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BRIEF REPORT

Primary classic Hodgkin lymphoma of the ileum and Epstein-Barr virus mucocutaneous ulcer of the colon: two entities compared

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Abstract

Primary classic Hodgkin lymphoma of the gastrointestinal tract represents a rare occurrence. A full patient's work-up is essential in order to exclude a secondary intestinal involvement. Histologically Epstein-Barr virus mucocutaneous ulcer closely resembles Hodgkin lymphoma. The differential diagnosis between these two entities is relevant, since both the therapeutic approach and the clinical behavior are different. Herein, we describe a case of primary classic Hodgkin lymphoma arising in the ileum and a case of Epstein-Barr virus mucocutaneous ulcer of the colon, focusing on the main clinicopathological differences.

Keywords Hodgkin lymphoma · Epstein-Barr virus · Mucocutaneous · Ulcer · Diverticulitis

Introduction

Gastrointestinal lymphomas may arise primarily in the gastrointestinal tract (GIT) or involve it secondarily. Classic Hodgkin lymphoma (cHL) generally presents with nodal involvement. Primary extranodal cHL [1] is rare (less than 1% of Hodgkin lymphomas (HLs)). Among the extranodal sites, the GIT [2–7] is the most commonly involved. The diagnosis of primary gastrointestinal cHL requires a complete patient's evaluation attesting the predominance of GIT involvement in the absence of peripheral lymphadenopathy, spleen, liver, and bone marrow involvement. Primary cHL of the GIT is often associated with immunodeficiency, although it can also arise in immunocompetent patients. cHL has been rarely described in the setting of inflammatory bowel diseases [6, 7]. GI involvement in cHL frequently appears as a stricture or an ulcer. A close differential diagnosis is represented by the recently described entity EBV-associated mucocutaneous ulcer (EBVMCU) [8], involving more frequently the mucosa of oropharynx, GIT, and skin. We report two paradigmatic cases of primary GI cHL and EBVMCU, focusing on the overlapping features.

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Clinicopathological findings

Case 1

A 42-year-old immunocompetent, HIV-negative man presented with acute abdominal pain. Computed tomography scan revealed distended small bowel loops and a short ileal stricture. A small bowel resection was performed. Macroscopically the small bowel specimen, 32 cm in length, showed a short stricture, 2 cm long. In the stenotic tract, the bowel wall was thickened, with a cobblestone appearance. Few perivisceral nodes appeared enlarged and whitish in color. Histologically, there was a diffuse infiltrate (Fig. 1a) extending from the mucosa through the whole thickness of the bowel wall, without serosal involvement or visceral perforation. The infiltrate was composed of small lymphocytes, plasma cells, histiocytes, neutrophils, eosinophils, and several, large mononucleated and binucleated cells with evident nucleoli (Fig. 1b). Perivisceral lymph nodes showed a similar

