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Assessing the reproducibility of the microscopic diagnosis of sessile serrated adenoma of the colon

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ABSTRACT

Introduction: sessile serrated adenoma (SSA) is a recently described lesion that may be related to the development of up to 15% of colorectal cancers (CRCs).

Objective: to determine the accuracy of morphological criteria for the diagnosis of SSA by assessing concordance between pathologists.

Material and methods: concordance between two pathologists in the diagnosis of serrated lesions of the colon was studied for 195 lesions (187 hyperplastic polyps and 7 serrated adenomas). Size, location, morphology, and sampling method were collected of each lesion. Both pathologists were unaware of the previous diagnosis, macroscopic characteristics, and location of lesions. Possible diagnoses were: SSA, traditional serrated adenoma (TSA), hyperplastic polyp (HP), serrated polyp, tubular adenoma, or mixed lesions. Diagnostic doubts had to be described. Concordance between both observers was assessed using the kappa index (κ). The influence of collected variables on concordance degree was also evaluated.

Results: overall agreement on the histological diagnosis was poor (κ = 0.14), and so was agreement on the diagnosis of SSA (κ = 0.23). Concordance in the diagnosis of SSA improved with size > 5 mm (κ = 0.64) and proximal location (κ = 0.43).

Conclusion: in a real clinical setting, the existing morphological criteria for SSA identification may be difficult to use.

Key words: Sessile serrated adenoma. Diagnosis. Colorectal cancer.

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INTRODUCTION

Under the former generic category of hyperplastic polyps, several morphologic subtypes have recently been differentiated, mainly conventional hyperplastic polyp (HP), traditional serrated adenoma (TSA), and sessile serrated adenoma (ASS) (1). Attention has been focused on the latter because of its implications in the origin of some types of colorectal cancer (CRC). The morphologic changes that characterize SSA stem from abnormal proliferation, which accounts for the growth of these lesions: crypt branching, crypt basement dilation, and "L" or "T" crypts, with growth in parallel to the *muscularis mucosae*. Moreover, with a high power field, mature cells in the proliferative area of crypt basements and the presence of serration at that level can be appreciated (Fig. 1). On the other hand, classic HPs keep narrow crypt bottoms lined by proliferative cells, while serration is limited to the upper third of crypts (2).

At a molecular level SSA also seems to be a distinct entity. A greater frequency of microsatellite instability (MSI) has been shown in SSA *versus* HP or TSA (3). SSA shows a higher frequency of CpG island methylation than conventional HP (4), while showing a higher frequency of *BRAF* gene mutations and a lower frequency of *K-ras* gene mutations *versus* conventional adenoma (5,6). Some authors have suggested that SSA may be a precursor lesion for at least a group of CRCs with MSI through a distinct carcinogenetic pathway known as the serrated pathway (7).

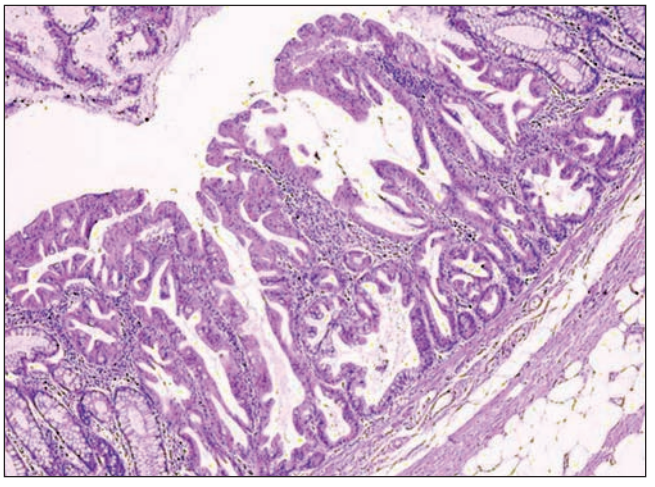

Fig. 1. Sessile serrated adenoma showing serration at the base of the crypt and eosinophilic change in the epithelium. Architectural distortion with hyperplastic changes and hypersecretion can also be found.
Imagen de un adenoma serrado sésil mostrando la serración en la base de las criptas y la presencia de células eosinófilas. Existe además una distorsión arquitectural global con cambios hiperplásicos e hipersecreción mucosa.

