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Nodular Lymphoid Hyperplasia of the Colon in an Adult Patient after Covid-19 Infection: A Case Report and Literature Review

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Abstract

Nodular lymphoid hyperplasia of the colon (NLHC) is an uncommon pathology in adults. The disease can be asymptomatic and discovered incidentally or symptomatic, which is often manifested by abdominal pain and motility disorders (diarrhea, constipation). The clinical presentation can also be alarming with rectal bleeding and obstructive symptoms that may be misinterpreted as a neoplastic process. In this paper, we report the case of a 58-year-old female patient with a previous history of appendicetomy. She presented with persistent abdominal pain, chronic constipation and black colored stools, following Covid-19 infection. The physical examination was unremarkable. Colonoscopy examination found a bulging, non-ulcerated mass, measuring 3.5 cm in greatest dimension, located at the right colic angle. Thoraco-abdomino-pelvic computed tomography was performed and showed right colonic wall thickening and enhanced nodule formation. Furthermore, metastatic localization was not detected. After a multidisciplinary meeting, a laparotomy with right hemicolectomy was performed. Histopathological examination of the surgical specimen revealed nodular lymphoid hyperplasia with CD20+, CD5−, CD10+ and BCL2− phenotype on immunohistochemistry. Besides, lymphocytes in interfollicular area are CD3+ T cells. Patient outcome was favorable after surgery and no additional treatment was necessary. Nodular lymphoid hyperplasia of the colon is a benign process whose endoscopic appearance can sometimes raise suspicion of malignancy. The diagnosis can only be established by histological evaluation. Immunohistochemistry is also essential to confirm the diagnosis and to rule out low-grade

lymphoma. Clinical evolution is often favorable. However, endoscopic follow-up is necessary in all cases.

Keywords

Lymphoid Hyperplasia, Lymphoid Follicles, Covid-19, Colon, Rectal Bleeding, Constipation

1. Introduction

Nodular lymphoid hyperplasia is a benign pathology that most often affects the ileum and is characterized by multiple nodular formations of the mucosa [1]. This pathology, observed mainly in children, is poorly described in adults and the colonic localization is not common [2]. Since its first description by Mahendra *et al.*, in 1978, in California, only 9 cases of lymphoid nodular hyperplasia of the colon in adult patients have been reported in the English literature (**Table 1**). In all these reported cases, the etiopathogenesis has not been clearly elucidated. The disease was revealed by rectal bleeding in 6 cases and was incidentally detected in the remaining cases. No complication, particularly no malignant transformation, was observed. However, local recurrences have been reported in one case after excisional biopsy [2] [3] [4] [5] [6]. In this paper, we describe another case of nodular lymphoid hyperplasia of the colon in a 58-year-old woman, following Covid-19 infection. The aim of this study was to provide a better understanding of this unusual entity and to highlight as well the anatomo-clinical approach in order to avoid diagnostic pitfalls.

2. Observation

A 58-year-old woman with a past history of appendectomy in her childhood, a mild COVID-19 infection in the previous year and no other specific personal or family history, presented for abdominal pain associated with episodes of constipation evolving for a year with occasional black stools. On physical examination, the patient was in good general condition, and afebrile. The abdomen was soft, flat, painless and the remainder of the examination was unremarkable. Colonoscopy revealed the presence of a bulging, non-ulcerated mass at the right colic angle which was biopsied (**Figure 1**). Histological examination of the biopsy specimen did not conclusively demonstrate specific feature. The colonic mucosa appeared edematous, sometimes punctuated by inflammatory infiltrate, mostly composed of lymphocytes. At the same time, a thoraco-abdomino-pelvic computed tomography was also performed and showed right colonic wall thickening (**Figure 2**) and enhanced nodule formation. No metastatic localization was detected. At the chest level, moderate interstitial lung involvement was identified, which may correspond to signs of infectious viral pneumonitis in remission. After discussion at a multidisciplinary meeting, a laparotomy with right hemicolectomy was performed and the surgical specimen was sent for pathological examination.