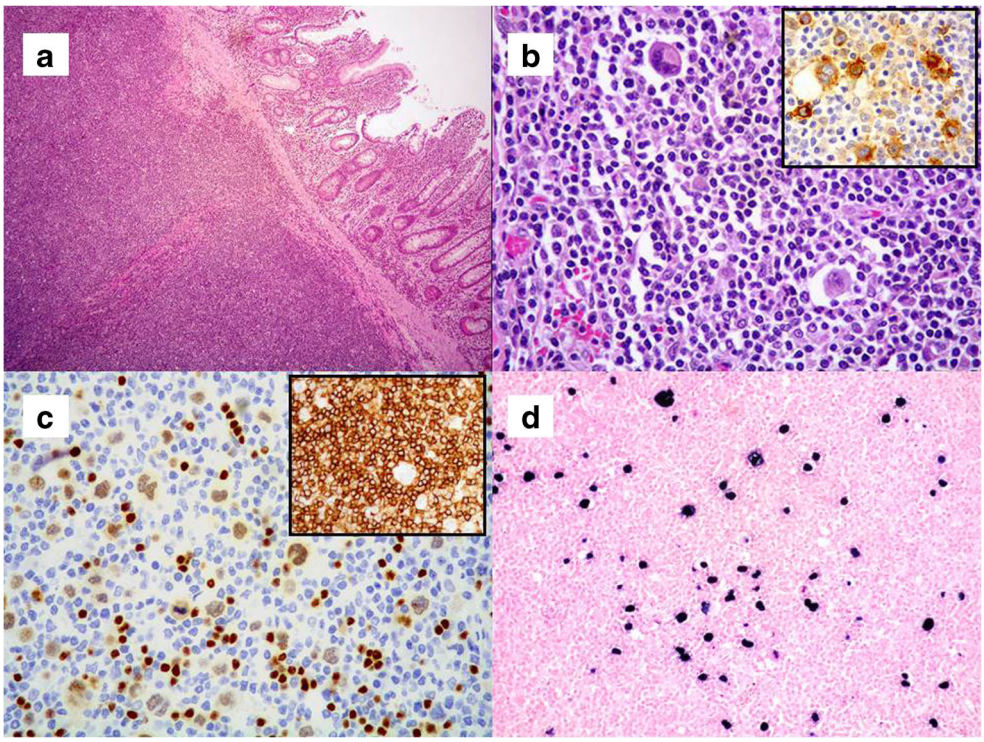

Fig. 1 **a** Hematoxylin & eosin at low power of view show a diffuse lymphoid infiltrate involving the whole thickness of the small bowel wall; **b** at high-power view, the polymorphus infiltrate includes large mononucleated atypical cells that stain positively with CD30 at immunohistochemistry (inset); **c** immunohistochemistry with PAX5 evidence a weak positivity in the large cells associated with a LCA-negative staining in the large, atypical cells (inset); **d** EBER is diffusely positive in the atypical cells

infiltrate. On immunohistochemistry, the large cells were positive for CD30 (Fig. 1b, inset), CD15, PAX5 (Fig. 1c), and MUM1/IRF4 and negative for CD3, CD20, CD79alfa, LCA (Fig. 1c, inset), OCT2, BOB1, and ALK1. In situ hybridization for EBV-encoded RNA (EBER) showed a positive staining in Hodgkin and Reed-Sternberg cells and in few small-sized cells (Fig. 1d). The small lymphocytes on the background were diffusely positive for CD45 and CD3. A full patient's work-up identified no other nodal or visceral involvement. A primary classic Hodgkin lymphoma of the ileum with local node involvement was reported. The patient denied any further treatment. Two years after diagnosis, he developed multiple hepatic and splenic lesions and retroperitoneal lymph nodes involvement and received chemotherapy based on ABVD regimen (Adriamycin, bleomycin, vinblastine, dacarbazine). Six months after the end of chemotherapy, the patient is in complete remission.

Case 2

An 83-year-old woman underwent sigmoid colon resection due to recurrent diverticulitis. She suffered of rheumatic polymyalgia on therapy with methotrexate (2.5 mg/die) and prednisone (5 mg/die) since 5 years. The sigmoid colon specimen (15 cm in length) showed multiple inflamed diverticula and a sharply circumscribed mucosal ulcer. Histologically, the ulcer (Fig. 2a) comprised a mixed infiltrate of small lymphocytes, plasma cells, neutrophils, and scattered, large atypical cells (Fig. 2b, inset) reminiscent of Hodgkin and Reed-Sternberg cells together with some plasmacytoid apoptotic cells. Necrosis was detectable. The infiltrate was well-circumscribed and superficial involving mucosa and submucosa. The large cells were strongly positive for CD30 (Fig. 2c), weakly positive for PAX5, CD79alfa, and MUM1/IRF4 with a variable staining for CD20. These cells were negative for CD15, CD3, BCL6, CD10, OCT2, and BOB1. EBER showed a diffuse positive staining (Fig. 2d) in a range of different cells, from small lymphocytes and plasmacytoid apoptotic cells to large cells with Reed-Sternberg-like cell morphology. Perivisceral nodes were free of disease. Radiological and laboratory exams for a complete postsurgical evaluation were normal. The final diagnosis of Epstein-Barr virus mucocutaneous ulcer was reached. Methotrexate was suspended and 4 months after surgery, the patient is asymptomatic.

Discussion

The GIT is a common extranodal site of lymphoma, more frequently of diffuse large B cell lymphoma (DLBCL) and mucosa-associated lymphoid tissue (MALT) lymphoma.

