ORIGINAL STUDY

Immunohistochemical insights into the pathogenesis of colonic sessile serrated lesions

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ABSTRACT

Background: Sessile serrated lesions (SSLs) are recognized as precursor lesions in the pathogenesis of colorectal cancer, particularly in the context of microsatellite instability (MSI). This study evaluates the role of immunohistochemical (IHC) markers in understanding the molecular and immunologic characteristics of SSLs. Materials and Methods: A retrospective analysis was performed on 45 colonic neoplastic lesions diagnosed as SSLs. An IHC staining panel was conducted, including MLH1, p53, CD44, CD3, CD8, MUC2, MUC5AC, MUC6, chromogranin and Ki67 antibodies. Results: MLH1 and p53 expressions showed correlations with dysplastic changes. Immunological markers CD3 and CD8 indicated a variable immune response, potentially reflecting the tumor's ability to evade immune surveillance in certain situations. CD44 was overexpressed in all SSLs. The number of neuroendocrine cells was overall reduced. Conclusions: SSLs are heterogeneous lesions, exhibiting a wide range of histological and molecular features. Using IHC might enhance diagnostic accuracy, particularly in lesions with ambiguous histological features, when dysplasia develops. Accurate identification of SSLs and understanding their molecular characteristics are crucial for assessing their malignant potential.

KEYWORDS: sessile serrated lesion; colorectal cancer; dysplasia; MLH1; CD44; microsatellite instability

INTRODUCTION

Colorectal cancer is one of the most prevalent cancers globally, ranking third in incidence [1]. There is a significant health concern due to its potential for early detection and treatment. Serrated lesions, such as sessile serrated lesions and traditional serrated adenomas, are important precursors to colorectal cancer. Serrated pathway is one of the major mechanisms, responsible for as many as 30% of sporadic colorectal cancers [2-4], distinct from the traditional adenoma-carcinoma sequence.

Sessile serrated lesions have distinct histological features that help differentiate them from conventional adenomas and other colorectal lesions. The most defining feature is the "sawtooth" or stellate architecture of the epithelium.

According to the World Health Organization (WHO) Classification of Digestive System Tumours, 5th edition (2019), serrated lesions are classified into four categories: hyperplastic polyps (HP), sessile serrated lesions (SSL), traditional serrated adenomas (TSA) and serrated adenomas, unclassified [4]. Various terms, such as sessile serrated adenoma or sessile serrated polyp, have been used to describe SSLs, leading to confusion in clinical practice. WHO 2019 recommends using the term sessile serrated lesion to provide clarity and consistency, emphasizing the need for careful evaluation due to their potential to progress to colorectal cancer.

The prevalence of serrated sessile lesions in the studies published in the literature varies between 3 and 20% among colorectal polyps. They represent 10-25% of all serrated lesions [5, 6]. The reported prevalence of SSL with dysplasia (SSLD) also varies widely, ranging from 3.7% to 42.9%, reflecting probably different study populations [5]. They are most commonly located in the proximal colon (70-80%), particularly in the cecum and ascending colon, sometimes on the top of a mucosal fold. These lesions are often larger than 5 mm, are sessile or flat, with poorly defined margins and an adherent mucous cap. When the bowel is inflated during endoscopy, SSLs may adopt a flatter appearance [4]. This makes them more difficult to visualize and overlook, or sometimes they are incompletely resected, important aspects which contribute to interval post-colonoscopy colorectal cancers [7,8]. Serrated polyps share common features with interval post-colonoscopy colorectal cancers, including location in the right colon and microsatellite instability, with a CpG island methylator phenotype-high [7].

SSLs present architectural alterations, including serrations involving the entire length of the crypts, dilation of the crypt base, asymmetric dilation, and horizontal growth along the muscularis mucosae, all of which are associated with an

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abnormal location of the proliferation zone. In order to diagnose a SSL at least one unequivocal architecturally distorted serrated crypt is required [4]. Well-oriented sections that adequately visualize the crypt bases are crucial for accurately assessing the architecture of the lesions.