Table 1. Characteristics of cases of nodular lymphoid hyperplasia of the colon described in adults in the literature.

Patient	Age - Sex (reference)	Localizations	Clinical presentation and associated pathological conditions	Endoscopy and imaging	Histopathological findings	Treatment	Evolution
1	69 - M (4)	Multiples: cecum, right colon, transverse colon, left colon, stomach, duodenum.	- Rectal bleeding - Immunocompetent patient. No dysimmune or inflammatory or neoplastic associated pathology was found.	Multiple polypoid nodules	- Hyperplastic lymphoid follicles with germinal centers. - Absence of neoplastic cell. Disorganized architecture of the mucosa	Therapeutic abstention	- Persistent nodules without complication.
2	23 - M (5)	Multiples and extents from the rectum to the transverse colon.	- Rectal bleeding - Normal immunity, no giardiasis.	Multiple small nodular formations.	Nodular lymphoid hyperplasia	Therapeutic abstention and endoscopic follow-up	- Not available
3	57 - F (6)	Right colon, cecum, terminal ileum.	- Rectal bleeding, abdominal pain, chronic diarrhea, obstructive symptoms. - History of appendectomy in childhood - High blood pressure		- Morphological features compatible with lymphoid lesion.	Laparotomy with right hemicolectomy.	Good evolution after surgery.
4	25 - F (3)	Rectum	- Chronic constipation and rectal bleeding	Nodular area of 3 cm located lower in the rectum, associated with hemorrhoids.	Lymphoid infiltrate in mucosa and submucosa.	Therapeutic abstention	After 2 months: persistent small nodules on sigmoidoscopy.
5	29 - F (3)	Rectum	Incidentally discovered during an antenatal examination.	Polypoid lesion measuring 3 cm in greatest dimension.	Lymphoid infiltrate in mucosa and submucosa.	Endoscopic resection	Good evolution, normal rectoscopy 3 years after resection of the lesion.
6	29 - M (3)	Rectum	Rectal bleeding evolving for 6 months	Nodular rectal mucosa extending over 3 to 4 cm, associated with hemorrhoids.	Lymphoid infiltrate in mucosa and submucosa.	Not available	Absence of complication after 5 years of evolution.
7	55 - M (3)	Rectum	Rectal bleeding	- Colonoscopy: four nodules of 2 to 3 mm in greatest dimension. - Barium enema: Absence of other localizations.	Lymphoid infiltrate in mucosa and submucosa.	Excisional biopsy of the 4 nodules	- Recurrence of the nodules respectively at 4 months and 4 years after their excision. - Good evolution, one year after the last excision.
8	37 - F (3)	Rectum	Incidentally discovered	Polypoid lesion of 3 × 1 cm.	Lymphoid infiltrate in mucosa and submucosa.	Excisional biopsy	Good evolution 20 years after excisional biopsy.
9	30 - F (3)	Rectum	Incidentally discovered	Polypoid lesion of 2 × 1 cm.	Lymphoid infiltrate in mucosa and submucosa.	Excisional biopsy	Absence of follow-up
10	58 - F (present case)	Right colic angle	- Abdominal pain, chronic constipation and rectal bleeding after Covid 19 infection. - History of appendectomy in childhood.	- Colonoscopy: presence of a bulging, non-ulcerated mass, measuring 3.5 cm in greatest dimension, located at the right colic angle. - Thoraco-abdomino-pelvic computed tomography: right colonic wall thickening and enhanced nodule formation.	-Presence of numerous hyperplastic lymphoid follicles in mucosa and submucosa. -Identical morphology within the remaining colonic and ileal walls with a variable amount of lymphoid follicles of varying sizes.	Laparotomy with right hemicolectomy.	Absence of recurrence or complication 6 months after surgery.

