Intestinal nodular lymphoid hyperplasia and extraintestinal lymphoma – A rare association

P. Monsanto[1], C. Lérias[1], N. Almeida[1], S. Lopes[1], J.E. Cabral[1], P. Figueiredo[1], M. Silva[2], M. Julião[2], H. Gouveia[1], C. Sofia[1]

(1) Gastroenterology Department, (2) Pathology Department, Coimbra University Hospital, Coimbra, Portugal.

Abstract

Nodular lymphoid hyperplasia of the gastrointestinal tract is characterized by the presence of innumerable small discrete nodules involving a variable segment of the gastrointestinal tract. The association between nodular lymphoid hyperplasia and other benign and malignant diseases has been clearly described, with an increased risk of gastrointestinal tumours, namely gastrointestinal lymphoma. However, the association with extraintestinal lymphoma seems extremely rare. The authors present a clinical case of a patient with nodular lymphoid hyperplasia of the small and large intestine that subsequently developed an extraintestinal lymphoma (diffuse large B-cell lymphoma). (Acta gastroenterol. belg., **2012**, 75, **260-262**).

Key words : endoscopy, Nodular lymphoid hyperplasia, Non-Hodgkin lymphoma.

Introduction

Gastrointestinal nodular lymphoid hyperplasia (NLH) is characterized by the presence of small and multiple lymphoid nodules, involving a variable segment of the gastrointestinal tract (1). It occurs in all age groups, but it is more often recognized in children and in adults with common variable immunodeficiency or *Giardia lamblia* infection (2). In the majority of patients it is asymptomatic and represents an incidental finding in ileocolonoscopy (2,3). When symptomatic, clinical presentation is variable and determined by the size and extension of the polypoid nodules and also by the presence or absence of immunodeficiency. Although many others conditions can have a similar appearance NLH is easily differentiated based on histological features. The nodules are found in the mucosa and submucosa and may look like small adenomatous polyps on gross examination. At microscopic level, lesions are characterized by markedly hyperplasic, mitotically active germinal centers with well-defined lymphocyte mantles (4). Immunohistochemistry of germinal centers for CD3, CD20 and Bcl-2 differentiates NLH from a follicular lymphoma presenting as a lymphomatous polyposis (2,3). Although considered benign by most investigators, several case reports document an association with intestinal lymphoma (2). It is also reported the association with acquired immunodeficiency syndrome and primary colon adenocarcinoma (5,6). However, the association between NLH and extraintestinal lymphoma is rare and has been reported only once in the literature, with the resolution of NLH following chemotherapy and recurrence after lymphoma relapse (7).

Diffuse large B-cell lymphoma is a fast-growing, aggressive form of non-Hodgkin lymphoma. It represents about 80% of aggressive lymphoma and about 30 to 35% of all non-Hodgkin lymphoma in adults. Almost 40% of cases have extra-nodal involvement, mainly of the gastrointestinal tract (stomach, ileocecal region), Waldayer's ring, lung, skin, testicle, kidney, bone, thymus or thyroid. Its etiology is not understood but immunosuppression is a risk factor.

The report hereby presented describes a patient who developed an extraintestinal diffuse large B-cell lymphoma after the diagnosis of small-bowel and colon NLH.

Case report

A 62-year-old woman underwent a screening colonoscopy. Numerous small nodular prominences, ± 4 mm length, were identified from descending colon to cecum. Microscopical examination of biopsy specimens showed multiple foci of follicular lymphoid hyperplasia. The patient denied abdominal pain, weight loss, diarrhoea, night sweats or fever. Her past medical history was irrelevant. Family history was negative for inflammatory bowel disease, polyposis syndromes and gastrointestinal malignancies. On examination, she appeared well, with no palpable enlarged lymph nodes. Laboratory tests were unremarkable with a normal complete blood count, erythrocyte sedimentation rate and lactate dehydrogenase, and stool specimens showed no bacteria, ova or parasites. Upper endoscopy was normal and there were no *Helicobacter pylori* or *Giardia lamblia* colonization in gastric and duodenal biopsies. Capsule endoscopy demonstrated innumerous polypoid lesions along the small-bowel. They were mostly diminutive and nodular/sessile except in the distal ileum where they were larger and stalk-like (Fig. 1). Double-balloon