Dysplasia can develop in some SSLs, with a larger variety of architectural and cytological changes compared to conventional adenomas. The latest WHO classification distinguishes between two main types of dysplasia in SSLs: serrated dysplasia, characterized by dense eosinophilic cytoplasm, reduced serrations, round atypical nuclei, with prominent nucleoli and adenomatous dysplasia, similar to dysplasia in conventional adenomas [4]. Other two types of dysplasia have been described in the literature: minimal deviation dysplasia, with subtle cytological and architectural abnormalities, which requires loss of MLH1 immunohistochemical expression to support the diagnosis and the most common variant - dysplasia, not otherwise specified, which encompasses cases that do not fit into the previous categories and frequently associate MLH1 loss [9,10].

The boundary between the dysplastic and non-dysplastic areas is usually well-defined, and this clear delimitation helps pathologists identify the extent of dysplasia and assess the risk for malignant progression. Grading dysplasia can be subjective and is not recommended in the latest WHO classification [4], due to significant morphological heterogeneity of SSLs. More than one pattern of dysplasia is usually identified in SSLs [9].

SSLs are characterized by BRAF gene mutation and are considered important precursors of sporadic colorectal carcinoma with a microsatellite instability phenotype, due to methylation of promoter region of MLH1 [2,4,11]. Still, despite all efforts, the progression of serrated lesions to dysplasia and cancer is not completely understood.

MATERIAL AND METHODS

This study is retrospective and includes 45 sessile serrated lesions, cases examined at the National Institute of Pathology "Victor Babes", from Bucharest, Romania, between January 1, 2021 - October 1, 2024. The polyps included in the study were removed by polypectomy (en bloc or piecemeal), by endoscopic mucosal resection or submucosal dissection, during colonoscopy. Cases diagnosed as SSL by biopsy were excluded from the study. The patient's personal data, including age, gender, location, and dimension of the lesions were collected from the pathology request form or colonoscopy report, when available. Also, we searched for relevant information related to the patient's history and to identify the presence, type, and number of any neoplastic precursor lesions in other regions of the colon. Statistical analysis was performed using the SPSS software.

Formalin-fixed, paraffin-embedded tissue blocks were initially sectioned for Hematoxylin–Eosin (HE) staining. Subsequently, other sections were performed for immunohistochemistry, used to assess the expression of MLH1, p53, CD44, CD3, CD8, MUC2, MUC5AC, MUC6, Ki-67 and chromogranin. Each sample, with a 4 µm thick section, was processed using either the BenchMark Ultra (Ventana) or Autostainer Link 48 (Dako Agilent), in accordance with the respective protocols.

Normal colorectal mucosa adjacent to the lesions was used as control, to establish baseline expression levels of these markers and provide comparative data for SSL and SSLD. A semiquantitative evaluation was performed. Each marker was evaluated based on staining intensity. The intensity was classified as weak, moderate, or strong intensity. Complete absence of nuclear expression within neoplastic cells was considered indicative of MLH1 deficiency, in the presence of a positive internal control. p53 expression was considered aberrant when strong, diffuse, or complete absence of nuclear reactivity was seen in most dysplastic cells. The pattern of mucin expression was classified as diffuse, focal, or absent. To quantify CD8+ T-cell intraepithelial lymphocytes, 100 epithelial cells were randomly selected and counted per tissue section. The presence of membranous CD44 staining intensity and its distribution pattern in epithelial cells was recorded.

The study was conducted in accordance with the Declaration of Helsinki and was approved by Ethics Committee of Victor Babeş National Institute of Pathology (approval number 126/13 May 2024). All the patients signed the written informed consent.

RESULTS

The information retrieved from colonoscopy reports includes: 19 males and 26 females, with a mean age of 61.51 ± 9.73 years, ranging from 37 to 80 years. Most SSLs were in the right colon (35) versus the left (10) and had a mean size of 11.24 mm (range: 5 mm – 25 mm). One patient had a history of colonic adenocarcinoma. Other polyps were removed during colonoscopy, including conventional adenomas that were found in 14 of our patients (ranging from 1 to 5 lesions, four of which were advanced). 11 patients had other serrated polyps, like SSLs without dysplasia, TSA developed on a SSL and hyperplastic polyps.