On macroscopic examination, the specimen consisted of a 34-cm segment of ascending colon, a 5-cm length of cecum and a 2-cm segment of terminal ileum. After opening, a firm, non-ulcerated, partially stenosing and semi-circumferential

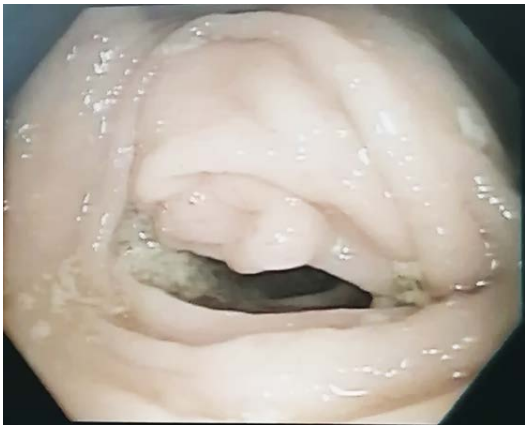

Figure 1. Presence of a bulging, non-ulcerated mass, measuring 3.5 cm in greatest dimension, located at the right colic angle.

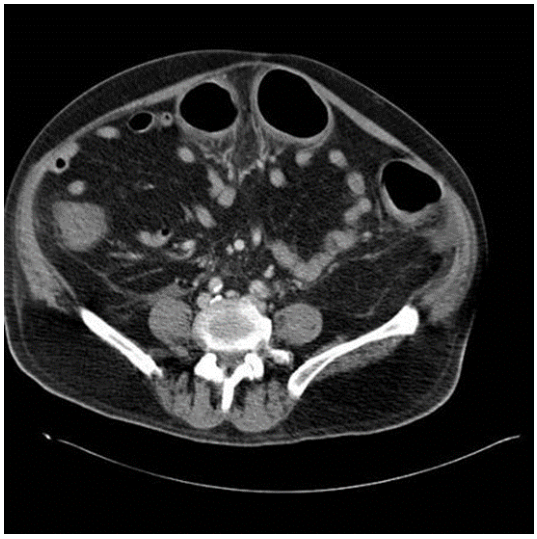

Figure 2. Colonic wall thickening on thoraco-abdomino-pelvic computed tomography.

nodule, measuring 3.5 cm in greatest dimension was observed. The nodule was located at 2 cm from the distal colic excision margin and at a greater distance from the ileal section. The rest of the colonic wall was irregularly thickened and a total of 15 lymph nodes were sampled from the mesocolon. On histology, the nodule reported on macroscopy corresponded to the presence of numerous hyperplastic lymphoid follicles with active and clearly visible germinal centers. These follicles were located in the mucosa and extended into the submucosa (**Figure 3**). The remaining colonic and ileal walls demonstrated identical morphology with a variable amount of lymphoid follicles of varying sizes and lymphocytic infiltrate. No malignant component was observed. All sampled lymph nodes showed follicular hyperplasia and dilated lymph sinuses. The diagnosis of nodular lymphoid hyperplasia was then established. On immunohistochemical examination (**Figure 4**), the lymphoid follicles observed within the nodule were of CD20+, CD5−, CD10+ and BCL2− phenotype, confirming the diagnosis. Besides, lymphocytes in interfollicular area are CD3+ T cells. Further assessment

