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Primary follicular lymphoma of the gastrointestinal tract: Endoscopic findings and role of capsule endoscopy☆

Linfoma folicular primario gastrointestinal: hallazgos endoscópicos y papel de la enteroscopia con cápsula

Primary lymphoma of the gastrointestinal tract is rare and is most commonly caused by secondary gastrointestinal invasion. Diffuse large cell lymphoma, MALT lymphoma and mantle cell lymphoma are the most common histological subtypes. Since 2008, the World Health Organisation has recognised a new lymphoma subtype, primary gastrointestinal follicular lymphoma (GI-FL). We present the cases of two patients diagnosed with primary GI-FL at our centre. The first case is a 56-year-old female carrier of an exon 12 mutation in the hMSH-2 gene that was discovered after surgery (hysterectomy with double adnexectomy) for ovarian adenocarcinoma 12 years previously (T1N0M0; TNM classification, 7th edition). Three years ago, she was diagnosed by chance with primary GI-FL of the duodenum after detecting a whitish nodular and elevated lesion close to the major duodenal papilla during a routine gastroscopy (Fig. 1A). The biopsies revealed B-cell lymphoid proliferation in the lamina propria comprising small and irregular lymphocytes and some isolated centroblasts. The immunohistochemical study was positive for the markers CD20, CD10, BCL-2 and BCL-6 and negative for CD3, CD5 and cyclin-D1 (Fig. 1B). The extension study (CT scan of the chest and abdomen, bone marrow biopsy and PET scan) ruled out distant cancer, although three further lesions of similar characteristics were found in the middle and distal jejunum and the terminal ileum during the capsule endoscopy (CE) (Fig. 1C). The patient achieved complete remission after four cycles of treatment with rituximab. A subsequent check-up two years later revealed endoscopic and histological recurrence, but without radiological progression. Given the patient's refusal to receive new treatment, conservative treatment was administered. Twelve months later, the patient remained stable and with no evidence of tumour progression. The second case concerns a 48-year-old woman who was admitted for a six-month history of asthenia, vomiting and abdominal pain caused by menstruation. A conventional endoscopic examination was performed (gastroscopy and ileocolonoscopy), which revealed some polypoid mucosal lesions in the terminal ileum consistent with lymphoid follicular hyperplasia (Fig. 2A). Given the persistent symptoms, an abdominal CT scan was performed, which found thickening of a short segment of the terminal ileum wall as well as regional and retroperitoneal lymphadenopathies, with no other relevant findings (Fig. 2B). The CE confirmed the radiological findings and also revealed a *de novo* mucosal stenosis that was impassable by the capsule (Fig. 2C). After two weeks of treatment with budesonide (9 mg/24 h), the device was expelled naturally without incident. The biopsies obtained previously were restudied, this time observing cell clusters with an immunophenotype consistent with primary GI-FL of the ileum. CHOP chemotherapy + rituximab was initiated, with radiological improvement observed on the control CT scan after two treatment cycles.

Primary GI-FL is a variant of nodal follicular lymphoma.[1] It is a rare lymphoma, accounting for between 1% and 3.6% of all primary lymphomas of the gastrointestinal tract.[2] Prevalence tends to be higher among middle-aged women. Although it is often asymptomatic (43%), the most common symptoms to manifest are abdominal pain (28%), nausea-vomiting (8%) and gastrointestinal bleeding (6%).[3] They tend to be unifocal tumours and most commonly arise in the second part of the duodenum close to the ampulla of Vater. Nevertheless, as was the case with our first patient, multifocal cases of primary GI-FL have been reported. In such cases, capsule endoscopy, which is a harmless and well-tolerated procedure, may be used extremely effectively to detect and locate all synchronous lesions. It can also serve as a guide for biopsy when the conventional endoscopy is negative.[4] Primary GI-FL often presents endoscopically as small polypoid lesions coated in normal mucosa. However, on rare occasions it manifests as ulcers, which can lead to stenosis of the intestinal lumen.[5,6] From a histological standpoint, they present a pattern of nodular growth comprising germinal centres made of centrocytes and centroblasts with an immunophenotype that is typically positive for the markers CD19, CD20, CD22 and CD79a and negative for CD43, CD5 and cyclin-D1.[7] The extension study should include an endoscopic examination, a CT scan of the chest and abdomen and/or PET scan, as well as a bone marrow biopsy.