At the colonoscopic examination these lesions were described as sessile or flat (Figure 1) and only one of them had a pedunculated appearance. This polyp had 22 mm in the largest dimension and presented intestinal dysplasia and pseudoinvasion. A pedunculated form of SSL is rare, and those polyps, especially of large dimensions, tend to develop more commonly dysplasia [5,12].

The diagnosis of SSL was established following WHO 2019 criteria [4]. 18 SSLs presented dysplasia, of which two had a diagnosis of high-grade dysplasia and one of intramucosal adenocarcinoma. None of the SSLs had serrated dysplasia or submucosal invasion. The remaining lesions were diagnosed as SSL without dysplasia.

The most obvious histological changes in SSLs without dysplasia that we examined are architectural abnormalities, including excessive serrations, unequivocally dilatation of the lower third of the crypts, "boot" or "anchor"- shaped crypts, branching of crypts. However, sometimes, especially in smaller lesions and due to lack of a proper orientation of the specimen, the serrate aspect was not so obvious, and additional sections were required in order to differentiate a hyperplastic polyp from a SSL. Neoplastic cells have abundant mucin, either in the form of microvesicular or large mucin droplets, with some goblet cells having a dystrophic aspect; extracellular mucin was also seen, in dilated crypts and in the case that associated pseudoinvasion (Figure 2). Small areas with eosinophilic cytoplasm and elongated penicillate nuclei, reminiscent of another serrated lesion (TSA), were seen, on the surface.

Crypt herniation, another common feature in SSLs [13], was identified in 6 cases. Herniation of crypts through the

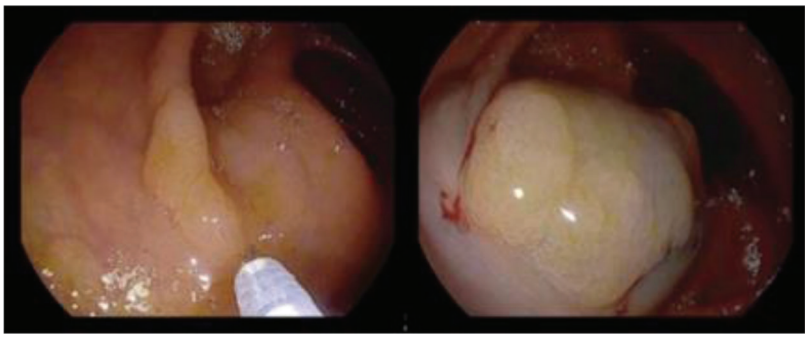

Fig. 1. Sessile serrated lesions, with a characteristic adherent mucous cap.

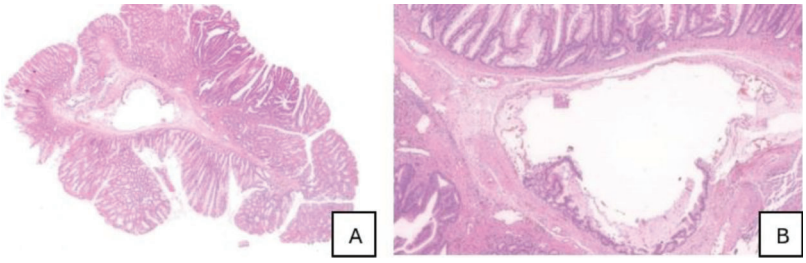

Fig. 2. A pedunculated sessile serrated lesion with intestinal type dysplasia (A; HE, x10), a horizontal growth of the crypts, along muscularis mucosae and an aspect of epithelial misplacement in the fibro-vascular core of the polyp (B; HE, x30).

muscularis mucosae into the submucosa, leading to an inverted growth pattern, can create diagnostic confusion, especially when the glands are dysplastic. Lymphoid aggregates were often seen in the submucosa. A polyp located in the rectum was diagnosed as SSL with intramucosal adenocarcinoma and presented lymphoglandular complexes in the submucosa, close to muscularis mucosae, composed of atypical glands, surrounded by lymphoid tissue (Figure 3). Rare cases of lymphoglandular complexes have been described in the literature, especially in adenomatous polyps [14,15]. This change also poses a potential diagnostic challenge and should not be mistaken for invasive adenocarcinoma.

