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Case Report

Nodular Intestinal Lymphoid Hyperplasia, a Rare Entity: A Case Report and A Literature Review

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ABSTRACT

The nodular intestinal lymphoid hyperplasia of the small bowel and colon is a rare condition characterized by the presence of one or multiple polypoid lesions. What is most important in the management of this disease is to understand whether or not to perform a surgical resection, which may be unnecessary. And this in light of the fact that there is no unanimous opinion on the carcinogenic potential of this lesion. The case presented by us concerns an ileocecal valve lesion, the preoperative characterization of which was not definitive. There are macroscopic and, above all, dimensional characteristics (during colonoscopy) that can help the clinician in the decision between surgery and conservative treatment. On the other hand, the precise pre-operative diagnosis is very complex. Therefore, taking charge remains difficult.

Our lesion was subjected to a surgical resection in the light of two considerations: 1) the suspicion of a syndromic nature of the pathology (the patient had two other rare lesions in anamnesis); 2) the fact that this lesion was enhancing on scintigraphy, together with the neighboring lymph nodes. The decision to perform a resection (for diagnostic purposes and in the suspicion of an underlying malignant lesion) should not be considered a mistake. In the absence of robust literature on the subject, the type of treatment must be chosen according to each individual case.

Keywords: Lymphoid hyperplasia; Surgery; Pathology; Immune globulins; Papillary tumor; Thyroid

INTRODUCTION

Nodular Intestinal Lymphoid Hyperplasia (NLH) is an inflammatory condition that can result from various pathologies, can be a precancerous condition and should always be investigated to find its origin. It may present with a diffuse nodular form or with a localized form; when in diffuse form it has the appearance of countless nodules of 2 mm-3 mm in diameter without exceeding 10 mm, while in localized form it appears almost always at the level of the rectum and looks like a polyp [1]. NLH defined by markedly hyperplastic, mitotically active germinal centers and well-defined lymphocyte mantles found in the lamina propria and/or in the superficial submucosa [2]. This condition may arise as compensation for insufficient intestinal lymphoid tissue in immunodeficiency, or it may be related to repeated immune stimulation of intestinal lymphoid tissue, such as infection, in immunocompetent patients [3]. It is associated with immunodeficiency, including Common Variable Immunodeficiency (CVID), selective IgA deficiency, and Human Immunodeficiency Virus (HIV) infection [4], and infections, such as Giardia lamblia and Helicobacter pylori.

Approximately 20% of adults with Common Variable Immunodeficiency Disease (CVID) are found to have NLH, an heterogeneous disease associated with a failure to produce immune globulins and protective antibodies. It is diagnosed by low

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levels of serum IgG, IgA, and/or IgM, impaired antibody production to vaccination, and the exclusion of other causes of failure of immunoglobulin production. Patients with this disease have recurrent bacterial infections, autoimmune disorders and a greater tendency towards malignancy.

Selective IgA deficiency is the most common primary immunodeficiency, estimated at 1 in 300 to 700 in Caucasians, (IgA<7 mg/dL with normal or increased levels of other immunoglobulins). Most patients are asymptomatic, although the absence of IgA has been associated with recurrent upper respiratory infections (frequently in those with concomitant deficiency of the IgG2 subclass deficiency), autoimmune disorders, allergic diseases and gastrointestinal diseases, namely NLH [3,5]. The association between NLH, hypogammaglobulinemia, and *Giardia lamblia* infection is known as Herman's syndrome [3,6]. Despite the fact that the small intestine comprises 90% of the mucosal surface area of the gastrointestinal tract, it is a rare site for neoplasia and only accounts for a little over 3% of tumors that arise in the digestive tract [7]; NLH can rarely evolve toward a malignant condition, especially when the cause is not clearly evident [2,8].Often the lesion is benign and indolent and is only found by chance during another examination or presenting nonspecific gastrointestinal signs such as abdominal pain, chronic diarrhea, bleeding, intussusception and obstruction [9]. Treatment is debated especially when the etiology is not obvious. When a trigger is evident, usually its treatment is sufficient to cure the NLH while in its absence the clinic or biopsy mainly influences the therapeutic choices. When possible the lesion can be kept in follow-up or be resected endoscopically. It is not recommended to respect the lesion, except for evidence of malignancy or mechanical/occlusive problems [9]. It is distinguished from a malignant lymphoma by the polymorphic nature of the infiltrate, the absence of significant cytologic atypia, and the presence of reactive follicles within the lesion, and by use of immunohistochemical or molecular analysis [3]. He Li, et al. found that in primitive follicular lymphoma the diameter and density of lymphoid follicles measured at the Whole Slide Imaging (WSI) were significantly greater from NLH [10].

