

Case Report

Alendronate-induced Esophagitis in an Elderly Woman

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Abstract: Ingestion of alendronate sodium (Fosamax) had been reported to sometimes cause erosive or ulcerative esophagitis. Despite its widespread use and several case reports describing the clinical and endoscopic presentation, there has been limited discussion on the histologic appearances of the esophagitis caused by the medication. Here we describe one case of an elderly woman who presented with alendronate-induced esophagitis. The histopathologic changes that make this case unique are the large, “bizarre” squamous epithelial cells and scattered dyskeratotic cells, two findings not well described in previous reports. These unique features add to the histologic spectrum of alendronate-induced esophageal injury, and shall help differentiating this type of esophagitis from those with other etiologies.

Key Words: Alendronate sodium, Fosamax, esophagitis

Introduction

Since becoming available in 1995 in the United States, alendronate sodium (Fosamax; Merck) has been widely prescribed for therapy of patients with Paget’s disease of the bone, glucocorticoid-induced osteoporosis, and post-menopausal osteoporosis [1, 2]. It functions as an antiresorptive agent by selectively inhibiting osteoclasts [3]. While its efficacy in preventing and treating disease has been shown, many case reports have described upper gastrointestinal tract damage with the drug’s use, particularly erosive or ulcerative esophagitis. These reports resulted in intervention by the FDA in 1996, which issued letters of warning to physicians, explaining the need to instruct patients using alendronate to take it with a full glass of water at least 30 minutes before the first oral intake of the day, and to remain in an upright position for a minimum of 30 minutes afterward [4]. The clinical symptoms of upper gastrointestinal /esophageal injury included odynophagia and dysphagia, retrosternal chest pain, epigastric pain and hematemesis [5]. We report one patient with alendronate-associated ulcerative esophagitis and describe the characteristic endoscopic and histopathologic features.

Case Report

An 88-year-old African American woman was admitted to the hospital with a one- to two-week history of odynophagia, dysphagia and retrosternal chest pain that radiated to the epigastric region and was exacerbated by oral ingestion to both solids and liquids. She denied a prior history of similar symptoms and did not attempt any self treatment. Prior to onset of symptoms she was able to tolerate oral intake without problems. The patient denied smoking, alcohol or drug use. Past medical history included GERD, hypertension, Alzheimer’s dementia, osteoporosis, stress incontinence, glaucoma, diverticulitis and generalized anxiety. Careful examination of medications included Cozaar, Tramadol, Imipramine, Miralax, Propanolol, Fosamax 70 mg weekly, Primidone, Nexium, Aricept and Xalatan. Family history was noncontributory. Review of systems was positive for presenting symptoms, without weight loss, nausea, vomiting, regurgitation of food, melena, fever, chills, dizziness, chest pain on exertion, cough, dyspnea, syncope, headaches, sore throat, blurred vision, or any rashes or joint pains.

Physical examination revealed tender to palpation over the epigastric region and left lower quadrant and suprapubic region, without guarding, rebound tenderness or hepatosplenomegaly. The remainder of the physical