Therefore, a reliable identification of SSA and its differentiation from other colonic serrated lesions has important clinical implications, and may condition therapeutic attitudes and endoscopic follow-up (8). However, the diagnosis of SSA based on morphological criteria is not an easy one, since there is some overlapping between SSA, HP, and TSA characteristics. Moreover, some mixed polyps are found that harbor characteristics of two or more morphological subtypes depending on the area (2). However, although this is a known difficulty, few studies have specifically evaluated the reproducibility of the pathologic diagnosis of these lesions, and none have done so in a real clinical setting.

The aim of this study was to assess the efficacy of morphological criteria for the diagnosis of SSA by evaluating agreement degree between pathologists for the differentiation of serrated polyps (SSA, TSA, HP).

MATERIAL AND METHODS

Prior to the beginning of the study a review and a discussion session on the morphologic criteria of SSA, TSA and HP was performed following the nomenclature and criteria of Snover et al. (2). Then, 195 lesions with a previous pathologic diagnosis of HP or serrated adenoma were selected from a database of 290 colonoscopies performed by the same endoscopist since May 2004 to January 2006. The database also included information about size, location, method of sampling [biopsy forceps, endoscopic mucosal resection (EMR), polypectomy], and on the morphology of lesions following the Paris Classification (9).

Two pathologists with special interest in gastrointestinal pathology evaluated those lesions giving a diagnosis of SSA, TSA, HP, serrated polyp, tubular adenoma or mixed lesions. If in doubt, a diagnosis was given but the doubt had to be described. Each pathologist was unaware of the diagnosis of the other pathologist, and both pathologists were unaware of the initial diagnosis, the morphologic characteristics, and the location of lesions. The results were included in a database specifically built by the only non-pathologist member of the group.

Overall agreement and agreement for SSA, TSA and HP diagnosis between the two observers were assessed by the kappa index (κ). The influence of the collected variables on κ was also assessed. To compare the characteristics of the lesions in which agreement was achieved to those of lesions without agreement, the Chi-squared test with Yates' correction or Fisher's exact test for qualitative variables and Student's t-test for quantitative variables were used as needed.

RESULTS

The initial diagnosis of the 195 lesions was HP in 187 (95.9%) and SA in 8 (4.1%) cases. Their main characteristics are summarized in Table I. From these lesions, pathologist 1 diagnosed 103 HPs (52.8%), 31 SSAs (15.9%), and 8 TSAs (4.1%), while pathologist 2 diagnosed 173 HPs (88.7%), 6 SSAs (3.1%), and 4 TSAs (2.1%).

Table I. Characteristics of all 195 lesions

	n (%)
Size ≥ 5 mm	12 (6.1)
Location proximal to splenic angle	25 (12.8)
Protruded morphology	90 (46.2)
Mucosectomy or polypectomy	2 (2.0)

Agreement in the diagnosis of both pathologists was found for 108 lesions (55.4%). Overall agreement was poor (κ = 0.14). In 93 out of 187 lesions with an initial diagnosis of HP, this diagnosis was confirmed by both pathologists (49.7%). The diagnosis was modified from PH to SSA by pathologist 1 in 30 lesions (16.0%), and by pathologist 2 in 6 lesions (3.2%). Four out of 8 SAs were confirmed as HP by both pathologists. Table II summarizes overall agreement and agreement as stratified by size, location, and morphology for the three categories. Table III summarizes the main characteristics of lesions with agreement and of those without agreement, as well

Table II. Agreement on each diagnosis

Category	κ *lesions > 5 mm*	κ *proximal lesions*	κ *protruded lesions*	κ *EMR lesions*	κ
SSA	0.64	0.43	0.29	0.5	0.23
HP	0.08	0.18	0.12	NC	0.12
TSA	NC	-0.05	-0.03	NC	-0.03
Overall	NC	0.24	0.14	NC	0.14

NC: non-calculable; EMR: endoscopic mucosal resection.

Table III. Characteristics of lesions with *vs.* without diagnostic agreement

	Agreement	*No agreement*	*Agreement on SSA*
n	108	87	5
Size (median, range)	3.7 (1-15)	3.6 (1-15)	7.6 (4-15)
Size > 5 mm	6 (5.3%)	6 (6.8%)	3
Protruded morphology	56 (51.9%)	49 (56.3%)	4
Proximal location	12 (11.1%)	13 (14.9%)	1
EMR	2 (1.9%)	2 (2.2%)	1

SSA: sessile serrated adenoma; EMR: endoscopic mucosal resection.

as the characteristics of lesions in which agreement on a diagnosis of SSA was achieved. Eighteen lesions were doubtful for pathologist 1 and 32 for pathologist 2. ASS *vs*. HP was the most frequent doubt for both pathologists (pathologist 1, 33.3%; pathologist 2, 54.8%).