We present the case of a patient with an NLH of the ileocecal valve, without any sign of complication (bleeding or occlusion or, in general, digestive disorders) who we decided to surgically treat with a right hemicolectomy. This decision was made on the basis of the fact that at the staging PET for a lymph node recurrence of papillary neoplasm of the thyroid, the presence not only of an uptake at the cecal level but also of an uptake at the level of the lymph node chain of the ileo-colic vessels. However, the definitive histological examination supported LNH; all the lymph nodes turned out to be the site of NLH [11].

CASE PRESENTATION

The case concerns a 48 year-old female patient, who came to our observation about two years earlier for the presence of a papillary tumor of the thyroid. In her clinical history, the patient had undergone a laparoscopic cholecystectomy ten years earlier and an open appendectomy in childhood. In addition, the neurosurgeons periodically observe her for a right sciatic nerve schwannoma, which is not associated with outright functional impotence. In 2020 she had undergone total thyroidectomy with lymphectomy followed by radio-metabolic therapy. It was a papillary neoplasm of the thyroid. At a routine ultrasound checkup two years after last surgery, the presence of a lesion was found in the right jugular region.

This lesion was then subjected to biopsy which documented the presence of disease recurrence. Immediately afterwards, the patient underwent a PET scan which not only highlighted the presence of the tracer at the cervical level, but also at the level of the cecum and ileocolic vessels (SUV>7). The patient was therefore subjected to a colonoscopy (Figure 1) which showed the presence of a polypoid formation of the ileocecal valve with probable intra-parietal starting, subjected to histological examination.

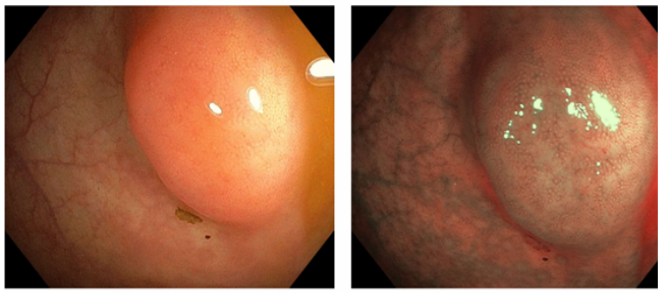

Figure 1: Endoscopic aspect of Nodular Intestinal Lymphoid Hyperplasia (NLH).

The histological report (Figures 2A and 2B) claims that the mucosa and submucosa are the site of edema, vascular congestion with focal blood extravasations and a chronic inflammatory infiltrate and an acute inflammatory granulocytic infiltrate, with the presence of eosinophils, in which no clear attack of the epithelial component is observed and there are no images of lymphatic and epithelial lesions. The immune histochemical study showed positivity for CD45 (LCA), CD 20 and CD3 and negativity for Cytokeratin AE1/AE3 (Figures 2C and 2D); finally, the research for KI67 and BCL-2 turned out to be non-contributory. Therefore, it can be said that the diagnosis of cecal neoformation was an incidentaloma. The patient, in fact, did not present any digestive symptoms. In front of the PET picture of lymph node extension of the uptake, despite the absence of symptoms, we considered it appropriate to operate the patient and to perform a regulated right hemicolectomy (in robotic surgery), the only intervention that would have allowed us to have a definitive histological diagnosis and evaluate the characteristics of the PET-enhancing superior mesenteric vessels lymph nodes. The postoperative course was uneventful. The definitive histological examination reads as follows: in one of the samples the infiltrate, consisting of a lymphocyte population mixed with T cells ($CD3^+$ and $CD5^+$) and B cells ($CD20^+$ and $CD79a^+$) assumes a diffuse distribution overcoming but muscularis mucosae until it infiltrates the lamina propria. This finding is compatible with NLH (lymphoid polyp). Moreover, the Immunohistochemical study performed for CD20, CD3, CD5, CD79a, CD43, BCL-2, BCL-6, CD10, Cyclin D1, CD23, K, Lambda and KI67 chains is compatible with this diagnosis. The removed lymph nodes are the site of reactive hyperplasia.