Correspondence to : Pedro Monsanto, M.D., Gastroenterology Department, Coimbra University Hospital, Praceta Mota Pinto, 3000-075 Coimbra, Portugal.
E-mail : pedromonsanto@gmail.com
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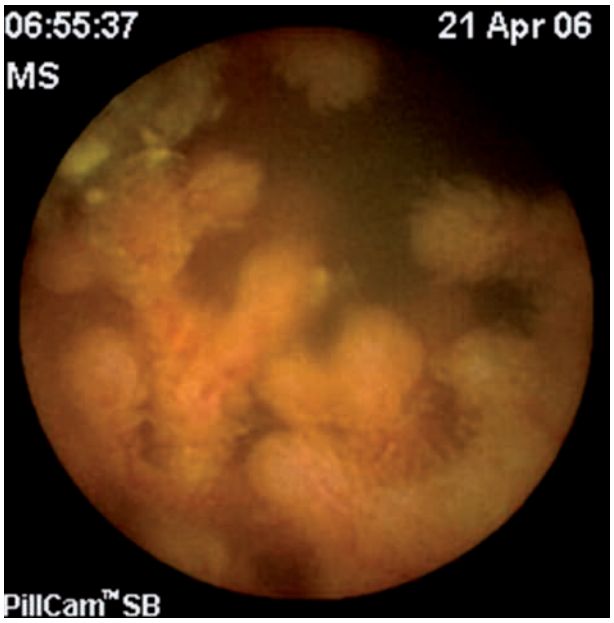

Fig. 1. — Capsule endoscopy : Innumerous polypoid lesions in small-bowel.

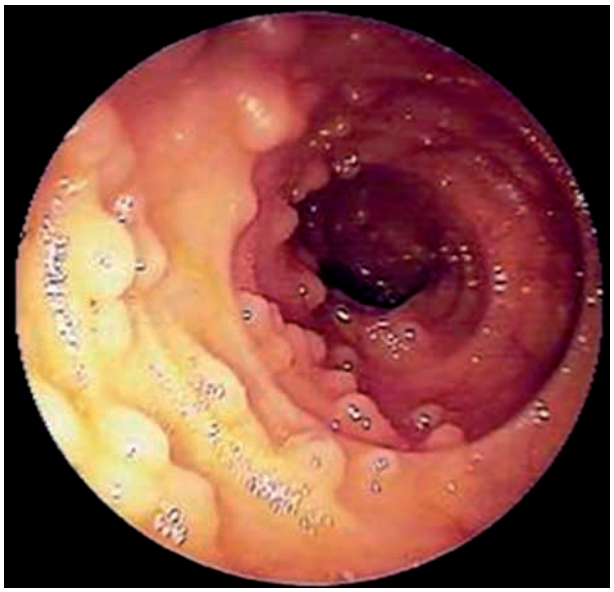

Fig. 2. — Double-balloon enteroscopy : Polypoid lesions in distal ileum.

enteroscopy using the anal route was performed (Fig. 2) and microscopical examination of ileal polypoid lesions was identical to the ones from the colon with immunohistochemistry for CD3, CD20 and Bcl-2 excluding an intestinal mantle cell lymphoma or lymphomatous polyposis. Immunologic and serologic studies (blood smear, immunophenotyping of blood lymphocytes, serum immunoelectrophoresis, serologic testing for human immunodeficiency virus, cytomegalovirus and Epstein-Barr virus) did not disclose any haematological, immunological or infectious disease. A thoracic, abdominal and pelvic computed tomography (CT) was performed with no evidence of enlarged lymph nodes.

