

mutation of the beta-catenin gene, non-steatotic and large hepatocellular adenomas.^{3-6,9,11} The correlation between tumour size and malignant transformation could not be confirmed statistically; however, MHAs are usually large (mean: 10.5 cm).⁶ The smallest malignant tumour measured only 3 cm, and only 5% of MHAs measure less than 5 cm.^{5,6} Currently, the standard treatment for all adenomas greater than 5 cm is surgical resection,^{5,9} since the risk of malignant transformation or bleeding in adenomas measuring less than 5 cm is extremely low.^{3,5,6,8}

The prognosis for MHA is unclear. Details of oncological follow-up are only available in 13 of the 19 patients mentioned above: 1 case of postoperative death, 2 tumour-related deaths at 5 and 7 months, and 1 case of recurrence 6 years after resection.⁶ Based on these data, overall disease-free survival at 5 years is 83%. It is unclear whether these patients received adjuvant treatment.⁶

In conclusion, MHAs are very rare. A number of factors are associated with malignant transformation, although not enough cases have been published to allow us to reach scientifically solid conclusions.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Melanos coli due to diacerein[☆]



Melanos coli asociada a diacereína

Melanos coli (MC) is a benign condition characterized by brown pigmentation of the colon mucosa, particularly in the proximal colon, with less discolouration in the distal colon. It is a non-specific marker of increased colonic epithelial apoptosis, usually caused by the toxic effect of anthraquinone, a substance commonly found in laxatives (cascara, senna, buckthorn, etc.).

Histological findings are an infiltrate of histiocytes containing lipofuscin (not melanin as the name suggests),

a pigment resulting from the structural degeneration of organelles.

Clinically, the condition is usually asymptomatic and occurs in patients with chronic constipation and habitual laxative use. The pigmentation usually appears after 3–13 months of continuous use,¹ and resolves 4–11 months after discontinuation.

Melanos coli is usually an incidental finding in colonoscopy performed for other reasons, and manifests as dark brownish polyhedral patches divided by thin lighter coloured lines. Radiological signs are a foreshortened, rigid colon with no haustration, called cathartic colon. However, very few cases have been described in the literature, and MC is currently attributed to substances no longer used in modern laxatives.¹

As mentioned, the lesions disappear after withdrawal of the laxatives, so the prognosis is benign and no specific treatment is required. Nevertheless, although the notion

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that anthraquinone laxatives can cause adverse structural and/or functional changes in the intestine is controversial, no studies to date have confirmed its role in colonic plexus damage. The importance of this clinical entity lies in its early association with adenomas and their potential progress to adenocarcinoma. However, evidence has shown that the relatively higher incidence of adenomas associated with MC is not due to increased polyp formation, but to the ease of detection of these within a dark-coloured colonic mucosa.²⁻⁴

We present here the first case in the literature of MC associated with diacerein use.

The patient is a 77-year-old woman with no personal history of note, but a family history of colon cancer. In January 2008, she started treatment for osteoarthritis with 100 mg/day oral diacerein (Galaxdar®).

In March 2010, in a routine follow-up colonoscopy performed in the relatives of patients with colorectal carcinoma, dark brown pigmentation of the colonic mucosa was observed and diagnosed as MC. She continued to take diacerein. The patient denied use of anthraquinone laxatives, and the colonoscopy performed immediately before the start of diacerein therapy was normal. The case was reported to the Regional Pharmacovigilance Centre.

This case of MC could, a priori, be considered atypical because diacerein is an active ingredient not included on the lists of causative agents in studies investigating this condition.

Following notification of the adverse reaction, we consulted the Pharmacovigilance Centre due to the difficulty in determining the aetiologic diagnosis in a patient with no history of anthraquinone laxative use.

A detailed study of the summaries of product characteristics of laxatives sold in Spain containing diacerein⁵ as the active ingredient revealed that "on rare occasions (1–10% of patient), pigmentation of the recto-colonic mucosa (melanosis coli) has been reported". This is plausible, since diacerein is a heterocyclic compound with an anthraquinone structure.

Anthraquinone laxatives are a subtype of plant-based stimulant laxatives. Their active ingredients are inactive glycosides together with anthraquinone and anthranol aglycones. Medicinal products containing these active ingredients include senna, cascara, aloe, buckthorn and rhubarb, and are by far the most widely used over-the-counter laxatives.⁶

A search of the literature did not bring to light any other reports linking MC with diacerein, nor does the Spanish Pharmacovigilance System FEDRA database contain any reports of diacerein associated with MC.

Diacerein, through its active metabolite rhein, modifies the symptoms of osteoarthritis by inhibiting interleukin-1 activity. Rhein is found in plants of the genus *Cassia*, and has moderate anti-inflammatory and analgesic properties, coupled with a mild laxative effect. Some studies have reported diarrhoea or soft stools in 20–30% of users following the first dose of diacerein.⁷ This could be because diacerein and some laxatives are heterocyclic compounds with a low molecular weight anthraquinone structure. They are not absorbed in the small intestine, but are hydrolysed by bacterial glycosidases in the colon before entering the

systemic circulation, and are absorbed, metabolized and subsequently excreted as rhein and its conjugates. These, in turn, stimulate intestinal peristalsis and fluid secretion, causing mucosal damage and leading to conditions such as MC.⁶

At the molecular level, destruction of the intestinal mucosal barrier seems to stimulate factor TNF- α release, leading to colonic epithelial apoptosis and the deposition of brownish pigments in colonic membrane macrophages.⁸

We believe it is important to raise awareness of this possible adverse reaction associated with diacerein use, above all among gastroenterologists, and to include it in the differential aetiological diagnosis of MC, together with laxative use.