Ki67 was performed to evaluate the proliferative compartment in SSLs, which are known to have irregular foci of proliferation along the sides of the crypt, making mature goblet or foveolar cells to be seen at the base of the crypts [16]. Ki-67 positive cells were found mainly in the lower third of the crypts, with asymmetric distribution (Figure 4A) and with a higher density in areas of dysplasia (Figure 4B).

15 SSLs had low-grade dysplasia, with elongated, hyperchromatic, pseudostratified nuclei and 3 lesions high-grade dysplasia or intramucosal adenocarcinoma, with both architectural and cytological atypia. In dysplastic areas, luminal serration was much reduced (Figure 3B). The areas of dysplasia were found within the polyps, were surrounded by serrated glands and the transition towards dysplasia was abrupt.

In our study patients with dysplastic polyps are older (mean age 67.56) compared to those that have no dysplasia (mean age 57.48), with a p-value of < 0.001, based on the hypothesis test. No statistical association was found between sex and dysplasia (p=0.712, Test Chi-square). Larger lesions tend to harbor dysplasia. However, 9 SSLs with dysplasia were smaller than 10 mm, 4 lesions measured between 10 mm and 19 mm and 5 lesions between 20 mm and 25 mm. No significant difference in size was observed between SSLs with dysplasia and those without dysplasia ($p = 0.568$, Mann-Whitney test).

To highlight molecular alteration of SSLs we performed MLH1 and p53 on all cases. Two cases showed a mutant p53 pattern (Figure 5A). One of the cases, with complete absence of p53 expression had low-grade dysplasia. MLH1 was found negative (Figure 5B) in 5 of the 18 cases of SSL with dysplasia (27.77%). One of them, on a second examination, was reconsidered as SSL with minimal deviation dysplasia, according to Pai et al criteria [9]. No abnormalities regarding the expression of p53 or MLH1 were seen in SSL without dysplasia.

We conducted a panel to assess the presence of mucin expression in SSLs, which included MUC2, MUC5AC and MUC6. MUC2 and MUC5AC were positive in all cases, but their expression was reduced in areas of high-grade dysplasia and intramucosal adenocarcinoma. The positivity and intensity of MUC5AC (Figure 6B) was more variable compared to MUC2 (Figure 6A). MUC6 had a focal expression, in 66.66 % of the cases. No differences in mucin expression were noted between right and left colonic lesions.

CD3 and CD8 were used to assess the immune microenvironment. Overall, these lesions showed a high density of lymphocytes (Figure 7), with frequent lymphoid aggregates in the submucosal layer. A higher number of intraepithelial CD8 positive T lymphocytes was observed in the serrated epithelium (up to 10 lymphocytes per 100 epithelial cells) compared to normal colonic mucosa. Furthermore, dysplastic areas with loss of MLH1 expression showed a higher count of intraepithelial CD8 positive T lymphocytes (up to 14 lymphocytes) compared to those with preserved MLH1 expression (a maximum of 1-2 lymphocytes per 100 intestinal-type dysplastic cells). A significant correlation

