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TERMINAL ILEUM OF PATIENTS WHO UNDERWENT COLONOSCOPY: endoscopic, histologic and clinical aspects

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ABSTRACT – ***Context*** - For the diagnosis of the diseases which affect the terminal ileum, the colonoscopy allows macroscopic evaluation and the performing of biopsies. Studies with criteria for the endoscopic and histological characterization of this segment are scarce and there are still some doubts about the need of biopsies in patients with normal ileoscopy. ***Objective*** - Study the terminal ileum of patients who underwent colonoscopy considering: endoscopic and histological correlation; agreement between results of the initial histological evaluation and slides review, and the chance of subjects with normal ileoscopy with abdominal pain and/or chronic diarrhea to show histological alterations. ***Methods*** - In a prospective study, 111 patients who presented smooth mucosa without enanthema in the endoscopic exam of the terminal ileum were selected. Biopsies of the ileal mucosa of such patients were performed, being the slides routinely examined and reviewed afterwards. ***Results*** - The correlation between patients with normal ileoscopy and ileum with preserved histological architecture was of 99.1%. The agreement between initial histological evaluation and slides review calculated by the Kappa test was 0.21. In patients with abdominal pain and/or chronic diarrhea, the chance of showing histological alterations was 2.5 times higher than the others. ***Conclusions*** - The correlation between endoscopic and histological findings was high. The agreement between the initial histologic evaluation and slides review was not satisfactory. The chance of subjects with normal ileoscopy with abdominal pain and/or chronic diarrhea, showing histological alterations was higher in relation to the asymptomatic ones or with other symptoms, although the clinical importance of this datum was not evaluated.

HEADINGS – Ileal diseases. Ileum, anatomy & histology. Colonoscopy.

INTRODUCTION

There can be, in the terminal ileum, toxical substances of bacterial or virus origin, resulting from food digestion, being the relation with the lymphoid tissue fundamental in the protection of this segment. The presence of lymphocytes, macrophages and mastocytes, as a reaction to luminal antigens, can be considered physiologic[4]. Several diseases affect the ileum, mainly in its terminal regions such as: intestinal inflammatory diseases, infectious-parasitary diseases, and less frequently neoplasic lesions.

According to BYRNE et al.[3], the most used exams in the diagnosis of the terminal ileum include radiologic study contrasting with barium and colonoscopy. Besides the macroscopic analysis, the greatest advantage of the colonoscopy is the possibility of performing biopsies[25]. Observing the terminal ileum by means of fiber colonoscopy, NAGASAKO et al.[14], suggested its endoscopic characterization based on the following findings: 1) absence or indistinction of the Kerckring folds; 2) mucosa surface being smooth or with granular appearance due to the lymphoid follicular hyperplasia (LFH); 3) possibility of the villus visualization; 4) thicker wall when compared with the colon; 5) difficulty in keeping distensibility, due to the easy propagation of the air in the cranial direction. Considering the LFH occurrence, NAGASAKO et al.[15] endoscopically classified the terminal ileum in four categories: degree zero – absence of or rarely found granules; degree 1 – scarcely distributed granules; degree 2 – diffuse granules in a not dense way; degree 3 – diffuse granules and density distributed, being able to form clusterings. LFH of the terminal ileum is more frequent in children and young adults, being asymptomatic at times, or manifesting as intussusception, appendicitis and digestive bleeding; in individuals aged over 25 this hyperplasia is rare, however it can be associated with giardiasis, hypogammaglobulinemia and cells B lymphomas[10, 18, 19].

MISRA et al.[13], evaluating 50 individuals with suspection of intestinal tuberculosis and normal ileoscopy, identified non-caseous granulomas in the terminal ileum mucosa membrane of two patients. GEBOES et al.[6], prospectively studied 257 patients with symptoms of inflammatory bowel disease who underwent ileoscopy with biopsy, from these, the histopathologic study was essential for the diagnoses

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of 2 patients with normal ileoscopy. Analysing the terminal ileum of 138 patients undergoing colonoscopy, ZWAS et al.[26] classified the diagnosis of 4 individuals with diarrhea and normal ileoscopy (Crohn's disease in 2 cases, microsporidiasis in 1 and *Mycobacterium avium* growth in 1). YUSOFF et al.[24] and SILVA et al.[21], respectively studying 152 and 162 patients with chronic diarrhea and normal ileoscopy, established that the terminal ileum biopsies were not useful in the diagnosis of these cases.