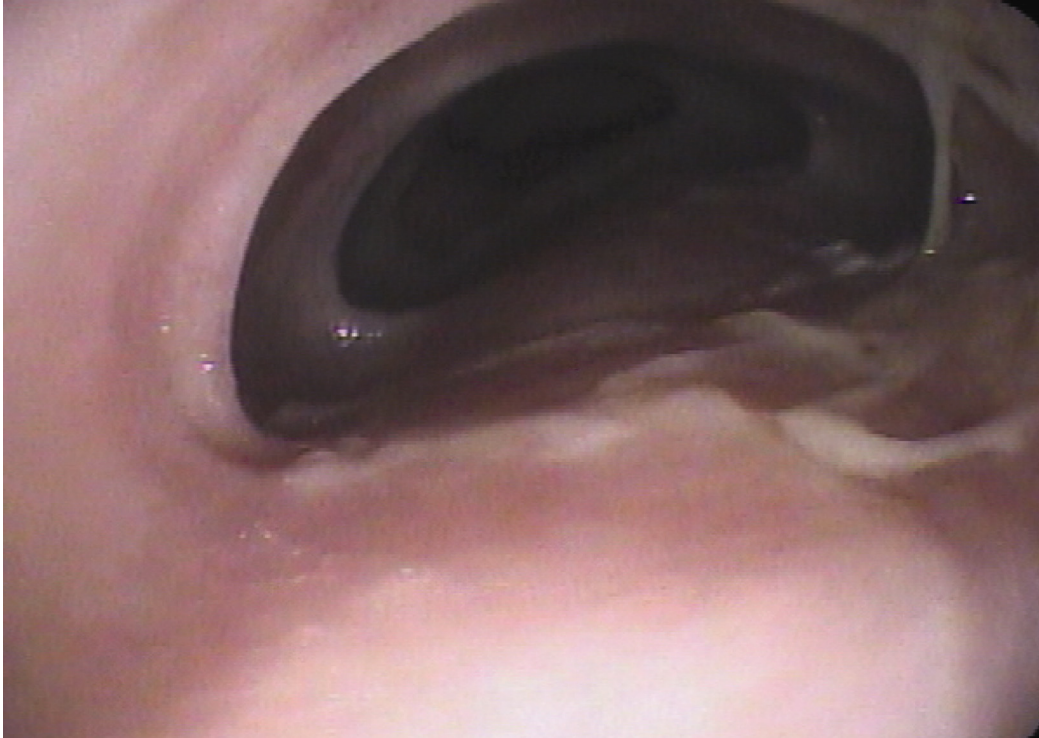


Figure 1 Endoscopic image showing esophagitis with ulcerations and exudates in the distal esophagus, in addition to multiple nonobstructing rings seen in mid to distal esophagus.

examination was within normal limits. However, a barium swallow revealed moderate esophageal dysmotility and minimal distal esophageal stricture which caused no obstruction to the passage of barium and no mucosal irregularity suggestive of neoplasm or inflammation.

An EGD was performed and was remarkable for esophagitis with ulcerations and exudates in the distal esophagus, in addition to multiple nonobstructing rings seen in mid to distal esophagus (**Figure 1**). On microscopic examination of the biopsy taken from the mucosa of the distal esophagus, there was granulation tissue with marked inflammatory cellular infiltration including lymphocytes, neutrophils and some eosinophils (**Figure 2A**). The adjacent squamous epithelium exhibits degenerative changes, with scattered dyskeratotic cells (**Figure 2B**), and some enlarged epithelial cells (**Figure 2C**). Although no characteristic cytopathic changes of viral effect were identified, the presence of these markedly enlarged cells with hyperchromatic nuclei, warranted the exclusion of the usual infectious etiology. Immunohistochemical stain for herpes simplex virus types 1 and 2, and

GMS and PAS stains for fungal organisms were therefore performed, and were all negative.

The patient was continued on Nexium twice daily, and Fosamax was discontinued for three weeks. Once restarted, she was instructed to take it with at least 8 ounces of fluids and maintain an upright position for at least 30 minutes to 1 hour post ingestion. In addition, she was advised to avoid non-steroidal anti-inflammatory drugs (NSAIDs).

Discussion

Alendronate-induced esophagitis is a clinical entity that deserves attention because of its wide-spread use. Within the first three years of its marketing in late 1995, at least 24 esophageal injuries were reported, as cases or case series [6]. In particular, the geriatric population was at greater risk of pill-induced esophageal damage, which maybe due to lack of full compliance when taking the medication and because of polypharmacy.

In this report we described a case of “pill” esophagitis with the clinical presentation of odynophagia, dysphagia, and retrosternal pain,

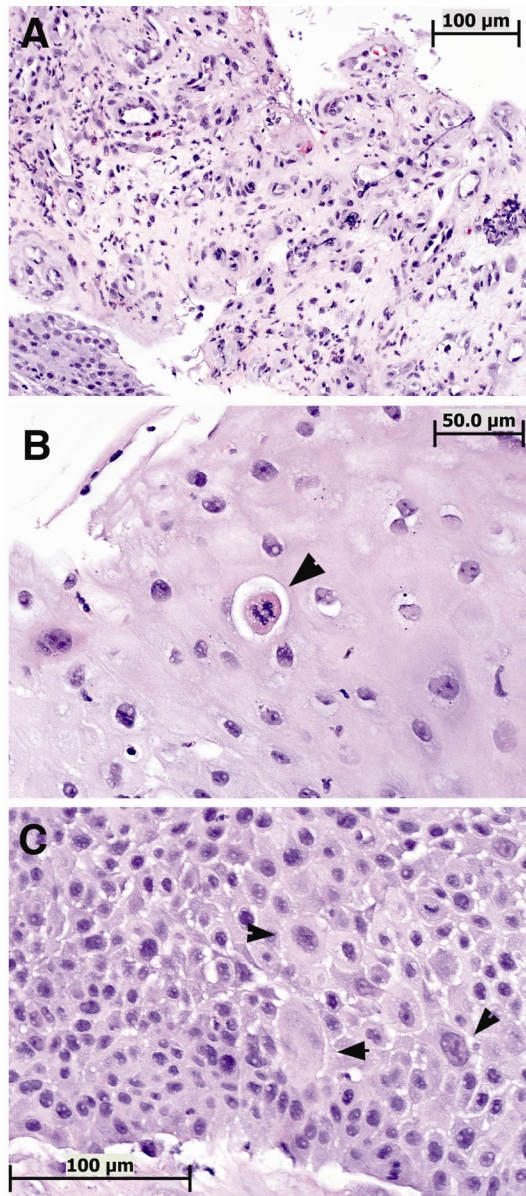


Figure 2 Photomicrograph of the esophageal biopsy. **A.** Granulation tissue with brisk capillary formation, edema, and inflammatory cellular infiltration, including lymphocytes, neutrophils, and some eosinophils. **B.** Adjacent squamous epithelium, with scattered apoptotic bodies (dyskeratotic cells); one example is shown here (arrow head). **C.** Within an overall background of reactive changes, near the basal layer of the squamous epithelium (bottom), many cells show cytoplasmic and nuclear enlargement (arrow heads), including some "large, bizarre" squamous cells (arrow). Note the relative lack of inflammatory cells in the epithelial layer (**A** and **B**).