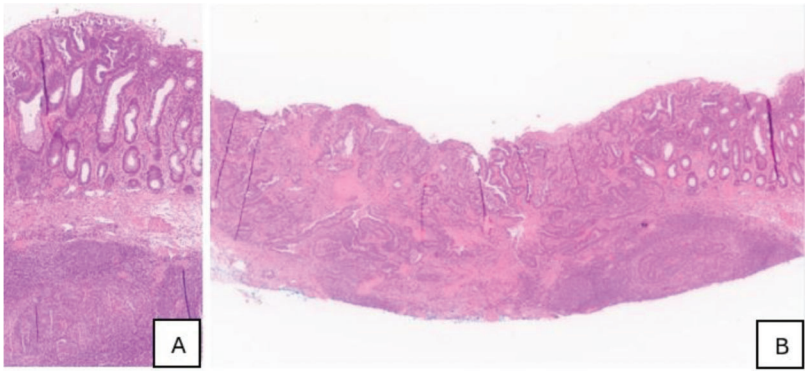

Fig. 3. Lymphoglandular complexes in a sessile serrated lesion with intramucosal adenocarcinoma and reduced serration (A; HE, x40). Multiple levels through the paraffin block were required to prove the continuity of submucosal glands with the overlying lesion and a non-invasive character of the proliferation (B; HE, x25).

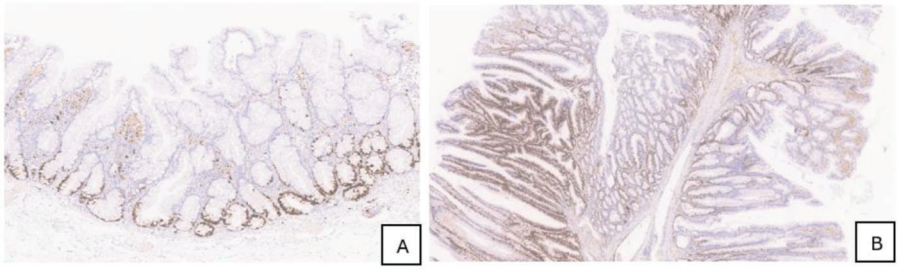

Fig. 4. Ki67 showing positivity mainly in the lower third of the crypts, with uneven arrangement of positive cells along the sides of crypts and scattered cells in the upper part of this proliferated mucosa (A; IHC, anti-Ki67 Ab, x70). A diffuse positive staining was noticed in dysplastic areas (B; IHC, anti-Ki67 Ab, x20).

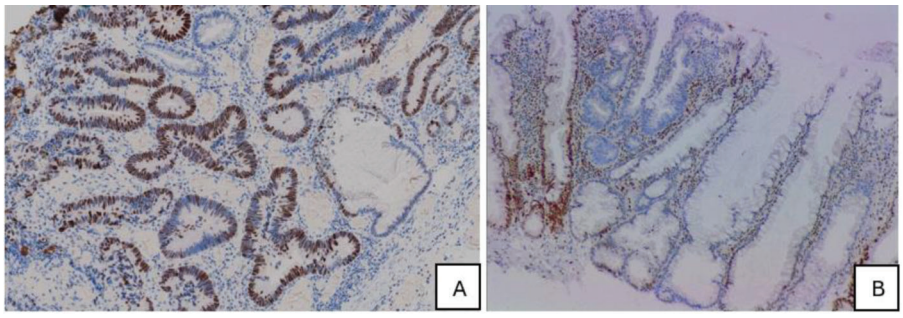

Fig. 5. Mutant p53 pattern in a SSLD (A; IHC, anti-p53 Ab, x100) and MLH1 loss in a dysplastic area of a SSLD (B; IHC, anti-MLH1 Ab, x100), with positive internal control.

was found between the loss of MLH1 and an increased number of intraepithelial CD8-positive cells ($p < 0.001$, Fisher's Test).

Anti-CD44 antibodies were used in the study to highlight the expression of this protein in normal colonic mucosa and in sessile serrated lesions, with or without dysplasia. In normal colonic mucosa the expression of CD44 was limited to the base of the crypts. In serrated areas without dysplasia the positivity of CD44 was seen in the lower half of the crypts (Figures 8A and 8B), while the upper half of the crypts presented almost no reaction. On the other hand, deficient MLH1 dysplastic cells presented an intense CD44 expression, extending to the surface of the lesion. Areas of dysplasia with retained MLH1 expression showed a positive reaction in 90% of cases, but at a lower intensity compared to MLH1 deficient areas. There was a strong correlation between CD44 positivity and MLH1 loss and between CD44 and Ki67 positivity ($p < 0.001$, test Fisher). The correlation between CD44 and MLH1 expression has not yet been investigated, as indicated by the searches conducted.