Due to the doubt concerning the need of the biopsies of the terminal ileum of patients with normal ileoscopy and also the scarceness of studies with criteria for its macro and micro characterization, the aim of this research was to study the terminal ileum of patients who underwent colonoscopy considering: endoscopic and histological correlation; agreement between results of the initial histological evaluation and slides review, and the chance of individuals with normal ileoscopy with abdominal pain and/or chronic diarrhea to show histological alterations.

METHODS

Patients

From June, 2005 to March 2007, patients seen at the Outpatient Department of Coloproctology of "Hospital de Base" (HB) of the Medical School of São José do Rio Preto (FAMERP), São José do Rio Preto, SP, Brazil were prospectively studied. These patients underwent colonoscopic exam by several indications, being them carried out at the Endoscopic Service of the HB by the author of this study himself. Patients with clinical history and or coagulopathy signals were excluded.

During these exams 111 patients were selected, being 47 (42.3%) male and 64 (37.7%) female, age range from 14 to 82 years (51.6 ± 15 years), independently of race, who presented in the endoscopic exam, macroscopically normal terminal ileum mucosa, that is, smooth (absence of granules) and without enanthema.

Initially, the patients were informed about the aim, the importance and the possible complications inherent to the procedures performed in this study and were only included after agreeing and signing the Informed Consent Term. This research was approved by the Research Ethics Committee of FAMERP.

Methods

The column preparation consisted of dieting without residues and ingestion of 750 mL of manitol 20%, initiated 6 hours before the exam. After monitoring the O_2 saturation and cardiac rate with wrist oximeter, patients underwent sedation and analgesia with chloridrate of midazolam at 0.05 mg/kg to 0.1 mg/kg and chloridrate of petidine at 50 mg to 100 mg, slowly ministrated by endovenous way. During sedation, supplementary oxygen in the flow of 2 to 4 L/min was ministrated. The exam was initiated after the patient's positioning at left lateral decubitus with the inferior limbs semi-flexed. The evaluation of the macroscopic characteristics of the terminal ileum was done by videocolonoscopic, Pentax EPM-3500 (Japan), after confirming that the mucosa was smooth and without enanthema, 4 circumferential biopsies were carried out in its distal portion. The samples fixed in formaldehyde were processed, being the histological sections stained in hematoxylin-eosin. The slides were routinely examined by different pathologists and reviewed by a pathologist who did not know the result of the initial evaluations and the clinical data of the patients. For the review, the recommendations of CUVELIER at al.[4] were followed.

Statistical analysis

Considering that the patients with mild ileitis have preserved histological architecture[4], the statistical analysis was done considering two histological conditions: three categories (normal ileum, mild ileitis, and moderate ileitis) and two categories (normal ileum and mild ileitis, and moderate ileitis).

The correlation analysis between the results of the endoscopic and histological evaluation (slides review) of these patients was done through the calculation of simple proportion between patients with macroscopically normal ileum and histologically normal ileum. The same calculation was applied by grouping patients with histologically normal ileum with those with mild ileitis. The agreement between results obtained in the initial histological evaluation, carried out by the routine pathologist and in the slides review done by another specialist, was analysed using the Kappa test[8]. To check whether the result of this test was satisfactory or not, the interpretation suggested by LANDIS and KOCK[11] was used, which consists in <0 (without agreement), 0 – 0.19 (poor), 0.20 – 0.39 (reasonable), 0.40 – 0.59 (moderate), 0.60 – 0.79 (substantial) and 0.80 – 1.00 (perfect). To statistically evaluate if there is significant difference between the chance of individuals with normal ileoscopy with abdominal pain and or chronic diarrhea (lasting for more than 4 weeks) and asymptomatic ones and or with other symptoms, presenting histological alterations identified in the slides review, the Fisher test was used and the Odds Ratio was calculated with the help of the StatsDirect Statistical software (1.617 version).