DISCUSSION

In recent years, the hypothesis of a serrated carcinogenetic pathway has been increasingly accepted. Following this hypothesis, a group of sporadic CRCs would originate in serrated lesions of the colon, mainly SSA. Around 8-15% of all CRCs may be originated in SSAs (10), therefore it is of utmost importance to accurately identify serrated lesions with predisposition to progress to CRC, and to differentiate them from those with less malignant potential. However, although SSA was described years ago, this diagnosis has not been widely used in daily practice. To this situation likely contributes the fact that morphological criteria are difficult to put into practice because of overlapping between different subtypes of serrated lesions and even within the same lesion. There is no clear consensus about the nomenclature of serrated lesions of the colon either (11). Finally, the risk of developing a CCR from these lesions is not fully characterized, and the endoscopic follow-up schedule is not defined.

Although many studies regarding serrated lesions have been recently published, most of them are reported by experts in specialized units; therefore their results may not be applicable to a majority of centers. In fact, the differentiation of serrated lesions may be more difficult in daily clinical practice since pathologist experience has been correlated in some reports with a correct diagnosis of these lesions (11).

Our results show that overall concordance for the diagnosis of serrated lesions of the colon is poor. Farris et al. (12), in the only report with a similar design, found a moderate overall concordance (κ = 0.55). However, in this study, polyps smaller than 5 mm were excluded, this size representing more than 60% of all adenomas found in some series (13), which thus limited the generalization of this result. Lesion size is relevant in order to obtain a reliable pathological diagnosis, since minute lesions removed with biopsy forceps are more difficult to position. Because most diagnostic characteristics are present in the crypt base, a well-oriented section is fundamental for the discrimination of serrated lesions. Therefore, the fact that in our report a large percentage of lesions (94%) had a size smaller than 6 mm may explain the low degree of overall agreement. To overcome this problem it is advisable, when facing minute lesions, to obtain multiple stepped sections of tissue to find a section with a well-oriented basal portion of crypts (2).

In our study the greatest agreement was obtained for the SSA diagnosis, and it was poor. However, agreement improved with size, removal using EMR, and proximal location. Size was the variable most related to degree of concordance, with good agreement for lesions larger than 5 mm. The slight influence of EMR removal on concordance may be explained because this technique was applied for lesions larger than 5 mm. No study has specifically assessed the influence of the sampling method on diagnostic agreement; therefore no comparisons can be done. However, other authors have shown that the classification of serrated lesions is more difficult to apply in superficial and tangentially cut lesions, and in small and fragmented lesions (14), while an en-bloc excised lesion is easier to orientate and diagnose.

The lesions in which agreement was achieved were similar to those without agreement, except for those diagnosed as SSA by both pathologists, which were larger and located in the right colon. These lesions might be most clinically relevant because of their greater MSI prevalence and their relationship with sporadic CRC with MSI at the same location (15). However, in spite of being similar to those of other authors, these results must be taken with caution since agreement on the diagnosis of SSA was only achieved for 5 lesions.

The most frequent doubt for both pathologists was between SSA and HP. This is also the most frequent doubt reported in the literature (2,11,12), and it is gen-

erally attributed to the intermediate characteristics of many lesions. In the present report, pathologists did not diagnose a SSA if clear architectural criteria were not present, thus explaining the low prevalence of these lesions in our sample. Probably, if pathologists had known more data, like the location and size of lesions, or if patients had more serrated polyps, more SSAs would have been diagnosed. However, some authors have not found any influence of knowledge of some lesion characteristics on the degree of concordance (12). Snover et al. (2) have suggested than the main difficulty is distinguishing SSA from microvesicular HP, but in this study HP subtypes were not taken into account.

SSA represents 10% of all colonic polyps and around 20% of all serrated lesions (6). In this series, which included only polyps with serration, 3% and 16% of lesions were classified as SSAs by pathologist 1 and pathologist 2, respectively, which was consistent with the literature (14). These are significant percentages, thus failing to accurately diagnose these lesions represents an incorrect assessment of CRC risk for some patients, with consequences for CRC screening and post-polypectomy follow-up programs.

In conclusion, our report suggests that, in daily practice, the existing morphological criteria for SSA diagnosis using routine histological techniques do not provide the necessary reproducibility for an accurate pathological diagnosis. Lesion size and sampling method influence classification; therefore the endoscopist must be especially careful in obtaining the best possible tissue specimen. Lastly, taking into account the clinical importance that a reliable diagnosis of SSA may have, and the difficulty of morphological diagnosis, the identification of specific biological markers for SSA seems necessary.

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