We investigated the distribution of neuroendocrine cells using chromogranin in both normal colonic mucosa and SSLs. Compared to the normal adjacent mucosa, we observed a general reduction in the number of neuroendocrine cells in SSLs. Some areas showed a complete absence of these cells, while others contained a reduced number of neuroendocrine cells, particularly those with less architectural distortion at the base.

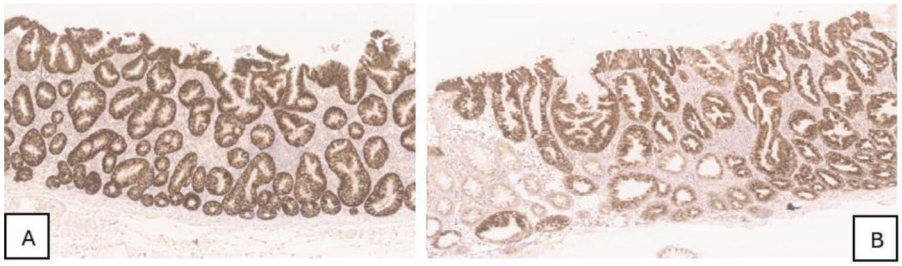

Fig. 6. MUC2 and MUC5AC positive in all cases, with a slightly more variable expression of MUC2 (A; IHC, anti-MUC2 Ab, x75) compared to MUC5AC (B; IHC, anti-MUC5AC Ab, x75).

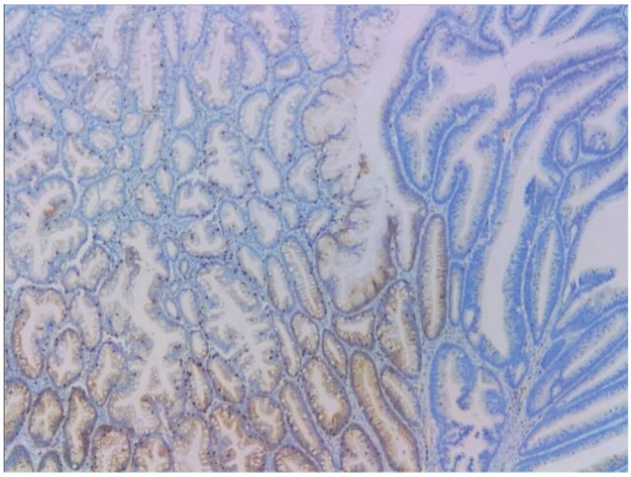

Fig. 7. The number of CD8+ intraepithelial lymphocytes is higher in serrated areas without dysplasia (left side) compared to areas with intestinal type dysplasia (right side) (IHC, anti-CD8 Ab, x50).

DISCUSSION

The study has limitations, due to a reduced number of cases, which originate from a single center. In our center prevalence of sessile serrated lesions is about 5% of neoplastic polyps, of which only 20% have dysplasia. Given that the literature states that up to 30% of colon cancers develop from serrated lesions and the prevalence of SSLD is overall reduced [5] the question arises whether these lesions are not diagnosed at a more advanced stage (of cancer), at least in Romania, where the implementation of screening programs has been slow. There is no significant difference in the mean age between patients having SSLs with dysplasia and those with serrated adenocarcinoma [16-18], supporting the idea of rapid malignant transformation and likely explaining why these lesions are seldom encountered during endoscopic examination.

Serrated adenocarcinoma is a subtype of colorectal cancer that arises from serrated lesions, first recognized in the fourth edition of WHO, characterized by a sawtooth architecture, abundant clear and eosinophilic cytoplasm, vesicular nuclei, mucin production and minimal to no necrosis [18].