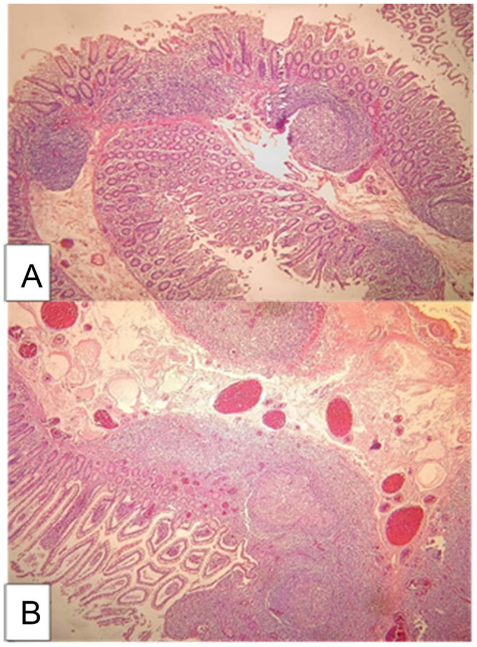

Figure 3. (A) colic mucosa; (B) ileal mucosa: Presence of numerous hyperplastic lymphoid follicles in mucosa and submucosa. (Hematein eosin staining × 200)

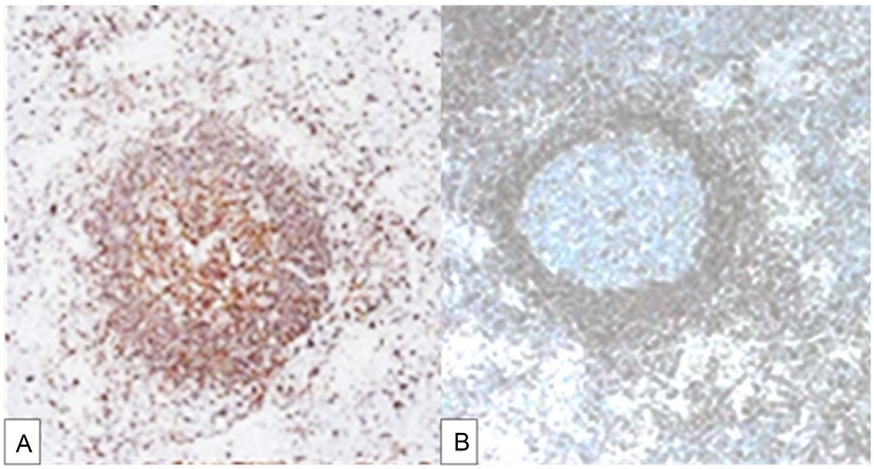

Figure 4. Hyperplastic lymphoid follicle, immunoreactive for CD20 (A) with BCL2 - negative germinal center (B).

was carried out to determine the etiology, including a complete blood count; serum protein electrophoresis; serological tests for hepatitis B, C and *HIV*; a stool testing for parasites, an upper gastrointestinal endoscopy to search for an identical lesion and a *Helicobacter Pylori* infection. All these investigations were normal and the clinical evolution was favorable. This evolution was marked by the resumption of normal transit, the disappearance of abdominal pain and the absence of complications 6 months after surgery.