RESULTS

From the 111 patients with normal ileoscopy (Figure 1), the results of the slides review showed that 72 presented mild ileitis (Figure 2), 38 showed histologically normal ileum (Figure 3) and 1 patient moderate ileitis. The correlation between patients with normal ileoscopy and histologically normal ileum was 34.2%. When the adding of patients with histologically normal ileum and mild ileitis was done, the correlation achieved was 99.1% (Figure 4).

The agreement between the initial histological evaluation and the slides review considering normal ileum, mild and moderate ileitis (Table 1) by the Kappa test was 0.10, that is, poor. Considering the categories A (normal ileum and mild ileitis) and B (moderate ileitis) (Table 2), the agreement was 0.21, that is, reasonable.

In patients with normal ileoscopy, with abdominal pain and or chronic diarrhea, the chance of presenting histological alterations, identified in the slides review was 2.5 times higher in relation to the asymptomatic ones and or with those with other symptoms (Table 3), being the difference statistically significant (OR = 2.515; IC = 1.044 to 6.060; $P = 0.0407$).

TABLE 1. Results of the initial histological evaluation and slides review, considering three categories

Category	Normal ileum[2]	Mild ileitis[2]	Moderate ileitis[2]	Total
Normal ileum[1]	12	15	0	27
Mild ileitis[1]	25	51	0	76
Moderate ileitis[1]	1	6	1	8
Total	38	72	1	111

[1] = initial histological evaluation carried out by the routine pathologist
[2] = slides review done by another pathologist

TABLE 2. Results of the initial histological evaluation and slides review, considering two categories

Category	Normal ileum and mild ileitis[2]	Moderate ileitis[2]	Total
Normal ileum/mild ileitis[1]	103	0	103
Moderate ileits[1]	7	1	8
Total	110	1	111

[1] = initial histological evaluation carried out by the routine pathologist
[2] = slides review done by another pathologist

TABLE 3. Chance of individuals with normal ileoscopy, with abdominal pain and or chronic diarrhea presenting histological alterations identified in the slides review (Fisher test)

	Pain and or diarrhea	Assymptomatics and or other symptoms	Total
Mild and moderate ileitis	32	41	73
Normal ileum	9	29	38
Total	41	70	111

P = 0.0407

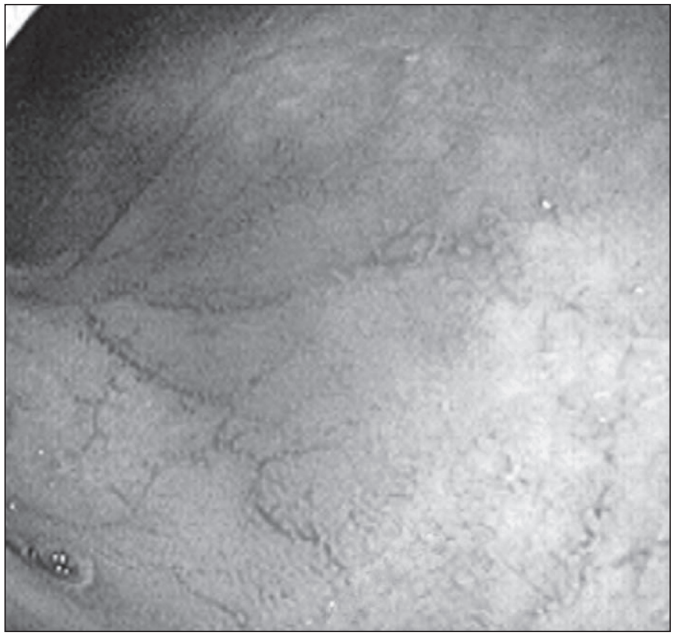

FIGURE 1. Photography showing normal endoscopic image of the terminal ileum (Patient #100, 26, female)

FIGURE 2. Photomicrography of the terminal ileum mucosa showing discrete villus flattening and increase in the quantity of lymphocytes characterizing mild ileitis. (hematoxylin-eosin, 40x) (patient #100, 26, female)

FIGURE 3. Photomicrography of the terminal ileum mucosa histological normal (hematoxylin-eosin, 40x) (patient #78, 57, female)