The patient was kept under clinical surveillance and after six months she developed various cervical, axillary and supraclavicular adenopathies. She complained of fatigue, sudoresis, anorexia, and weight loss. Cervical and thoracic CT revealed multiple submental, submandibular, axillary and paratraqueal lymphadenopathy. An excisional biopsy of an axillary adenopathy was performed and microscopical examination demonstrated a large cell lymphoma. On immunohistochemistry this neoplasm was positive for CD20 and CD30 but negative for ALK (anaplastic lymphoma kinase) and Bcl-2, compatible with an anaplastic variant of diffuse large B-cell lymphoma. After a short period the patient developed acute renal failure and nephrotic syndrome requiring haemodialysis, and although chemotherapy with a CHOP protocol (cyclophosphamide, doxorubicin, vincristine, and prednisone) has been initiated, the outcome was fatal.

Discussion

The present case illustrates the development of an extraintestinal lymphoma in a patient with NLH of the gastrointestinal tract, the greatest immunologic organ of the human body. Endoscopically, the NLH was characterized by the occurrence of numerous polypoid formations along the small-bowel and part of the colon, whose anatomopathological examination revealed lymphoid hyperplasic follicles shaping the mucosa in discrete protuberances. There are no definitions or valid criteria for when a normal lymphoid tissue becomes hyperplastic, or for when hyperplasia becomes pathologic. The dividing line between physiologic nodules and hyperplasia is thus imprecise (4). In this case report, immunohistochemistry analysis of follicular germinal centers for CD3, CD20 and Bcl-2 excluded an intestinal lymphoma presenting as lymphomatous polyposis.

Although intestinal NLH was initially believed to occur rarely in the absence of overt humoral immunodeficiency, there have been many reports with no abnormalities in humoral immunity (4). The association with immune deficiency, accentuating the role of an inadequate function of lymphoid intestinal tissue, is suggested by the concomitant occurrence of common variable immunodeficiency, hypogammaglobulinaemia and recurrent infections, particularly by *Giardia lamblia*. Approximately 20 percent of adults with common variable immunodeficiency are found to have NLH, usually manifested as chronic or recurrent diarrhea associated with *Giardia lamblia* infection, intestinal malabsorption

or protein-losing enteropathy (4). In the present case, immunoglobulin levels were normal and *Giardia lamblia* identification was negative. The pathogenesis of NLH is unknown, but in concern to the association with hypogammaglobulinemia, Herman's *et al*. suggested that hyperplasia was the result of the accumulation of plasma-cell precursors due to a maturation defect in the development of B-lymphocytes in order to compensate for functionally inadequate intestinal lymphoid tissue (8). On the other hand, the common association between NLH and *Giardia lamblia* infection in the absence of humoral immunodeficiency, provides another explanation for the development of hyperplasia as a result of chronic or recurrent intestinal infection (4). A transition between NLH and lymphoma has been proposed in the presence of atypical cell populations within hyperplastic lymphoid nodules, but till now there is no molecular evidence for a genetic change correlating with such proposed progression (2).

