Introduction

Serrated lesions are a heterogeneous group of colonic lesions considered to be precursors of colorectal cancer through the serrated pathway of carcinogenesis. They can be classified according to the 2019 consensus of the World Health Organization (WHO) into hyperplastic polyp, serrated sessile lesion and traditional serrated adenoma. Hyperplastic polyps are further subdivided into microvesicular hyperplastic polyps and goblet cell-type hyperplastic polyps (►Table 1). Its morphology during the colonoscopy examination can be either polyloid, flat or laterally growing, and its diagnosis is sometimes challenging for the colonoscopist, due to its morphological characteristics and its coloration, sometimes similar to the normal colonic mucosa.

The main serrated lesion precursor of colorectal cancer, through the serrated pathway of carcinogenesis, is the sessile serrated lesion (SSL). SSls account for approximately 20% of all serrated lesions of the colon and compared to the other two subtypes of serrated lesions, they present an intermediate risk of neoplastic degeneration. The hyperplastic polyp is the most...
frequent serrated lesion, corresponding to 75% of serrated lesions, but it is also considered the most innocuous among the three. Traditional serrated adenomas, despite being the least frequent (approximately 5% of the serrated lesions found), have the greatest potential for neoplastic degeneration.1

The serrated lesions carcinogenesis pathway was recently discovered and is now considered to be the precursor pathway of up to 30% of colorectal cancers. This pathway is marked by BRAF gene mutation, CpG island methylation and microsatellite instability.2–22 No genetic cause, however, has been unequivocally identified as being responsible for serrated polyposis syndrome, although a small proportion of cases are related to mutations in the RNF43 gene.3

Serrated polyposis syndrome (SPS) is considered the most prevalent colonic polyposis syndrome in the world. This syndrome, like its analogue for adenomatous polyps, familial adenomatous polyposis (FAP), denotes an increased overall risk of colorectal cancer (CRC) for its carriers. Its diagnosis, treatment and follow-up are hot topics in congresses of coloproctology, gastroenterology and digestive endoscopy, which sometimes lack consensus among specialists.

In this article we will review the most current literature on serrated polyposis syndrome. Our focus will be on practical issues such as diagnosis, treatment and follow-up of these patients, as well as their families. To illustrate the review, we present some reports of cases treated in our department.

**Methodology**

In order to prepare the case reports of the two aforementioned patients, data were collected retrospectively from medical records.

The literature review used the Medline, Lilacs, Scielo and Pubmed database, in addition to consulting journals and textbooks in the area. Scientific articles related to the following theme were used: Serrated Polyposis Syndrome.

**Case Report**

**Case 1**

MIPL, female, 70 years old, asymptomatic, underwent screening colonoscopy on 16/03/2016. The exam pointed eight flat lesions of the colon, with sizes varying between 1 and 2cm. (►Figs. 1 and 2) the lesions were all removed in monobloc, some with a cold snare and others by endoscopic mucosectomy. The anatomopathological analysis evidenced six sessile serrated lesions without atypia, one sessile serrated lesion with mild atypia, and one sessile serrated lesion with moderate atypia.

The endoscopic follow-up recommendation for this patient was annual. Therefore, a new colonoscopy exam was performed on 07/08/2017. The new exam pointed numerous sessile and flat polypoid lesions, as well as scars from previous polypectomies. Five lesions were removed for histopathological sampling and genetic study. (►Fig 3) The anatomopathological analysis showed four sessile serrated lesions that did not evidenced any atypia and one sessile serrated lesion displayed moderate atypia.

After the colonoscopy done in 2017, the risks and therapeutic possibilities were discussed with the patient, and it was then decided to perform a laparoscopic total colectomy, with ileorectal anastomosis and complete mesocolon excision. The surgery was successfully executed on 04/12/2017. The post-surgical anatomopathological study of the specimen showed thirty-nine polyps with a size between 2 and 6mm, twenty serrated sessile lesions and nineteen hyperplastic polyps. The presence of mild atypia was identified in...
4/20 SSL. No intense atypia or malignancy criteria were detected in the specimen examined.

Case 2
NCS, female, 61 years old, asymptomatic, underwent a screening colonoscopy in 2014, in which a serrated sessile lesion was removed. The patient was submitted to a new colonoscopy in 2014, when three other serrated sessile lesions were removed, one of which was larger than 1cm. In 2019, she underwent another colonoscopy, with the removal of a new serrated sessile lesion measuring 1.5cm.