The Spanish Agency of Medicinal Products and Medical Devices recently published a note⁹ that advises against starting new treatments with diacerein, and recommends reassessing existing treatments due to the high risk of severe diarrhoea (8.5–50% of patients treated) and acute severe liver damage. For this reason, and for its association with MC, we believe this active ingredient should be closely monitored by health professionals, above all in patients who obtain no clear clinical benefit, who present liver damage, and in those at risk for diarrhoea in the context of an underlying gastrointestinal pathology.

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Endoscopic retrieval of multiple large sharp foreign bodies from the stomach. Testing the limits of endoscopy[☆]



Extracción endoscópica de cuerpos extraños múltiples, grandes y cortantes. Transitando los límites de la endoscopia

Accidental or intentional ingestion of a foreign body is one of the most common emergency situations for endoscopists. In most cases, a conservative approach should be taken, since objects will generally pass through the intestinal tract without incident.¹ The need for retrieval is mainly determined by the characteristics of the object ingested, such as its size and shape, the presence of sharp-edged or pointed objects, or the time elapsed since ingestion. Other factors to be taken into consideration are the clinical situation of the patient, or the locations of the object within the digestive tract. Certain ingested objects also require special consideration. For example, batteries and magnets nearly always require endoscopic extraction, while drug packets should always be left to transit naturally due to the risk of breakage and poisoning. A common situation is ingestion of metallic and/or sharp objects for the purpose of self-harm, above all in inmates in prison hospitals or psychiatric patients. In the case of large, pointed or sharp objects, retrieval is mandatory. This is usually performed endoscopically, with surgery being the last resort if endoscopy fails due to complications or the size and characteristics of the ingested object.^{2,3} We present here a rare case of endoscopic extraction of several, large, sharp objects.

A 37-year-old man, a prison inmate, was taken to the emergency room following ingestion of several metallic objects. The patient had a history of endoscopic extraction⁴ and gastric surgery in similar circumstances. The patient reported no symptoms. Simple abdominal X-ray showed a sharp-edged, 14 cm long metallic object and at least 2 other sharp, flat objects measuring at least 20 mm in width. Despite its limitations, endoscopy was considered the safest extraction method, with a surgical team on stand-by if the procedure failed.

The patient was taken to the operating room, anaesthetised and intubated. Endoscopy was performed (Fig. 1A)

with a standard Olympus GIF-H190[®] gastroscope, 9.2 mm diameter, 2.8 mm working channel, and an Olympus GIF-2T160[®] two channel therapeutic gastroscope, 13.2 mm diameter with 2.8 and 3.7 mm working channels, a US endoscopy[®] overtube, 2 cm calibre, and a rubber hood attached to the tip to protect objects that exceed the diameter of the overtube.⁵ Using this equipment, we successfully retrieved several sharp objects (Fig. 1B). We decided to first extract the larger, longer, pointed objects, as this was technically more complex and more likely to cause injury to the gastric wall. Following this, the flat objects were extracted in descending order of size.

The 2 largest objects were retrieved through the overtube, using a polypectomy snare and a conventional endoscope. The third object retrieved, which was one of the sharp, flat objects, was shorter and wider than the previous 2, and during extraction became lodged in the overtube after grasping it with a conventional polypectomy snare and large forceps passed through the two channel gastroscope, thus making it difficult to manoeuvre the object.

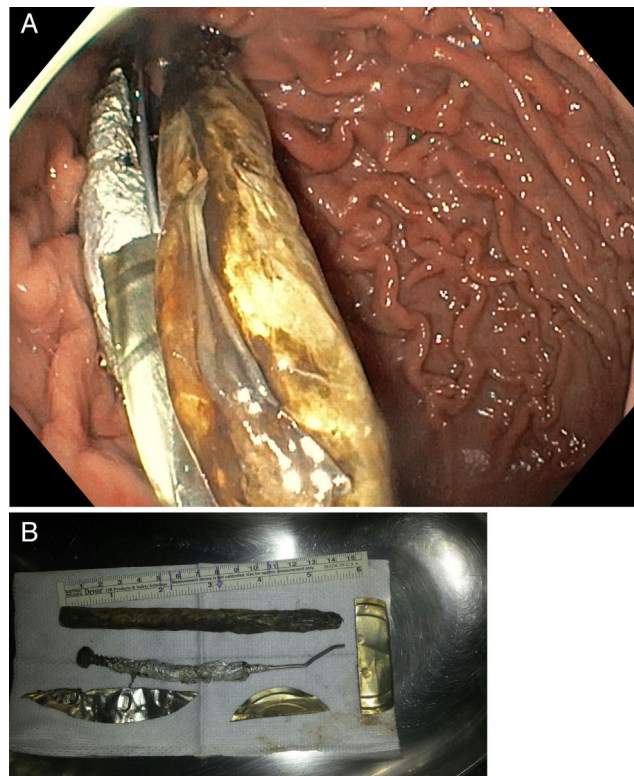


Figure 1 (A) Endoscopic view of gastric cavity containing the foreign bodies. (B) Foreign bodies.

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