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BRIEF REPORT

Lymphoepithelioma-like carcinoma of the large intestine: A case report and literature review

Cristina Díaz del Arco[a,*], Fernando Esteban Collazo[b], Mª Jesús Fernández Aceñero[a]

[a] *Department of Surgical Pathology, Hospital Clínico San Carlos, Madrid, Spain*
[b] *Department of General and Gastrointestinal Surgery, Hospital Clínico San Carlos, Madrid, Spain*

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Abstract Lymphoepithelioma like carcinoma (LELC) is a well-known neoplastic lesion that mainly involves the stomach and which has been linked to Epstein Barr virus infection. There are exceptional cases of intestinal involvement by LELC, with 7 reported cases to date.

We report a new case of LELC affecting the right colon and review the literature on this rare disorder, with special emphasis on pathogenesis, molecular features and differential diagnosis.

PALABRAS CLAVE
Linfoepitelioma;
Carcinoma;
Colon;
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Linfocitario

Carcinoma tipo linfoepitelioma de intestino grueso: descripción de un caso y revisión de la literatura

Resumen El carcinoma tipo linfoepitelioma es una entidad conocida que suele afectar al estómago y se ha relacionado con infección por el virus de Epstein-Barr. La afectación intestinal es mucho más infrecuente, y en la literatura en inglés se han publicado solo 7 casos hasta la fecha.

Describimos un caso de carcinoma tipo linfoepitelioma que afectó al colon derecho y realizamos una revisión de la literatura con especial énfasis en su patogenia, características moleculares y diagnóstico diferencial.

* Corresponding author.
E-mail address: crisdelarco@gmail.com (C. Díaz del Arco).

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Introduction

Lymphoepithelial carcinomas (LEC) are undifferentiated carcinomas with a prominent lymphoid stroma. They were reported for the first time in the nasopharynx, where they are associated with Epstein–Barr virus (EBV) infection.[1] Lymphoepithelioma-like carcinomas (LELCs) are rare tumors, histologically indistinguishable from undifferentiated nasopharyngeal carcinomas, and they have been reported in salivary glands, thymus, larynx, lung, uterine cervix, urinary bladder and skin.[2] In the gastrointestinal tract they have been described in the esophagus, stomach, colon and rectum. We report the eighth case of colonic LELC.

Case description

An 86-year-old woman, with a clinical history of allergy to penicillin and hemolytic anemia due to G6PD deficiency, was diagnosed and treated in 2011 for a low-grade intestinal adenocarcinoma of the usual type affecting the sigmoid colon (pT3 pN0). Four years later a follow-up a colonoscopy revealed an ulcerated infiltrative mass located in the splenic flexure. The biopsy showed a high grade adenocarcinoma with an immunophenotype consistent with an intestinal origin, and the patient underwent a right hemicolectomy. The tumor was ulcerated and measured 4.5×3 cm. Light microscopy revealed a solid carcinoma with peri and intratumoral lymphocytes (Fig. 1A and B). The aggregates of tumor cells were broken by the presence of lymphocytes and epithelial cells were polygonal with enlarged nuclei and eosinophilic nucleoli. The inflammatory infiltrate was dense and homogeneous. Immunohistochemistry was performed on formalin fixed sections using CDX2, the four mismatch repair proteins (MLH-1, MSH2, PMS-2 and MSH-6) and LMP-1: CDX2 showed extensive nuclear staining and tumor cells showed loss of expression of MLH1 and PMS2 with preservation of MSH2 and MSH6 (Fig. 2). Subsequent molecular studies revealed a V600E mutation of the BRAF gene. The tumor was microsatellite unstable but due to the V600E mutation detected it was supposed to be sporadic and unrelated to Lynch syndrome. LMP-1 and EBER in situ hybridization were negative. The cancer was staged as a pT3 pN0 (IIA) lesion. The patient developed postoperative paralytic ileus, which responded well to standard conservative management, and a urinary tract infection by Enterococcus faecium with a good response to antibiotics. She was discharged with no further adjuvant therapy, due to the lack of lymph node involvement. 22 months after surgery, she remains well with no evidence of recurrent disease.