Primary GI cHL is rare [1, 6, 7] representing less than 5% of GIT lymphomas. The primary nature is established by disease limited to the GIT with or without locoregional node involvement, in the absence of peripheral lymphadenopathy and/or liver, spleen, or bone marrow involvement. GI cHL generally appears macroscopically as stricture, ulceration, or

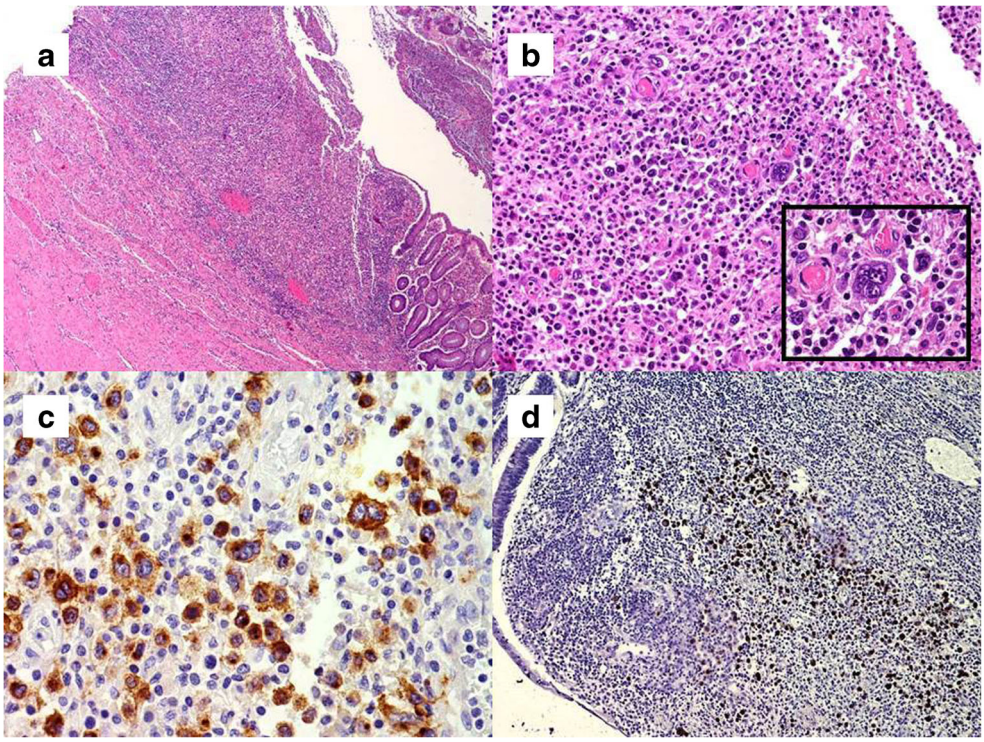

Fig. 2 **a** Hematoxylin & eosin at low-power view show the superficial nature of the lymphoid infiltrate; **b** High-power view shows a mixed infiltrate comprising large, mononucleated, and multinucleated cells which are positive for CD30 at immunohistochemistry (**c**) and for EBER at in situ hybridization for EBV (**d**)

mass-forming lesion associated with transmural neoplastic infiltration.

A challenging differential diagnosis is represented by EBVMCU [8], a recently recognized entity characterized by EBV-positive, isolated and well-circumscribed ulcers involving the oropharyngeal and GIT mucosa or the skin. Firstly described by Elaine Jaffe group [8] in 2010, it is currently identified by the WHO [8] classification of hematological neoplasms as a provisional entity among the EBV lymphoproliferative disorders. EBVMCU is associated with immunosuppression, either therapy-induced or age-related. The hallmark is the superficial nature of the ulcer, in the absence of a tumor-forming lesion. The presence of lymph nodes, spleen, liver, or bone marrow involvement makes the diagnosis of EBVMCU very unlikely. Histologically, the ulcers are characterized by a polymorphus infiltrate including atypical cells with Hodgkin-like features. Plasmacytoid apoptotic cells and necrosis can be present. The base of the ulcer is commonly well-defined by a rim of small CD8+ T lymphocytes. The HRS-like cells show strong CD30 and EBV positivity, with variable expression of B cell markers such as CD20 and variable CD15 expression. The atypical cells generally retain PAX5 and the transcription factor Oct-2, with variable Bob1 expression. In common with cHL, the atypical cells have a post-germinal center phenotype with MUM1 positivity, in the absence of CD10 and BCL6. In up to 40% of cases, monoclonal immunoglobulin heavy chain and T cell receptor (TCR) rearrangement have been identified, suggesting a clonal proliferation. EBVMCU generally pursues an indolent behavior with regression spontaneously or upon reduction of immunosuppressive treatment.