A careful examination of the lesion's margins, in search of a serrated component, is essential for correctly classifying the lesion and avoiding underdiagnosis, given that in areas of dysplasia, which are typically the focus of the examination, the serration is often significantly reduced.

The results of the present study show that SSLs with dysplasia appear at older ages, data that is in accordance with the literature [5]. No statistical association was found between dysplasia and sex. Half of SSLD were smaller than 10 mm, which highlights the importance of a careful endoscopic examination.

Morphological changes seen in SSLs with dysplasia are heterogenous [8], with a large spectrum of architectural and cytologic abnormalities. These changes are crucial for detecting dysplasia, a key indicator of potential malignant transformation. SSLs with dysplasia are rare and represent 2–5% of all sessile serrated polyps [9,16,17,19]. 18 cases included in the present study exhibited dysplasia, of which five had focal loss of MLH1 and two cases had a mutant p53 pattern, suggesting that these SSLs could have progressed toward cancer through either the microsatellite instability (MSI) pathway or possibly via a TP53 mutation. Intense diffuse nuclear expression or total absence of p53 antibody staining by immunohistochemistry is significantly linked to TP53 gene mutations. TP53 mutation is typically considered a late event in the adenoma-carcinoma sequence [20] and rarely occurs in SSLs [4,25]. One case had absence of p53 expression in an area showing low-grade dysplasia, raising the question of whether TP53 mutation in SSLs might be an earlier event in the progression to cancer compared to conventional adenomas.

Considering that most carcinomas arising from serrated precursors do not have an obvious serrated morphology and the serrated pathway is heterogenous, all colonic cancers should be investigated from a molecular point of view, with a panel including BRAF mutation, which is seen in up to 90% of SSLs [4, 26-28]. This way, patients could benefit from more effective therapies [29].

The number of intraepithelial T cell lymphocytes was lower in areas of intestinal dysplasia with preserved MLH1 expression, whereas areas with MLH1 loss exhibited an increased number of intraepithelial CD8+ T cells. The microsatellite instable phenotype of colorectal cancer, due to hypermethylation of MLH1 is characterized by distinct features, including poor differentiation, mucinous or signet ring histology, prominent lymphocytic infiltration, and right-side location [4]. Our findings support that intraepithelial lymphocytic infiltration is a key feature of MLH1 deficient SSLs in their progression to cancer.

SSLs often show abnormal mucin expression when compared to normal colonic mucosa. Mucin proteins are important glycoproteins that help in cell adhesion, protection of epithelial surfaces and in immune responses. While MUC2 is a common mucin in the colon, MUC5AC and MUC6 are usually associated with mucus production in the stomach.

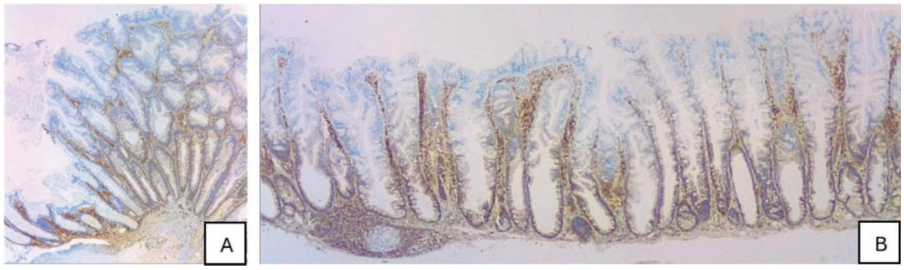

Fig. 8. CD44 in normal colonic mucosa (A) and non-dysplastic serrated areas (A and B) (positive in the lower half of the crypts) (IHC, anti-CD44 Ab, x100).