The patient was admitted in our service in 2021, when we repeated the colonoscopy. In this new exam, we identified a flat 2cm lesion with a depressed central area and a non-lifting sign, with high suspicion for malignant neoplasm. Biopsies were performed and, in the same exam, three flat lesions were removed, as well as three sessile polyloid lesions. (Fig 4).

The result of the biopsy of the suspicious area was compatible with serrated adenomatous neoplasm fragments with high-grade dysplasia. Among the resected lesions, the anatomopathological study evidenced two TSAs with low-grade dysplasia, one SSL, two hyperplastic polyps and two tubular adenomas with low-grade dysplasia.

Laparoscopic total colectomy was indicated, with ileorectal anastomosis and total excision of the mesocolon, which was successfully performed on 15/10/2021. (Figs. 5 and 6)

The anatomopathological study demonstrated:
- Well-differentiated adenocarcinoma with submucosal infiltration, originating from a serrated sessile lesion with high-grade dysplasia in the right colon. Submucosal invasion thickness of 3.4mm. No angiolymphatic, perineural invasion or tumor budding was identified. Pathologic staging pT1pN0.
- Ten polyps, five serrated sessile lesions and five hyperplastic polyps, measuring between 2 and 15mm. Presence of mild atypia in one of the serrated sessile lesions.

Epidemiology
SPS is a condition previously considered rare, but which today has an estimated prevalence of 1:238 to 1:127 of colonoscopies performed in patients with positive occult blood in the feces,4 therefore being considered the most prevalent polyposis syndrome in the world.23 A possible explanation for this phenomenon of paradigm shift would be the lack of knowledge about the disease by general practitioners and the underdiagnosis of the condition, as well as the technical difficulties for the colonoscopy diagnosis of the type of lesion that characterizes the syndrome. This condition is usually diagnosed in the fifth decade of life and shows no sex predilection.
The importance of studying this syndrome is linked to its relationship with CRC. Estimates of the incidence of colorectal cancer in SPS carriers, based on some cohort studies, vary widely, with rates between 15% and 35%. Such information corresponds to a CRC risk approximately 5 times greater than that of the general population.

The relationship between smoking and the appearance of serrated lesions is widely disseminated in the literature, which also suggests a potential role for smoking as a causal or triggering factor for SPS. Muller et al. demonstrated a risk of CRC at the time of the initial diagnosis of SPS of 14.7%.

The relationship between smoking and the appearance of serrated lesions is widely disseminated in the literature, which also suggests a potential role for smoking as a causal or triggering factor for SPS. Curballal et al., in 2016, reported in their series that 74% of patients diagnosed with SPS had a personal history of smoking.

Similarly, several studies also demonstrate a relationship between the incidence of SPS and previous treatment for Hodgkin's lymphoma, which suggests that chemotherapy for this condition can mimic cytogenetic changes found in serrated polyposis syndrome.

Diagnosis

The fifth edition of the classification of tumors of the digestive system, carried out in July 2019 by the WHO, established new diagnostic criteria for SPS. The new criteria include:

1) 5 or more serrated lesions proximal to the rectum, all >4mm in size, with at least two >9mm in size.
2) 20 serrated lesions of any size located anywhere in the large intestine, with >4 lesions proximal to the rectum.

To discuss the diagnosis of SPS, we also need to mention the colonoscopy diagnosis of the lesions that characterize the syndrome — the serrated lesions. As already emphasized in previous topics, despite sharing certain characteristics in common, they are a heterogeneous group of colonic lesions, with distinct morphological and pathophysiological behavior.

The hyperplastic polyp, the most common serrated lesion, is found more frequently in the distal colon and rectum, usually has a sessile morphology and a size smaller than 5mm. The opening pattern of crypts is Kudo type II.

The serrated sessile lesion is more commonly found in the proximal colon and its more traditional morphology is the slightly raised one, pattern 0–II of the Paris classification. The crypt opening pattern is type II-O, a variation of Kudo’s II pattern, characterized by more open crypts (O = “open”, open) and fine stippling between the crypts — Figs. 7 and 8.

The traditional serrated adenoma has a more frequent distribution in the left colon and its most common morphology is sessile (1 s of Kudo). The most common crypt opening pattern is IV-S, a variation of Kudo’s original IV pattern, but with poor vascularization, which is characteristic of all serrated lesions — Figs. 8 and 9.