Since the first description, 20 further cases [8–15], including the present case, of EBVMCU affecting the GIT have been reported (Table 1).

The patients (8 females and 12 males) ranged in age between 26 and 83. The sites of GI involvement were as follows: large bowel [8, 11–15] (8), esophagus [8, 10] (3), stomach [15] (2), small intestine [11, 15] (4), cecum and terminal ileum [14] (1), and the anal region [9, 15] (2). Notably, irrespective of site, no mass lesion was detected.

The most common clinical setting was iatrogenic immunosuppression either in post-transplant patients [8, 11, 15] (7) or in the context of inflammatory bowel diseases [8, 9, 12, 13] (4), rheumatoid arthritis [8] (2), and rheumatic polymyalgia (our case). Two cases [15] arose in the context of non-transplant-related iatrogenic immunosuppression for unspecified diseases. In one case, EBVMCU occurred in a patient suffering from hypogammaglobulinemia [10] and it was just EBVMCU identification which prompted further investigation discovering the underlying hypogammaglobulinemia. Three cases [14, 15] of EBVMCU affected elderly patients, with only age-related immunosuppression.

Most GI EBVMCU followed a benign course, responding to reduction of immunosuppression. An exception was the case, by Moran et al. [12], arising in the context of iatrogenic immunosuppression for Crohn disease and progressing to widespread cHL.

Table 1 Features of the reported EBVMCUs of the gastrointestinal tract

Ref.	Sex/age	Site	Clinical setting	Source of immunosuppression	Therapy	Outcome
Dojcinov (2010)	69/F	Colon	Rheumatoid arthritis	MTX	NA	NA
Dojcinov (2010)	78/M	Rectum	Ulcerative colitis	CYA	Reduced IS	CR
Dojcinov (2010)	75/F	Esophagus	Rheumatoid arthritis	AZA	Reduced IS	CR
Dojcinov (2010)	64/F	Colon	Stem cell transplant for MDS	CYA	Reduced IS	CR
Matnani (2014)	63/M	Anus	Crohn's disease	AZA	Cessation of IS	CR
Kleinman (2014)	61/F	Esophagus	Hypogammaglobulinemia	Underlying immunodeficiency	R + IVIG + B	PD
Hart (2014)	61/M	Esophagus	Renal transplant	MMF + prednisone	Reduced IS	CR
Hart (2014)	70/M	Rectum	Renal transplant	MMF + prednisone	Reduced IS + R + velcade	CR
Hart (2014)	32/M	Terminal ileum	Lung transplant	MMF + prednisone + T	Reduced IS + R	CR
Moran (2015)	53/F	Colon and rectum	Crohn's disease	MTX + anti-TNF (adalimumab + infliximab)	Reduced IS	Progression to HL
Juan (2017)	26/M	Rectum	Crohn's disease	AZA + anti-TNF (infliximab)	Cease IS	No benefit, therefore surgery
Osman (2017)	60/F	Cecum + terminal ileum	1 year history of diarrhea + abdominal pain + weight loss	None	Surgery	CR
Natkunam (2017)	79/M	Colon	NA	None	None	PD
Natkunam (2017)	65/F	Stomach	NA	None	NA	NA
Natkunam (2017)	67/M	Intestine	NA	A/I	Reduced IS	CR
Natkunam (2017)	57/M	Small intestine	PT	NA	NA	NA
Natkunam (2017)	68/M	Stomach	PT	NA	Reduced IS	CR
Natkunam (2017)	32/M	Small intestine	PT	NA	R + reduced IS	CR
Natkunam (2017)	64/M	Anus	A/I	NA	R + reduced IS	CR
Present case no. 2	83/F	Sigmoid colon	Rheumatic polymyalgia + diverticulitis	MTX	Surgery	CR