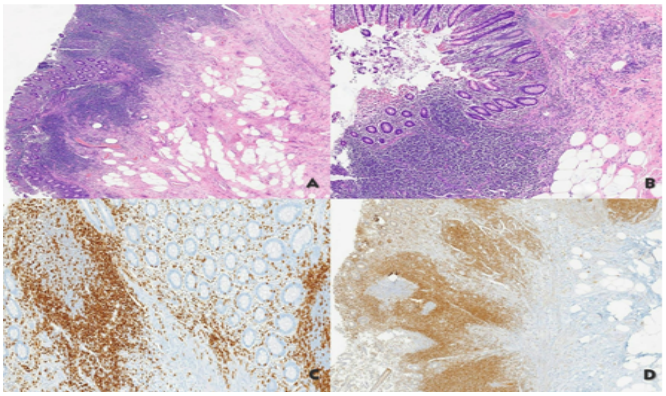

Figure 2: Histological examination endoscopic aspect of nodular intestinal lymphoid hyperplasia. **Note:** A) Benign reactive lymphoid follicles covered by columnar epithelium present in lamina propria and in submucosa; B) Intraepithelial lymphocytes are commonly present over a lymphoid polyp and should not be considered as pathological; C) Positive immunoistochemistry for CD3 in lymphocytes of peripheral zone of germinal centers; D)Positive immunoistochemistry for bcl-2 in lymphocytes of peripheral zone of germinal centers

RESULTS AND DISCUSSION

The problem that arises in reference to NLH is not so much the diagnosis but the treatment. Diagnosis is often complicated and the endoscopic characteristics of the lesion, described as early as 1995 by Bharadhwaj G, et al [12]. in "Colonic lymphoid nodules may appear as red macules, as circumferential target lesions (halo sign), or as raised papules. Nodules may involve the mucosa or the submucosa, in the form of either lymphoid aggregates or lymphatic nodules" are not easily distinguishable by the endoscopist, especially given the rarity of this condition. The same argument can undoubtedly be made for histology. In addition, few cases are described in the literature which does not help us to understand if this condition has no clinical significance and what is the true potential for malignant transformation. In our case, the endoscopist had suspected that it was a Gastrointestinal Stromal Tumor (GIST) and the pathologist could not rule out a lymphomatous lesion. Furthermore, there was a PET uptake not only of the "primitive" nodule, but also of the neighboring lymph nodes. The patient did not have immunodeficiency and infections frequently associated with this disease (*G.Lamblia, H.Pylori*) but had other neoplastic pathologies in her history. Although not symptomatic, in the suspicion of being faced with a "syndromic" neoplastic pathology, we decided, after multidisciplinary consultation, to carry out a regulated resection surgery, which in the end allowed us to exclude the hypothesis of a malignant disease. She will repeat a PET in 6 months and a colonoscopy in a year. Unfortunately, in the literature, even the follow-up modalities of this condition are debated and obscure. The patient, meanwhile, also underwent revision surgery of the neck, which showed, as suspected, the presence of a recurrent lymph node from thyroid carcinoma.

CONCLUSION

Colonic NLH is an extremely rare condition and there are no strict indications for both the diagnostic modalities and the type of therapy. Furthermore, the magnitude of the potential for malignant transformation is unknown. In general, unless there is the appearance of digestive symptoms and the lesion does not exceed 12 mm-15 mm in maximum diameter, careful surveillance is required. However, the decision to perform a resection (for diagnostic purposes and in the suspicion of an underlying malignant lesion) should not be considered a mistake. In the absence of robust literature on the subject, the type of treatment must be chosen according to each individual case.

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