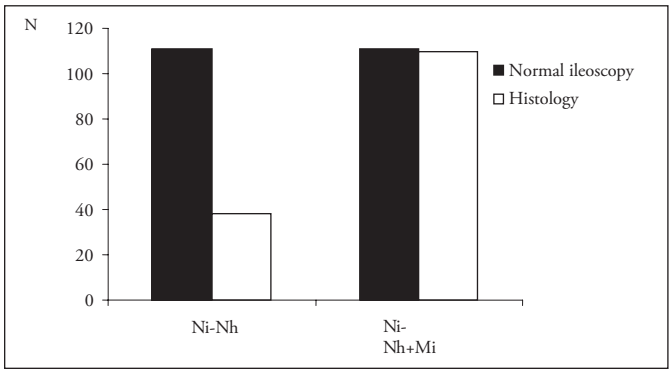

FIGURE 4. Distribution of patients with normal ileoscopy who underwent histological evaluation of the terminal ileum considering normal ileoscopy and normal histology (Ni – Nh) and normal ileoscopy, normal histology plus mild ileitis (Ni – Nh + Mi)

DISCUSSION

In the present research, the terminal ileum of patients undergoing colonoscopy was investigated concerning the endoscopic, histological and clinical aspects. The results showed that the correlation between the endoscopic and histological analysis was high, suggesting that biopsies of this segment can be unnecessary. The agreement between results of the initial histological evaluation and slides review was not satisfactory indicating the need of standardization the terminology and histological parameters as well as the definition about physiological and pathological alterations, using, if possible, clinical data. Individuals with normal ileoscopy, with abdominal pain and/or chronic diarrhea presented 2.5 times more histological alterations in the terminal ileum, although they have been classified as mild ileitis in most of the cases; these findings justify the carrying out of studies about the clinical importance of such alterations.

Only three publications about the description of the endoscopic characteristics of the terminal ileum have been found in the literature. In 1971, NAGASAKO et al.[14], visualized the terminal ileum by means of a fiber colonoscope and described its endoscopic characteristics. GAISFORD[5], in 1974, analyzing 75 ileoscopies, also describes endoscopic aspects of this segment in a similar way to the one described by NAGASAKO et al.[14]; differing only in the age range of the occurrence of lymphoid follicular hyperplasia (LFH). In 1973, endoscopically evaluating the terminal ileum of 66 patients and considering the LFH occurrence, NAGASAKO et al.[15] classified the terminal ileum in categories.

More than three decades later, although it has been possible to carry out ileoscopy in 93% of the patients undergoing colonoscopy[1], both the description and the endoscopic classification of the terminal ileum have stayed unchanged, perpetuating doubtful criteria as the consideration of LFH normal endoscopic aspect. Presently, it is known that LFH in individuals over 25 years of age can be related with infections and neoplasies[7, 9, 10, 12, 18, 19, 22, 23]. Even though there have not been found descriptions or classifications in publications which mentioned endoscopic aspect of the terminal ileum, being reported only as normal ileum[3, 6, 13, 20, 21 24, 26]. It strengthens the idea of the lack of knowledge or not acceptance of them by the scientific community.

Based on such information, the casuistic have been standardized, including only patients with smooth mucosa and free of inflammatory signals. Therefore, in this research, the classification of NAGASAKO et al.[15] was not used, as all the categories included the presence of granules.

In the present study, complications inherent to the biopsies performed in the terminal ileum were not observed, however there are reports of perforation by the biopsy forceps, bleeding, transitory bacteremia e possibility of transmission of a variant of Creutzfeldt-Jakob disease during this procedure[2, 16, 17].

In the terminal ileum the presence of lymphocytes, macrophages and mastocytes, with a reaction to luminal antigens, can be considered physiological, being denominated controlled inflammation, what makes possible the use of different nomenclatures for similar characteristics. Thus and according to CUVELIER et al.[4] it was possible to consider mild ileitis as controlled inflammation along with cases of histological normal ileum mucosa form an only group, as all of them presented preserved histological architecture, in a way that the correlation between macroscopy and microscopy of 34.2% moved to 99.1%. These data suggest that the terminal ileum with smooth mucosa and without enanthema, will have to be considered endoscopically normal.

