Clinicopathologic Findings of Colorectal Traditional and Sessile Serrated Adenomas in Korea: A Multicenter Study

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Key Words
Traditional serrated adenomas · Sessile serrated adenomas

Abstract
Background/Aims: Serrated polyps have emerged as important evidence supporting the serrated polyp-neoplasia pathway in colorectal carcinogenesis, an alternate to the classical adenoma-carcinoma sequence. However, there is confusion over the diagnostic criteria for serrated polyps including traditional serrated adenoma (TSA) and sessile serrated adenoma (SSA). In addition, clinical and pathologic characteristics of each are largely unknown and need further exploration. Methods: The 753 polyps that were previously diagnosed as serrated adenoma (SA) from 14 tertiary care university hospitals in Korea between 2003 and 2005 were evaluated for the clinicopathologic findings of TSA and SSA.

Results: Among 753 cases, 420 (55.8%) were reclassified as TSA and 56 (7.4%) as SSA. Among the pathologic parameters, crypt branching, crypt dilatation, and horizontal crypts were more frequent in SSA than in TSA (p < 0.001). SSA was larger than TSA (12.6 ± 7.3 vs. 9.8 ± 6.9 mm, p = 0.005), was more likely to be flat type (p = 0.006), and was more frequently located in the proximal colorectum (p = 0.012). There were no significant differences in age, sex, and body mass index between TSA and SSA. Conclusions: Location and endoscopic features of the polyps with abnormal crypt morphology in histologic findings could be helpful for the diagnosis and classification of SAs.

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Introduction

During the past decade, major advances have been made in the understanding of the molecular events that lead to colorectal adenocarcinoma through a variety of potential pathways. The precancerous potential of the colonic adenoma is undisputed, but appreciation has steadily grown for the significance of the so-called serrated polyp. Studies have shown that sporadic colorectal cancer with a high grade of microsatellite instability most often evolves from serrated polyps and not from adenomas [1–3].

Serrated polyps include hyperplastic polyp (HP) of the goblet cells and microvesicular subtypes, traditional serrated adenomas (TSA), the recently described sessile serrated adenomas (SSA), and mixed polyps [4]. In 1984, Urbansky et al. [cf. 5] reported a case of adenocarcinoma arising from a 'mixed hyperplastic adenomatous polyp', and in 1990, Longacre and Fenoglio-Preiser [cf. 6] designated these polyps as 'serrated adenomas'. Torlakovic and Snover [7] characterized a group of patients with serrated adenomatous polyposis, which showed similar features to HPs but with a sessile pattern of growth. These polyps were termed SSA, distinguishing them from the traditional type of serrated adenoma (SA). More recently, the concept of SA has expanded to include the variants of HPs showing architectural atypia with indiscernible cytologic dysplasia [10]. Due to the rapid evolution and expansion of the definition of SA, the issue of distinguishing SSA and TSA from HP or conventional adenoma with villosity has been problematic not only for pathologists but for endoscopists as well. Moreover, in spite of the partial similarities between SSA and TSA, there is much evidence of histologic, epidemiologic, and genetic differences between the lesions [4, 8, 9]. In the present study, we microscopically reclassified 753 serrated polyps previously diagnosed as SA from large-scale multicenters in Korea and compared the clinicopathologic findings between TSA and SSA in order to find parameters that would allow for the reliable identification of SSA and TSA from the other morphologically similar lesions.

Materials and Methods

Study Subjects

753 polyps pathologically diagnosed as SA from 14 tertiary care university hospitals in Korea from January 2003 to December 2005 were consecutively collected for the study project of the Korean Association for the Study of Intestinal Diseases. Pathologic diagnosis of polyps was identified from the prospective database of each institution. These polyps were obtained from 727 Korean patients (506 males and 221 females; mean age 59.2 years, range 24–88) by endoscopic polypectomy or concurrent surgical resection. Case notes for patients with SA were reviewed to record their age, sex, body mass index (BMI), family history and past history of sporadic colorectal cancer or polyps, indications for colonoscopy, site/size/number of SA, and presence of other polyps as seen at colonoscopy. Site of polyp was categorized into proximal (above splenic flexure) and distal (below splenic flexure).