The association between NLH and other benign and malignant diseases has been clearly described. Concomitant HNL, hypogammaglobulinemia and *Giardia lamblia* infection is known as Herman's syndrome (8). Also, in a review of the literature, Jonsson *et al*. documented sixteen cases of NLH associated with intestinal lymphoma, ten of them with no humoral immunodeficiency and all with gastrointestinal symptoms at diagnosis (7). Thus, in the absence of immunodeficiency, the relation between NLH and primary intestinal lymphoma is much stronger. In another review of the literature, Harris *et al*. reported ten cases of non-Hodgkin's lymphoma of the intestine complicated by NLH (9). In a recent series, Rubio-Tapia *et al*. reported eighteen cases of NLH, three of them (17%) associated to lymphoma : nodular sclerosing-Hodgkin's disease on the mediastinum, jejunal lymphoma and gastric lymphoma (10). Only Jonsson *et al*. reported one case of an association between NLH and non-Hodgkin's lymphoma outside the gastrointestinal tract, with complete disappearance of the hyperplasic tissue after chemotherapy at remission of lymphoma and reappearance at relapse. It was suggested that the lymphoid follicles might become hyperplastic due to an intestinal response to an unknown antigen stimulus or could correspond to a paraneoplastic syndrome (7). In the present case there is a chronological association between NLH and diffuse large B-cell lymphoma. It was uncertain if the non-Hodgkin's lymphoma developed from an underlying low-grade lymphoproliferative disorder like NLH (that belongs to the ample spectrum of gastrointestinal lymphoproliferative disorders) or if NLH was the earliest sign of a systemic lymphoproliferative disorder with a preliminary gastrointestinal manifestation. In this latter hypothesis, a chronic non-identified immunologic stimulus, initially manifested by NLH, may perhaps facilitate the selection and development of abnormal B-cell clones and, in last analysis, the progression to non-Hodgkin's B-cell lymphoma.

In conclusion, the fact of patients with NLH present an association with intestinal lymphoma, other intestinal tumours, immunologic disorders and, as demonstrated in this case, extraintestinal lymphoma, makes the clinical and endoscopic surveillance of NLH of critical importance.

References

1. RANCHOLD M., LEWIN K., DORFMAN R. Lymphoid hyperplasia of the gastrointestinal tract. *Am. J. Surg. Pathol*., 1978, **2** : 383-400.
2. SCHWARTZ D.C., COLE C.E., SUN Y., JACOBY R.F. Diffuse Nodular Lymphoid Hyperplasia of the Colon : Polyposis Syndrome or Normal Variant ? *Gastrointest. Endosc*., 2003, **58** : 630-632.
3. MUKHOPADHYAY S., HARBOL T., FLOYD F.D., SIDHU J.S. Polypoid Nodular Lymphoid Hyperplasia of the Terminal Ileum. *Arch. Pathol. Lab. Med*., 2004, **128** : 1186-1187.
4. WANG T.C., ZUKERBERG L.R. Case records of the Massachusetts General Hospital. Case 8-1997 — A 65-Year-Old Man with Recurrent Abdominal Pain for Five Years. *N. Engl. J. Med*., 1997, **336** : 786-793.
5. LEVENDOGLU H., ROSEN Y. Nodular lymphoid hyperplasia of gut in HIV infection. *Am. J. Gastroenterol*., 1992, **87** : 1200-1202.
6. KOREN R., KYZER S., RAMADAN E., GELBER E., VELTMAN V., DREZNIK Z. *et al*. Nodular lymphoid hyperplasia of the small bowel associated with two primary colonic adenocarcinomas. *Tech. Coloproctol*., 1999, **3** : 161-163.
7. JONSSON O.T., BIRGISSON S., REYKDAL S. Resolution of nodular lymphoid hyperplasia of the gastrointestinal tract following chemotherapy for extraintestinal lymphoma. *Dig. Dis. Sci*., 2002, **47** : 2463-2465.
8. HERMANS P.E., DIAZ-BUXO J.A., STOBO J.D. Idiopathic late-onset immunoglobulin deficiency. Clinical observations in 50 patients. *Am. J. Med*., 1976, **61** : 221-228.
9. HARRIS M., BLEWITT R.W., DAVIES V.J., STEWARD W.P. High-grade non-Hodgkin's lymphoma complicating polypoid nodular lymphoid hyperplasia and multiple lymphomatous polyposis of the intestine. *Histopathology*, 1989, **15** : 339-350.
10. RUBIO-TAPIA A., HERNÁNDEZ-CALLEROS J., TRINIDAD-HERNÁNDEZ S., USCANGA L. Clinical characteristics of a group of adults with nodular lymphoid hyperplasia : a single center experience. *World J. Gastroenterol*., 2006, **12** : 1945-1948.