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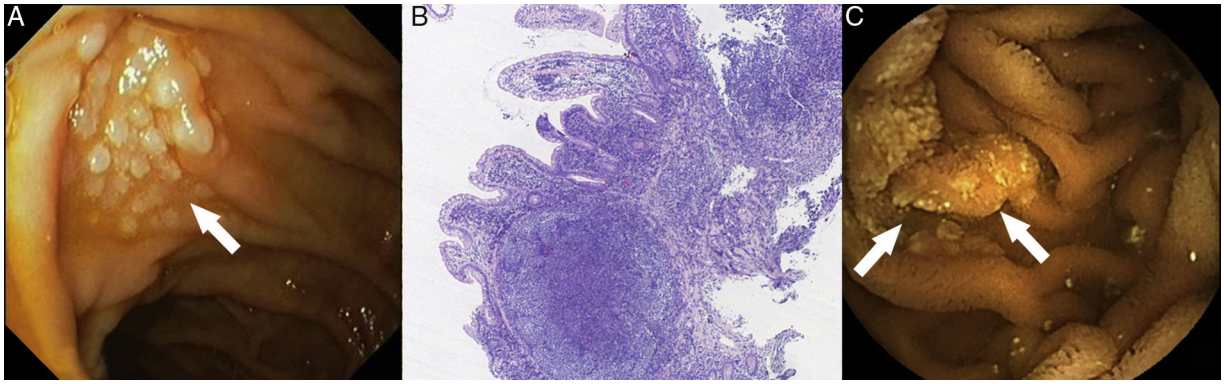

Figure 1 (A) Juxtapapillary, nodular, elevated whitish lesion, with (B) B-cell proliferation composed of centrocytes and centroblasts (H&E ×40). (C) Primary GI-FL of the duodenum by capsule endoscopy.

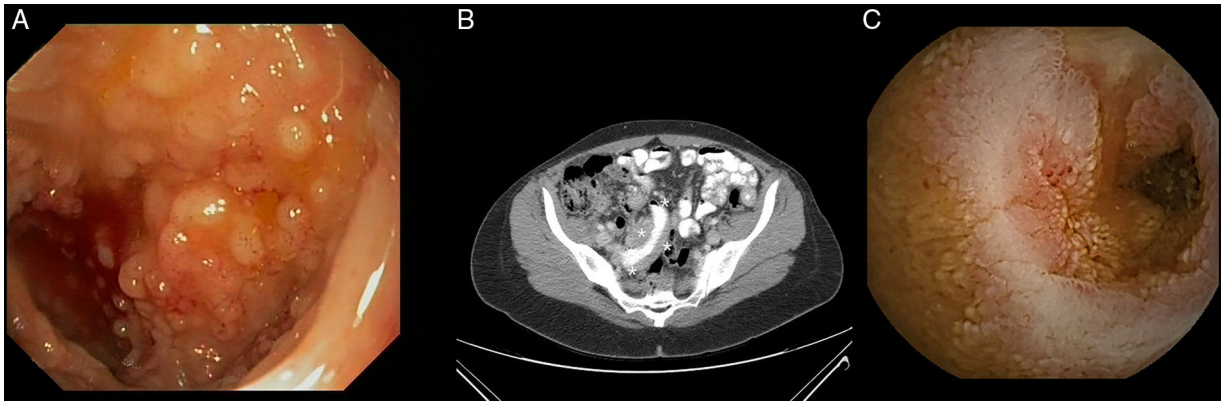

Figure 2 (A) Polypoid lesions in the terminal ileum, with (B) thickening of the ileum wall on the CT scan. (C) Ulcerated and impassable ileal stenosis during the capsule endoscopy.

Both the Ann-Arbour and Lugano classifications are useful for tumour staging, with the Lugano classification being particularly relevant for multifocal primary GI-FL.[8] As an optimal treatment strategy has yet to be established, this must be personalised to suit the particular characteristics of each individual patient. In asymptomatic patients with localised cancer, expectant management may be appropriate. However, treatment should be started as soon as patients manifest symptoms and/or disease progression based on the histological and clinical grade. Radiotherapy tends to be the treatment of choice in patients with localised disease and no poor prognostic factors, reserving monotherapy with rituximab (anti-CD20 monoclonal antibody) for select cases where the adverse effects of radiotherapy are to be avoided. If, on the other hand, the disease has spread or the patient presents poor prognostic factors, systemic chemotherapy (CHOP, CVP) with or without rituximab is indicated.[9]

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Anorectal melanoma: An atypical cause of rectorrhagia

Causa atípica de rectorragia: melanoma anorrectal

We present the case of an 81-year-old man with previous diagnose of hypercholesterolemia, benign prostate hyperplasia and seborrheic keratosis. He presented a two-months history of rectorrhagia episodes without any other symptoms. In the laboratory tests there was no anemia and the tumor markers were negative. A rectoscopy was performed identifying from the anus to 6 cm beyond the dental line a pseudo-polyp mameloned tumor with hyperpigmented base evolving a quarter of the whole circumference of the rectum (Fig. 1A).