3. Discussion

Nodular lymphoid hyperplasia of the colon is a benign condition that could be

divided into focal form and diffuse form. The diffuse form, observed in our case, is the most common form. The disease can be also classified into child type and adult type. The child type is often related to viral infection and food allergies. The adult type is less common and little-described [1] [2]. Only 9 cases have been reported to date in the English literature (**Table 1**), including 6 cases localized in the rectum and 3 cases of diffuse forms, extended on the colon and the rest of gastrointestinal tract [2] [3] [4] [6]. In adults, nodular lymphoid hyperplasia can also be observed in other organs (liver, lungs, breasts, etc.) and is frequently described in association with immune system abnormalities (dysgammaglobulinemia, autoimmune diseases, acquired immune deficiency) [7]. In addition, several other conditions can also be implicated, such as infections with *HIV*, hepatitis A, B and C viruses, *Helicobacter Pylori*, *Giardia intestinalis* or celiac disease [1] [7]. The 9 cases of nodular lymphoid hyperplasia of the colon described in the literature were essentially observed in immunocompetent individuals, with no other specific associated diseases [2] [3] [4] [5] [6]. A history of appendectomy was however noted in one of the cases as well as in our patient [6]. According to Dasso and Joseph F. in 1996, an appendectomy could lead to a decrease in secretory IgA of the intestinal mucosa (sIgA) and in serum immunoglobulin concentration, thus possibly constituting another etiopathogenic factor of this disease [8]. Furthermore, the amount of mucosal sIgA is negatively correlated with age, which could support the hypothesis of a local immune deficiency involved in the pathogenicity of this rare pathology with poorly understood causes [9]. In our case, the patient was 58 years old and in the literature the average age of patients was 40.44 years with a sex ratio of 0.8 [2] [3] [4] [5] [6]. Regarding the clinical symptoms, nodular lymphoid hyperplasia of the colon may be asymptomatic and discovered incidentally after paraclinical investigations performed for another reason. Symptomatic forms are often manifested by abdominal pain, chronic diarrhea or an alarming clinical presentation such as rectal bleeding, chronic constipation, or obstructive symptoms that can raise suspicion for a malignant process [6]. In our case, the patient had abdominal pain with chronic constipation and black stools. These clinical manifestations appeared after Covid 19 infection, which could also suggest that this virus may play a role in the pathogenesis of this disease. The diagnosis of nodular lymphoid hyperplasia of the colon is mainly based on endoscopy or barium enema and is confirmed by histology [1]. The lesion is described as a nodule or sessile polyp, 2 to 10 mm in greatest dimension, can reach up to 3 cm and is often multiple [1]-[6]. In our patient, a partially stenosing nodule, measuring 3.5 cm in greatest dimension was detected through colonoscopy, that is suspicious for adenocarcinoma and a laparotomy with right hemicolectomy was performed. The histolopathogical findings of the surgical specimen demonstrated numerous lymphoid follicles that often contained a clear center. These follicles were found in the mucosa and sub-mucosa associated with lymphocytic infiltrate and no lympho-epithelial lesion was noted [2] [3] [4] [5] [6]. Furthermore, the first biopsy performed on the nodule revealed a subnormal, inflammatory colonic mucosa

and could suggest that the sample was superficial, hence the necessity of a deeper and multiple samples to be contributory to the diagnosis. The histologic examination is thus very useful in the diagnosis and particularly to avoid over-treatment of this benign pathology. The main histopathological criterias of nodular lymphoid hyperplasia are characterized by the presence of hyperplastic lymphoid follicles in the mucosa and/or submucosa, associated with mitotically active germinal centers with well-defined lymphocytes mantles [10]. Those criteria were present in our case. Regarding the immunohistochemical profile of these lesions, the lymphoid population is mainly of type B (CD20+) in the follicles and germinal center cells express CD10 but are BCL2− [7] [8] [9] [10] [11]. Immunohistochemical study is often useful to confirm the diagnosis and rule out low-grade lymphoma, which is the main differential diagnosis for this lesion. In the absence of complications, nodular lymphoid hyperplasia of the colon does not require any particular treatment [2] [3] [4] [5] [6]. Therapeutic management is often related to associated pathological conditions (*Helicobacter Pylori*, giardiasis, celiac disease, etc.) [1]-[12]. The evolution is generally favorable, however clinical and endoscopic follow -up is necessary to detect the occurrence of lymphoma or malignant transformation or any possible recurrence [12]. For our patient, no additional treatment was performed and the evolution was favorable 6 months after surgery.

4. Conclusion

Lymphoid nodular hyperplasia of the colon is rarely seen in adults. Although it is benign, the clinical symptomatology and the endoscopic feature can sometimes raise suspicion of a malignant process and lead to overtreatment. The main histopathological differential diagnosis is low-grade lymphoma, hence the interest of immunohistochemistry. The etiology of this disease is still poorly understood. However, several hypotheses have been put forward, including the possible involvement of the SARS-CoV-2 virus mentioned in our case.

Informed Consent

Patient's informed consent has been obtained.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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