Due to the immunological characteristics of the terminal ileum, the line between normal and mild ileitis (controlled inflammation) is not precise and indicates subjective criteria, which have probably contributed to the poor agreement among pathologists, when considering the three categories: A - normal ileum (preserved mucosa architecture); B - mild ileitis (preserved mucosa architecture) and C - moderate ileitis (architectural alterations of the mucosa). However, when two categories were considered (preserved mucosa architecture and architectural alterations of the mucosa) it has been noticed a reasonable agreement, probably due to the existence of defined morphological differences between them. These results point the need of establishing objective criteria in the microscopic evaluation of the ileum and considering the existence of cases with inexact alterations in which it is essential to gather clinical and endoscopic information for the diagnosis.

Several authors suggest performing biopsies of the terminal ileum of normal endoscopic aspect in patients with chronic diarrhea and or abdominal pain[3, 6, 13, 20, 26]. Because from the histological study of these cases that the diagnosis of diseases as the Crohn's disease[6, 26], intestinal tuberculosis[13], cytomegalovirus infection[20] and microsporidiasis[26] were possible. On the other hand, YUSOFF et al.[24] and SILVA et al.[21] verified that the microscopical evaluation of patients with chronic diarrhea and normal ileoscopy did not contribute to their patients diagnosis. The non-utilization of a detailed endoscopic description or classification by these authors did not make possible the comparison with the results obtained in the present study.

In this research individuals with normal ileoscopy, with abdominal pain and or chronic diarrhea presented histological alterations 2.5 times higher in relation to the asymptomatic ones and or with other symptoms. Most of these alterations were classified as mild ileitis, being necessary the following up of such patients to evaluate the clinical importance of these findings. Considering that the histologically normal ileum does not totally exclude inflammatory or infectious processes, as in some diseases such as enterocolitis by HIV or bacterious infections with toxins production, mucosa alterations can be minimal or even inexistent[4]; for the diagnosis of the diseases which occur in this segment it would be useful the association between clinical, endoscopic and histological data.

CONCLUSION

In patients with smooth terminal ileum mucosa, without enanthema, the correlation between endoscopic and histological findings was high. The agreement between the initial histological evaluation and the slides review was not satisfactory. The chance of individuals with normal ileoscopy, with abdominal pain and/or chronic diarrhea, presenting histological alterations was higher in relation to the asymptomatic ones or with other symptoms.

Melo MMC, Cury PM, Ronchi LS, Gonçalves-Filho FA, Cunrath GS, Netinho JG. Íleo terminal de pacientes submetidos a colonoscopia: aspectos endoscópicos, histológicos e clínicos. Arq Gastroenterol. 2009;46(2):102-6.

RESUMO – ***Contexto*** - Para o diagnóstico de doenças que afetam o íleo terminal, a colonoscopia permite avaliação macroscópica e realização de biopsias. Estudos com critérios para caracterização endoscópica e histológica desse segmento são escassos e ainda persistem dúvidas quanto à necessidade de biopsias em pacientes com ileoscopia normal. ***Objetivo*** - Estudar o íleo terminal de pacientes submetidos a colonoscopia, considerando correlação endoscópica e histológica; concordância entre resultados da avaliação histológica inicial e revisão de lâminas e chance de indivíduos com ileoscopia normal, com dor abdominal e ou diarreia crônica apresentarem alterações histológicas. ***Métodos*** - Estudo prospectivo, no qual foram selecionados 111 pacientes, que apresentaram ao exame endoscópico do íleo terminal mucosa lisa e sem enantema. Foram realizadas biopsias da mucosa ileal nesses indivíduos, sendo as lâminas examinadas rotineiramente e revisadas posteriormente. ***Resultados*** - A correlação entre pacientes com ileoscopia normal e íleo com arquitetura histológica preservada foi de 99,1%. A concordância entre avaliação histológica inicial e revisão de lâminas calculada pelo teste de Kappa, foi 0,21. Nos pacientes com ileoscopia normal, com dor abdominal e ou diarreia crônica, a chance de apresentarem alterações histológicas foi 2,5 vezes maior em relação aos demais. ***Conclusão*** - A correlação entre achados endoscópicos e histológicos foi elevada. A concordância entre avaliação histológica inicial e revisão de lâminas não foi satisfatória. A chance de indivíduos com ileoscopia normal, com dor abdominal e ou diarreia crônica, apresentarem alterações histológicas foi maior, porém a importância clínica desse dado não foi avaliada.

DESCRITORES – Íleo, anatomia e histologia. Íleo, patologia. Colonoscopia.

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