worsening with swallowing. The differential diagnosis of an elderly patient with this clinical presentation obviates the need to rule out

cardiac, pulmonary, cerebral, infectious and other etiology. However, the index of suspicion for alendronate-associated esophagitis remained high given the history of the patient; that is, she is a post-menopausal female, with a known history of osteoporosis, currently being treated with alendronate, and furthermore, the biopsy did not show other histologically recognizable causes for esophageal ulceration.

It is of particular interest that the histopathologic changes described in this report included two findings not well described or mentioned in previous case reports of alendronate-induced esophagitis. First, there were scattered dyskeratotic cells amongst largely normal adjacent squamous epithelium, as characterized by scattered eosinophilic inclusions or apoptotic bodies (**Figure 2B**). These changes suggest that alendronate induce apoptosis of the squamous epithelial cells, through unknown mechanism. Secondly, there were large, bizarre squamous cells in the involved area located within an overall background of reactive changes, near the basal layer of the mucosa rather than the luminal side (**Figure 2C**). These cells exhibit both cytoplasmic and nuclear enlargement and had prominent nucleoli. The significance is undetermined, but likely represents a degenerative change related to toxic effects of alendronate. They may be similar to the "giant cells" described in a case series by Abraham *et al* [7] and in a single case by Singh and Odze [8]. Even though more cases need to be studied in order to determine how often these changes occur, it is important to recognize this unique feature, so that the right differential diagnosis will include "pill" esophagitis.

In case reports described by Abraham SC *et al* and Ribeiro *et al*, most, if not all, histopathologic findings showed granulation tissue and inflammatory exudates at the site of ulceration, similar to our findings [7, 9]. However, Abraham *et al* showed a 60% prevalence of biopsies containing polarizable foreign material that had a clear, refractile, crystalline appearance and admixed with the inflammatory exudates, alluding to a prolonged contact time between the pill and mucosa [7]. Ribeiro *et al* also demonstrated this finding in two of the five patients studied and proposes that most cases of medication induced esophageal mucosal injury are due to an injury from prolonged contact of the pill to

the esophageal mucosa [9]. Other pathologic features of alendronate-induced esophagitis reported include multinucleated giant cells within the inflammatory exudates, enlarged, hyperchromatic reactive squamous cells adjacent to the site of ulceration, multinucleated squamous epithelial giant cells and fibrinous inflammatory exudates [7, 9]. Secondly, the large cell changes sometime resemble viral cytopathic effect, such as HSV, it is important to rule this out, by performing immunohistochemical stains, as was done in our case.

Another mechanism that may further exacerbate esophageal injury caused by alendronate may occur in patients with a history of gastroesophageal reflux, as our patient did have. Alendronate exists as a monosodium salt at pH more than 3.5; however, at pH less than 2 it is primarily in a free acid form that is more irritating to the mucosa [10]. Therefore, especially in patients who do not remain upright for the required amount of time after ingesting the tablet, the dissolved alendronate may cause a specific toxicity to the distal esophagus [7]. This could even explain the absence of tablet crystalline material in our biopsy and those not found in other reports. Whether or not patients with a history of decreased esophageal peristalsis are at increased risk for pill retention is an important factor to consider. In our case, the barium swallow was consistent with moderate esophageal dysmotility, a finding that could have contributed to her presentation. Chart review of the patients did not elucidate any additional information on this, however.

In summary, odynophagia with dysphagia in the setting of recent alendronate ingestion allows one to immediately consider pill esophagitis. While a thorough patient history and upper endoscopy are essential to come to this diagnosis, histologic studies of the injured mucosa allow us to better rule out other causes of esophageal injury. The presence of nonspecific inflammatory changes and crystalline material in distal esophagus, and absence of viral, fungal and bacterial infection all aid in the diagnosis of alendronate-induced esophagitis. In this report, the findings of large bizarre squamous epithelial cells and dyskeratotic cells favor more towards the cause of the esophagitis as being from an external toxic insult, such as a medication. It would be of great interest to look for these

latter changes in future cases of alendronate-induced esophagitis. With more reports now discussing not only endoscopic but histopathologic changes in alendronate included-esophagitis, we may be able to more confidentially make this diagnosis.

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