 1979;99(2):244-246.


 **Mycoplasma pneumoniae: The Other Masquerader**

 *Mycoplasma pneumoniae* is a bacterium in the class of Mollicutes and is a common cause of atypical pneumonia, particularly in children and young adults. *Mycoplasma* infection primarily manifests as a respiratory tract disease, but an extrapulmonary 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.5 Ocular disease from *M pneumoniae* has also been reported, with conjunctivitis being the most frequent finding.2 Less common ophthalmologic manifestations of *M pneumoniae* include cranial neuropathies, optic papillitis, and anterior uveitis.2 We present herein 1 case of bilateral optic papillitis and 2 cases of uveitis secondary to *M pneumoniae* infection.

 **Report of Cases.**

 **Case 1.** A 20-year-old man presented with a 1-month history of blury vision. Prior to presentation, he completed a 1-week course of oral levofloxacin for community-acquired pneumonia. His visual acuity was 20/25 in the right eye and 20/30 in the left eye. The opthalmologic findings were normal, except for bilateral optic disc edema (Figure 1A 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 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 dilated fundus examination showed 2+ cell in the vitreous and bilateral optic disc edema and serous macular detachments (Figure 2A and B). There...