The biopsies showed extended small round cells proliferation with necrosis. Neither melanic pigment nor mucosa was observed probably because superficial biopses where taken on the surface of the tumor. The immunophenotype was negative to S-100 and positive to Melan-A and MITF (microphthalmia-associated transcription factor) so the diagnose of a rectal melanoma was performed (Fig. 2A and B). The study was completed with colonoscopy (three adenomatous polyps were removed), pelvic magnetic resonance (Fig. 1B) and computed tomography of the thorax and abdomen without mesorectal lymph nodes or distal metastasis. The case was presented in the multidisciplinary comity and a surgical approach was chosen. An endoanal resection was performed, because of the absence of distal or local invasion and the patient age and comorbility, without complications. The surgical piece showed deep infiltration even throws muscular propia, an ulcerated mucosa and the presence of melanophages. The patient remains asymptomatic and with good quality of life.

Mucosal melanomas (MM) are rare (0.4–1.6% of total malignant melanomas). Both cutaneous and mucosal melanomas contain melanocytes, but have important differences such as the exposure of ultraviolet light (clearly related with cutaneous melanoma), localization, appearance (40% in MM are amelanotic) age of presentation and prognosis (poorly in the case of MM).[1–5]

The anus is the third most common location of melanomas after the skin and the eyes.[1,3,4] MM arise primarily in the head and neck (55%), anorectal (24%) and vulvovaginal (18%) regions and are in 20% of cases multifocal.[1,3,5] They are frequently found within 6 cm of the anal rim: rectum (42%), anal canal (33%) or both. Other infrequent sites include urinary tract, gall bladder and small intestine. The median age of presentation is 70 years (except those located in oral cavity found in younger people). There is a female preponderance of cases and HIV infection has been implicated as a risk factor for anal localization in young male patients.[1,2,6] The incidence of anorectal melanoma (AM) increases over time, and it remains highly lethal, with a 5-year survival rate of 6% to 22%. The simplified staging system which was originally developed for melanomas of the head and neck in 1970 by Ballantyne is used for the primary site including three stages Stage I: Localized disease; Stage II: Locoregional nodal involvement and Stage III: distant metastatic involvement.[7] The most common presenting symptoms are nonspecific and include rectal bleeding followed by pain, the sensation of a mass, constipation, diarrhea, abdominal pain, weight loss, and tenesmus. All of them present in such common conditions as are hemorrhoids, rectal polyp or prolapse. As the diagnose is usually late the tumors may attain a large size before being correctly diagnosed. Metastases are present at the time of diagnosis in more than half of patients.[2,4,5,7-9] Although melanomas develop throughout the anus, two thirds arise in the proximal portion of the pecten and transitional zone around the dentate line (within 6 cm of the anal rim). Twenty to fifty percent of tumors are pigmented but others remain amelanotic.[1,2] Histologically the cells are often large with an epithelioid appearance and finely distributed pigment giving the cytoplasm a dusty-tan appearance. We can find large hyperchromatic nuclei with well-dispersed chromatin, multinucleated and polymorphic giant cells. Some melanomas (small round cell melanomas) contain atypical round cells resembling lymphocytes. Intraepithelial extensions of malignant melanoma may be confused with Paget disease. Immunohistochemistry studies can be useful, as AM stains positive for anti S-100 protein, HMB-45 (as the S-100 is a monoclonal antibody, HMB-45 that reacts against an antigen present in melanocytic tumors such as melanomas, and stands for human melanoma black 45) and Melan-A, while are usually negative for AE1/AE3 cytokeratines.[4]

A correct diagnose includes radiological exams including tomography scan (for the evaluation of distal dissemination), magnetic resonance (for local evolving) and even endoscopic procedures such as ecoendoscopy for a detailed examination of the area in order to a better surgical approach.[8,9]

Given the rarity of this neoplasia, optimal treatment is still controversial and surgery seems to be the only curative treatment. Surgical approaches include wide local excision (WLE) and abdominoperineal resection (APR), although no