The morphological appearance, mainly of the serrated sessile lesion, as well as the light color like the normal colonic mucosa, which is inherent to all serrated lesions, make its colonoscopy diagnosis challenging. To make this diagnosis even more difficult, the serrated sessile lesion, the main precursor of the serrated pathway, is more frequently found in the right colon, where the detailed examination tends to be technically more difficult. In this context, to optimize this diagnosis, adequate training of the colonoscopist is very important, as well as the use of some tools such as conventional and virtual chromoscopy, the use of 5% acetic acid solution and image magnification.

Treatment

The European Society of Gastrointestinal Endoscopy (ESGE) suggests for patients with serrated polyposis syndrome, in its...
most recent guideline, the removal of all serrated lesions >4mm and those that, regardless of their size, are suspected of having dysplasia on examination of colonoscopy.\(^{21}\)

Sometimes several colonoscopies are necessary to remove all lesions due to their large number and, sometimes, the high degree of technical difficulty of removal. In these cases, the interval between one colonoscopy and the next should be as short as possible, with a return visit being recommended in 1-3 months.

Surgery is usually reserved for invasive lesions or for lesions that cannot be resected endoscopically. For these patients, the decision on the surgical technique to be used is up to the assistant surgeon, but the option of segmental resection should be considered, unlike FAP, which requires a total colectomy.

We emphasize that, even for those patients without the classic indications, the option of surgical treatment can be offered to the patient, which should be discussed on a case-by-case basis with the multidisciplinary team.\(^{24}\)

**Follow-Up**

Once all relevant serrated lesions (>4mm or signs of dysplasia) have been removed in patients with SPS, ESGE suggests surveillance with annual or biannual colonoscopy based on previous colonoscopy findings.

1) Annual: if serrated lesion with dysplasia or >4 relevant serrated lesions on previous examination.

2) Biannual: if there are no criteria for annual surveillance.

The duration of surveillance is not consensual and should be individualized according to the patient’s clinical conditions and life expectancy.

Although some studies suggest a slight increase in the incidence of some extra-colonic neoplasms in patients with SPS, there is no robust evidence that indicates any screening test for extra-colonic neoplasms in this population.

The diagnosis of SPS increases the risk of first-degree relatives of the “index patient” developing colorectal neoplasia. Therefore, a more aggressive family screening in these cases should be considered, such as that suggested by the ESGE (colonoscopy of first-degree relatives of SPS patients aged 45 years and a 5-year interval between one exam and another).

**Discussion**

It is consensual that SPS is a multifactorial condition. There is a wide spectrum of severity among carriers that cannot
simply be ignored for treatment and follow-up purposes. Most cases must be individualized. As an example, we have patient “A”, with SPS due to the diagnosis of 20 hyperplastic polyps measuring 5mm in routine colonoscopy, and patient “B”, with the same syndrome due to the diagnosis of several serrated sessile lesions of up to 2cm scattered throughout the colon, some already with dysplasia. It is evident that management cannot be the same for both patients. When it comes to serrated polyposis syndrome, the guidelines help qualified physicians to seek the best possible management for their patients, however, cases should always be individualized and discussed in a multidisciplinary team.

Another important topic of discussion concerns the diagnostic criteria for SPS proposed by the WHO. This institution stipulates an arbitrary number of lesions, above which the diagnosis of SPS is established. Obviously, the regulation considers epidemiological data from the literature, however, it does not consider other variables such as family history or even distinguish between the three subtypes of serrated lesions, gathering together lesions with very different behavior and rate of neoplastic degeneration such as hyperplastic polyps and the traditional serrated adenoma. This normative, apparently incomplete, portrays the lack of data and knowledge on the part of the world medical community about SPS.

Conclusion
Serrated polyposis syndrome is a condition that was recently discovered and still needs more study. Most guidelines have a low level of evidence, based on expert opinion and case reports. The syndrome, therefore, lacks further scientific basis through randomized and prospective studies to better explain its pathophysiology and biological behavior. We believe the stratification risk for the development of colorectal neoplasia among patients with SPS will be improved with further studies. Thus, a better propaedeutic approach can be used in order to optimize the diagnosis, treatment and follow-up of the patient and his family, as well as to avoid unnecessary and costly tests for both the patient and the health system.

Funding
None.

Conflict of Interest
There is no conflict of interest for any of the authors.

Bibliography