Severe drug-induced oesophagitis in a young male patient

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DESCRIPTION
A man in his 30s presented with a 4-day history of severe epigastric pain, described as a 7/10, with dorsal irradiation and progressive dysphagia for solids. He denied vomiting, altered gastrointestinal transit, gastrointestinal bleeding, fever and loss of weight. He denied any previous gastrointestinal complaints. Regarding previous medical history, he was prescribed an oral film-coated alendronate tablet, 70 mg/month, after an atraumatic vertebral fracture 2 years ago with the diagnosis of osteoporosis of unidentified aetiology. He had taken the oblong-shaped pill, with around 13 per 8 mm of size, 2 days before the onset of symptoms, with some water and recumbent position immediately after. He denied any other medications. Family history was unremarkable. On clinical examination, his vital signs were normal, and he had epigastric abdominal tenderness without peritoneal irritation signs. The laboratory findings showed elevation of the inflammatory parameters (leucocyte count: 19.7×10⁹/L, n: 4–10, and C reactive protein: 3.85 mg/dL, n<0.5). Thoracoabdominal radiography did not show mediastinal enlargement or evidence of perforation. Electrocardiogram and myocardial necrosis markers showed no cardiac ischaemic changes. Abdominal ultrasound was normal. As he maintained the complaints, he was referred to our unit and underwent upper endoscopy, revealing, as shown in figure 1A,B, a circumferential ulceration of almost all oesophageal mucosa, except for a small portion of the proximal oesophagus, with extensively desquamation and friability. Additionally, a deeper longitudinal ulceration was seen in the middle third of the organ (figure 1C). No gastroduodenal lesions were observed. The patient was admitted due to food intolerance.

He was started on twice daily intravenous proton pump inhibitor therapy and four times daily oral sucralfate. Due to prolonged food intolerance, parenteral nutritional support was needed.

The diagnostic workup excluded infectious aetiology by herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, HIV and mycobacterium tuberculosis. Cervicothoracic computed tomography showed some enlarged lymph nodes near the esophagogastric junction, without any suspicious lesions, pneumomediastinum or pneumothorax. The histological analysis revealed, as shown in figure 1D, an extensively ulcerated mucosa with fibrinopurulent debris, without microorganisms, or neoplastic cells.

Immunofixation for herpes simplex virus and cytomegalovirus were negative.

When asked directly, the patient revealed an inadequate way of taking the alendronate pill, with minimal water ingestion and supine position afterwards. The patient was released 15 days after admission, without complaints and tolerating solid diet. He was referred to a rheumatology consultation and maintains intravenous alendronate.

Figure 1 (A) Upper endoscopy revealing an extensive oesophageal injury with an easily sliding fibrinopurulent exudate and a friable mucosa. (B) Lower oesophagus with an extensively desquamation of the mucosa. (C) Middle third of the oesophagus with a deeper longitudinal ulceration. (D) Oesophageal biopsies showed a wide ulceration with a dense inflammatory infiltrate and fibrinopurulent exudate, compatible with pill-induced esophagitis. No microorganisms, dysplasia or neoplastic cells were identified.

Figure 2 Upper endoscopy 3 months after admission with complete resolution of the oesophageal lesions.
Follow-up endoscopy at 3 months showed complete resolution of the oesophageal lesions (figure 2).

Drug-induced esophagitis represents an infrequent aetiology of dysphagia in young patients and an overall overlooked entity with a non-negligible morbidity. Among the most common causative agents are antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and bisphosphonates.1 Second-/third-generation bisphosphonates differ from first-generation bisphosphonates in that they contain nitrogen in their composition.2 Alendronate is a first-line nitrogen-containing bisphosphate used for osteoporosis treatment. The critical point is its oral bioavailability under fasting since it is poorly absorbed in the gastrointestinal tract (<1%). This is because alendronate is a hydrophilic leading to frequent gastrointestinal symptoms and poor patient adherence.3–4 In contrast, intravenous formulations require less frequent dosing and are not associated with gastrointestinal symptoms.2 Its pathogenic pathway is associated with chemical direct lesion of the oesophageal mucosa caused by the tablet passing through the oesophagus and possibly the reflux of drug-containing gastric content. Alendronate replaces hydrophobic and acid-resistant phospholipids, as a competitive binding of phosphatidylcholine, in the mucosal barrier, weakening its defences and leading to erosion and ulceration of the upper gastrointestinal mucosa (figure 3).5–7 There is not yet a known molecular-based pathogenic pathway for alendronate toxicity in the oesophageal epithelium, the speculated mechanism based on animal models being the competitive binding of alendronate to phosphatidylcholine disintegrating the protective hydrophobic mucosal barrier and allowing direct acid injury. The molecular therapeutic mechanism of alendronate is known at the osteoclast level, which by inhibiting the pharnesyl diphosphate synthase of the mevalonate pathway, blocks the phenylation of small signalling proteins required for osteoclast function and survival, leading to osteoclast inactivation/apoptosis and inhibition of bone resorption. In the literature there is also a speculative mechanism for alendronate ocular injury generating a self-limited systemic inflammation mediated by increased serum levels of interleukin 1, interferon-α and interferon-γ mediated by monocytes/macrophages and T lymphocytes.8 In figure 3 is represented the data known so far of the pathogenic/toxic effect of this drug on the oesophageal mucosa—a competitive binding mechanism on the phospholipid bilayer instead of phosphatidylcholine leading to an injury of the protective mucosal barrier and exposure to gastric acid, with consequent chronic irritation, inflammation, erosion and ulceration of the oesophageal mucosa. Nevertheless, oesophageal adverse events are reported in around 0.04% of patients under alendronate treatment and severe ulceration is even rarer.6 9 Symptoms and severity of oesophageal injury increase with old age, gastro-oesophageal reflux disease, oesophageal stricture or oesophageal dysmotility as they can prolong mucosal exposure to the drug, and also the concomitant use of antithrombotic agents or NSAIDs.10–11 Recommendations such as swallowing the pill with at least 180–240 mL of water, without chewing or crushing the tablet, and avoiding recumbent position for at least 30–60 min after should be given to the patient requiring bisphosphonates. The tablet should also be taken at least 30 min before breakfast, because some foods or beverages, as coffee, juices and mineral water, antacids and even dietary supplements or medicinal products containing multivalent cations (eg, calcium, magnesium, aluminium, chromium or iron) are likely to reduce the absorption of alendronate. The above-mentioned measures will facilitate the delivery of the tablet to the stomach, minimise the risk of interactions, and thus reduce the potential of oesophageal lesions.3 4 10–11 In addition, oral administration of second-/third-generation bisphosphonates with less frequent dosing or intravenous formulations also limit or avoid gastrointestinal adverse effects.3

Learning points

- A detailed clinical history is crucial as it can lead to the correct diagnosis and an attempted treatment.
- A high index of suspicion is needed to identify less common aetiologies of dysphagia in young patients.
- Education towards adequate administration of medications, especially when commonly associated with pill-induced esophagitis, is essential while prescribing in order to avoid potential severe complications.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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