Discussion

In the gastrointestinal tract, LELCs have been reported in esophagus, stomach, colon and rectum. They are more frequent in the stomach, where approximately 200 cases have been described. We have found only 24 cases in esophagus[1] and 7 cases in colon and rectum[2–8] in the literature.

The clinical and main pathological features of large intestine tumors are summarized in Table 1, including the present case. Patients' age ranged from 25 to 86 years (mean: 65.1 years) and there were 4 males and 4 females. 2 patients complained of abdominal pain, 2 had diarrhea or changes in bowel habit, 1 had iron deficiency anemia and in one patient the tumor was an incidental finding. In the case reported by De Petris et al.[5] the patient had diarrhea, but we cannot attribute the symptoms to LELC as he had 4 synchronous lesions (the largest being an ulcerated and perforated mucinous adenocarcinoma measuring 8 cm). The tumors were widely distributed from the ascending colon to the rectum; the sigmoid colon being the most frequent location. Maximum size ranged from 0.5 to 12 cm (mean: 3.8 cm). Macroscopically, there were 3 ulcerated infiltrative or stenosing lesions, 2 exophytic polypoid tumors and 2 submucosal lesions. In 6 of them, a preoperative biopsy was performed, but a suspected diagnosis of LELC was made in only 2 cases. EBV was found to be positive in one case and two cases were microsatellite unstable. Most of LELCs were first treated by wedge resection. 3 tumors were stage I and 2 were stage IIA. We have not been able to stage the remaining tumors from the data in the reports. Only one showed lymph node metastases. No recurrences were seen after a mean follow up of 7.6 months.

Because of the lack of detailed pathogenetic information on colorectal LELCs, we have summarized the main characteristics from the available literature of gastric LELCs.

Gastric LELCs represent around 1 to 4% of all gastric tumors and 80% of them are VEB positive.[9] VEB-positive tumors can be subdivided into ordinary type and LELC; 15–25% are LELC.[10] The exact mechanism of EBV infection is not known. Gastric epithelial cells do not express CD21 (EBV receptor), but they may express another receptor, or they may interact directly with EBV-infected cells, such as lymphocytes or oropharyngeal epithelial cells.[9] In addition, it has been reported that EBV and MSI are mutually exclusive in gastric LELC. Thus, they can be subdivided in VEB positive and MSI associated, which may have two separate carcinogenic pathways.[11]

In EBV-positive gastric cancer, endosonography typically shows a hypoechoic mass in the third layer, with a larger maximum thickness-to-width ratio than EBV-negative gastric cancer. Using computed tomography (CT), Maeda et al.[12] found that early LELCs showed a focally thickened and enhanced mucosa and advanced lesions presented an obvious thickening of the wall. Kim et al.[13] concluded that the most frequent morphology of gastric LELC was eccentric wall thickening (67.7%), with heterogeneous enhancement (67.2%) or central ulcerations (64.7%). Endoscopically, LELCs usually occur as depressed lesions surrounded by a raised margin, covered with normal mucosa.[14] Preoperative biopsy usually renders insufficient tissue with many artifacts, making a histopathological diagnosis difficult.[1]

Macroscopically, LELCs are ulcerative, expansive and well circumscribed masses. They can be multiple and tumor size ranges from 4 to 32 mm (mean: 10.1 mm).[9,13] When LELC invades the submucosa, a gastrointestinal stromal tumor (GIST), lymphoma, or carcinoid tumor should be suspected.

Microscopically they are undifferentiated carcinomas with cells arranged in nests, tubules or trabeculae with unclear margins (Regaud type), or isolated cells (Schminke type), with a dense intratumoral and peritumoral infiltration of lymphocytes. Plasma cells, eosinophils and neutrophils can be observed and the inflammatory infiltrate typically