Legend: *MTX*, methotrexate; *CYA*, cyclosporine-A; *AZA*, azathioprine; *MMF*, mycophenolate; *T*, tacrolimus; *R*, rituximab; *B*, brentuximab; *NA*, not available; *IS*, immunosuppression; *PT*, post-transplant; *A/I*, autoimmune or iatrogenic immunosuppression; *CR*, complete remission; *PD*, persistent disease; *HL*, Hodgkin lymphoma;

Table 2 Clinicopathological features of LYG, EBVMCU, EBV+DLBCL-NOS, and cHL

	LYG	EBVMCU	EBV+ DLBCL-NOS	cHL
Clinical course	Grades 1 and 2: uncertain malignant potential (spontaneous remission: 25%) Grade 3: poor prognosis (median survival: 14 mo).	Indolent (resolution upon immunosuppressive therapy reduction). Possible local recurrences	Median survival: 2 years	Mixed Cellularity cHL CR after therapy in 80%
B-type symptoms	Common (often with respiratory symptoms)	No	60%	30–40%
Epidemiology	Underlying primary or secondary immunodeficiency	Underlying immunosuppression (iatrogenic, age-related, post-transplant)	Often no evidence of immunodeficiency	Often no evidence of immunodeficiency
Age	Most frequent in young adults (30–40 yrs)	Mean age > 70 yrs	Most > 50 yrs 10% < 50 yrs	Bimodal distribution 15–25 and 45–50 yrs
Sex	M:F = 2:1	F > M	M:F = 1.4:1	Mixed cellularity cHL: M > F
Site	Lung > 90% (often bilateral); CNS; Skin Liver; Kidney. Uncommon: lymph-node; BM; Spleen; GIT	Superficial ulcers: (skin; oropharyngeal mucosa; GIT)	Extranodal (common: lung, GIT) 70%: extranodal + nodal Only lymph-node: 30% BM: 10%	Lymph-node: common Extranodal involvement rare
Histology				
EBV+ cells	EBV+ large cells, (variable in number according to disease grading)	EBV+ cells of different size (HRS-like cells, plasmacytoid apoptotic cells, small lymphocytes)	Monomorphous subtype: sheets of large EBV+ cells Polymorphous subtype: broad spectrum of EBV+ cells including HRS-like cells	HRS cells (EBV+ in 75% of cases)
Phenotype atypical cells	PAX5+; CD79a+; CD20+; CD30+/−; CD15−; CD45+	PAX5+/−; CD79a+/−; CD20 +/− CD30+ ; CD15 +/−; CD45+/−	PAX5+; CD79a+; CD20+; CD30+/−; CD15−; CD45+	PAX5+ weak; CD79a−/+variable; CD20−/+ variable; CD30+; CD15+/−; CD45-
Reactive T cells	Predominantly CD4+	Many reactive T cells, predominantly CD8+	In polymorphous subtype: reactive cytotoxic T cells	Predominantly CD4+
Vascular change	Frequent lymphocytic vasculitis	NO	NO	Uncommon
Necrosis	Variable and centered around vessels	Necrosis and angioinvasion: 25% of cases	Coagulative necrosis (geographic necrosis)	Geographic necrosis less common
Clonality	Monoclonal IgH rearrangement LYG grade 3: 70%; grade 2: 50%; grade 1: 10%	B or less often T cell clonality may be present (about 40%)	Monoclonal IgH rearrangement in most cases	Monoclonal IgH rearrangement in HRS cells shown by single cell analysis

LYG, Lymphomatoid granulomatosis; *EBVMCU*, Epstein-Barr virus mucocutaneous ulcer; *EBV+ DLBCL-NOS*, EBV+ diffuse large B cell lymphoma not otherwise specified; *CR*, complete remission; *cHL*, classic Hodgkin lymphoma; *mo*, months; *yrs*: years; *HRS*, Hodgkin-Reed-Sternberg; *BM*, bone marrow; *GIT*, gastrointestinal tract

The present case of EBVMCU arose in colon diverticulitis, in an elderly patient on methotrexate for polymyalgia rheumatica. Two main risk factors for developing EBVMCU were present: firstly, long-term, methotrexate-related immunosuppression and secondly, advanced age. An additional risk factor could be the local irritative spine represented by diverticulitis. To the best of our knowledge, this represents the first report of EBVMCU in colon diverticulitis. Chronic and localized mucosal irritation, represented either by IBD [8, 9, 12, 13] or possibly by diverticulitis, may favor the localized proliferation of EBV-infected cells, especially in the setting of immunosuppression.