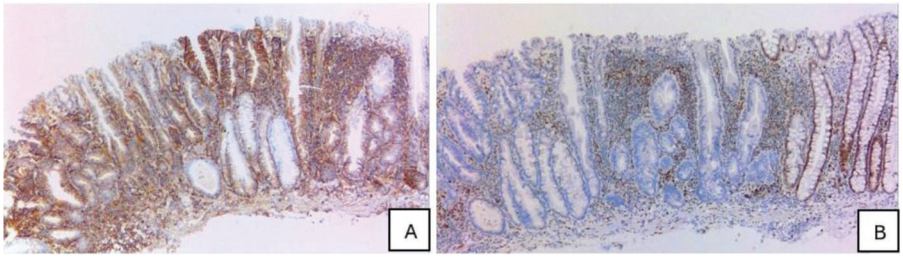

Fig. 9. Overexpression of CD44 (A) in MLH1 deficient areas (B) showing reduced serration, crypt branching and mild nuclear enlargement (IHC, A: anti-CD44 Ab; B: anti-MLH1 Ab, x100).

MUC2 and MUC5AC were expressed in all cases and were reduced in areas of high-grade dysplasia. MUC6 was also expressed in more than half of our cases. The role of mucins in serrated pathway of carcinogenesis is still unknown [21].

CD44 is a ubiquitous transmembrane glycoprotein, distributed in normal adult and fetal tissues, including colonic mucosa, that plays a crucial role in various cellular processes, such as cell adhesion, migration, proliferation, and differentiation. CD44 is often used as a stem cell marker in various tissues, particularly in cancers, as it is overexpressed on the surface of cancer stem cells [22]. These cells are thought to play a key role in tumor initiation, metastasis, and resistance to therapy [23].

The stem cells in normal colonic mucosa are critical for the maintenance and regeneration of the lining of the colonic mucosa, allowing it to heal from damage and maintain its essential functions [24]. The stem cells are located at the base of the crypts, where they divide to produce differentiated cells, such as absorptive cells, goblet cells, Paneth and neuroendocrine cells. In SSLs, the crypts are often dilated, elongated, and branched, which alters the typical architecture of the epithelium. This structural change can influence the behavior of stem cells in the lesion. In SSLs, stem cells might show abnormal behavior, such as increased proliferation and enhanced self-renewal. Our results regarding Ki67, CD44, and chromogranin immunostaining might support this affirmation. In serrated lesions, CD44 overexpression may contribute to abnormal cell migration and disorganized tissue architecture, which is characteristic of serrated morphology.

An abnormal behavior of stem cells might lead to the overproduction of crypt mucin containing cells (which would explain a reduced number of neuroendocrine cells), leading to the abnormal crypt architecture and accumulation of cells that do not undergo proper maturation. Also, the expression of CD44 in dysplastic areas supports its role in promoting tumor progression. The correlation between intense CD44 positivity and MLH1 loss could suggest a higher likelihood of malignant transformation.

Another important aspect which is worth mentioning is that some of the polyps presented positive resection margins or were removed piecemeal and the completeness of the polypectomy could not be assessed. It is essential for pathologists and clinicians to carefully evaluate these lesions and ensure that all potentially neoplastic tissue is removed.

CONCLUSION

Sessile serrated lesions represent an important group of colorectal lesions that have gained significant attention due to their potential to progress to colorectal cancer through the serrated pathway. SSLs are often challenging to diagnose and differentiate from other types of colorectal polyps due to overlapping histological features. While it is diagnostically helpful, it is difficult in practice to subtype dysplasia in SSLs. More important is to recognize the morphologic heterogeneity of these lesions. Immunohistochemistry might be a useful tool in recognizing subtle changes and in providing crucial information on the molecular characteristics of SSLs. MLH1 may be particularly useful for those who are less familiar with dysplastic changes in SSLs. As SSLs advance towards dysplasia, the expression of CD44 becomes more pronounced, emphasizing its role in the progression of these precancerous lesions. The correlation between CD44 overexpression and microsatellite instability is an area that requires further exploration.

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Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and was approved by Ethics Committee of Victor Babeş National Institute of Pathology (approval number 126/13 May 2024). All the patients signed the written informed consent.

Conflict of Interest

The authors declare no conflict of interests.

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