The differential diagnosis between EBVMCU and other EBV-related lymphoid proliferations can be challenging and has to be based on the combination of both clinical and pathological features (Table 2).

EBV-positive diffuse large B cell lymphoma, not otherwise specified (DLBCL-NOS) [16], can involve nodal and extranodal sites, diffusely effacing the tissue structure, often with geographic necrosis. A broad histological spectrum, from monomorphic to polymorphic lesions, can be present. The monomorphic subtype resembles a DLBCL-NOS, composed of sheets of large cells. The polymorphic subtype is made up of more scattered large B cells, with Hodgkin-Reed-Sternberg-like cells, admixed with many reactive elements. CD30 positivity, associated less often with CD15 expression, can cause difficulties in the differential diagnosis with cHL. However, different from cHL and EBVMCU, EBV-positive DLBCL-NOS shows a clear-cut activated-B cell phenotype, being positive for pan-B cell antigens (CD20, CD79alfa, PAX5) and MUM1/IRF4 and negative for BCL6 and CD10.

Lymphomatoid granulomatosis (LYG)[18] is a rare EBV-driven lymphoproliferative disorder occurring more frequently in patients with underlying immunodeficiency. It is an extranodal disease with exceptional nodal involvement. Lung is the most commonly affected site at presentation, often with multifocal lesions. Patients show respiratory and systemic B-symptoms. Other sites involved with disease progression are the skin, brain, kidney, and liver. Gastrointestinal involvement is rare [17]. LYG consists of a polymorphous infiltrate rich in T lymphocytes, predominantly CD4 positive, and a variable number of EBV-positive B cells, showing an angiocentric distribution. Lymphocytic vasculitis is common in LYG. The disease grading is based on the number of EBV-positive B cells. Distinguishing features of LYG grade 3 compared to EBV-positive DLBCL-NOS are as follows: the absence of a diffuse growth pattern; necrosis centered around vessels; angioinvasion of vessels by CD4-positive T cells.

Classic HL (in particular the mixed cellularity variant) and EBVMCU show some overlapping features. However grossly, primary GI cHL shows a transmural involvement, whereas EBVMCU is a superficial mucosal ulcer, with no mass. A key histological feature of EBVMCU is the large number of EBV-positive cells, including plasmacytoid apoptotic cells, small lymphocytes, and HRS-like cells. An additional feature, not common in cHL, is a rim of small CD8-positive T lymphocytes at the base of the lesion. Noteworthy is that cHL had rarely arisen in the setting of inflammatory bowel disease [6, 7]. Interestingly, Elaine Jaffe group in 2000 [6] reported EBV-associated cHLs (or Hodgkin-like lesions) in a small group of patients with inflammatory bowel disease with features, at least in part, similar, in retrospect, to EBVMCU. Therefore, some of the previously described GI cHL could be reinterpreted as EBVMCU. In the setting of immunosuppressive conditions (as suggested from a personal Elaine Jaffe observation), it could be hypothesized that cHL and EBVMCU may represent different points in the spectrum of an EBV-driven lymphoproliferative disorder. The localized, self-limiting nature of EBVMCU could be owing to a minimal, localized lapse in immunosurveillance over EBV. The identification of EBV in primary GI cHL, arising in the context of inflammatory bowel disease [7] as well as in EBVMCU, supports a pathogenetic role for the virus similar to the lymphoproliferative disorders arising in other immunodeficiency states.

Additional studies are necessary to investigate the spectrum of EBV-driven lymphoproliferative disorders arising in the gastrointestinal tract in conditions of immunosuppression.

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Author contributions MZ made the diagnosis of EBVRMCU and wrote the paper; MCM is the corresponding author and collected the medical history of the patients; RV reviewed the literature data and contributed to the discussion; EF took the photos and made the immunohistochemical analysis of the case of EBVRMCU; AB made the molecular investigations; MZ performed the surgical resections; LDM reviewed the literature data and contributed to the discussion; SA made the diagnosis of LH, took the photos, and made the immunohistochemical analysis of the case of LH. All the authors have reviewed and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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