Pathologic Assessment

Each hematoxylin-eosin-stained slide was reviewed by six specialized gastrointestinal pathologists (H.J.C., C.K.P., J.H.S., S.Y.J., M.S.C., and H.K.C.) with multihead light microscopes. The diagnostic criteria for TSA and SSA were based on guidelines outlined by Bariol et al. [10] and Torlakovic et al. [11], respectively. In brief, histologic confirmation of TSA was made by nuclear dysplasia and serration in ≥20% of crypts (fig. 1a, b). Histologic confirmation of SSA was made by sessile growth and architectural abnormalities including dilatation, branching, or broad bases in basal crypts (fig. 1c, d). All polyps were reclassified into TSA, SSA, mixed hyperplastic adenomatous polyp (MHAP), conventional adenoma, and HP. Using the above diagnostic criteria, mixed TSA- or SSA-conventional adenomas were classified into TSA or SSA. In order to characterize the histological findings of TSA and SSA, each slide was re-evaluated for the following histologic parameters: (1) association with conventional adenoma; (2) association with carcinoma; (3) presence of cytologic dysplasia and its grade; (4) amount of serration; (5) presence of eosinophilic cytoplasm; (6) presence of basal crypt branching; (7) presence of basal crypt dilatation; (8) presence of horizontal crypts, and (9) presence of dystrophic goblet cells.

The conventional adenomas were classified as tubular, tubulovillous, or villous according to the predominant architecture of the dysplastic crypts [12]. Cytologic dysplasia was graded as low or high grade [13]. Low-grade dysplasia was composed of minimal to moderate epithelial atypia, and high-grade dysplasia was composed of only severe epithelial atypia without invasion.

Statistics

Clinical and pathologic findings between TSA and SSA were compared using the $\chi^2$ test or Student’s t test. $p < 0.05$ was considered statistically significant.

Results

Reclassification of Pathologic Diagnosis

The original pathologic diagnoses of 753 polyps were of TSA in 717 cases (95.2%), SSA in 32 (4.3%), and MHAP in 4 (0.5%). Among the 753 cases, 420 cases (55.8%) were reclassified into TSA, 56 cases (7.4%) into SSA, 20 (2.7%) into MHAP, 154 (20.4%) into conventional adenoma, and 103 (13.7%) into HP (table 1). Among the 717 polyps originally diagnosed as TSA, 408 (56.9%) were reclassified into TSA, 41 (5.7%) into SSA, 20 (2.8%) into MHAP, 154 (21.5%) into conventional adenoma, and 94 (13.1%) into...
Among the 32 polyps originally diagnosed as SSA, 15 (46.9%) were reclassified into SSA, 9 (28.1%) into TSA, and 8 (25%) into HP.

Pathologic Features of the TSA and SSA

The histopathologic features of TSA and SSA are summarized in Table 2. TSA and SSA were associated with conventional adenomas in 22.1 and 14.3% of cases, respectively (p > 0.05) and were associated with carcinoma in 0.7 and 1.8% of cases, respectively (p > 0.05). There was a significant difference in cytologic dysplasia between the two groups (p < 0.001). SSA showed various degrees of dysplasia, from absence of dysplasia (10.7%) to high-grade HP. Among the 32 polyps originally diagnosed as SSA, 15 (46.9%) were reclassified into SSA, 9 (28.1%) into TSA, and 8 (25%) into HP.

Table 1. Original and reclassified diagnoses of colorectal polyps

<table>
<thead>
<tr>
<th>Original diagnosis</th>
<th>Original diagnosis n (%)</th>
<th>Reclassified diagnosis n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional serrated adenoma</td>
<td>717 (95.2)</td>
<td>420 (55.8)</td>
</tr>
<tr>
<td>Sessile serrated adenoma</td>
<td>32 (4.3)</td>
<td>56 (7.4)</td>
</tr>
<tr>
<td>Mixed hyperplastic adenomatous polyp</td>
<td>4 (0.5)</td>
<td>20 (2.7)</td>
</tr>
<tr>
<td>Conventional adenoma*</td>
<td>0 (0)</td>
<td>154 (20.4)</td>
</tr>
<tr>
<td>Hyperplastic polyp</td>
<td>0 (0)</td>
<td>103 (13.7)</td>
</tr>
<tr>
<td>Total</td>
<td>753 (100)</td>
<td>753 (100)</td>
</tr>
</tbody>
</table>

* Tubular, tubulovillous, or villous adenoma.
dysplasia (3.6%), whereas 97.6% of TSA showed low-grade dysplasia. Serration was more prominent in TSA than in SSA (p < 0.001). Crypt branching (27.9 vs. 71.4%), crypt dilatation (22.1 vs. 91.1%), and horizontal crypts (2.6 vs. 42.9%) were more frequent in SSA than TSA (p < 0.001).

There was no significant difference in the frequency of eosinophilic cytoplasm or dystrophic goblet cells between the two groups.

Among the histopathologic features, the most sensitive and specific parameter for identification of SSA was crypt dilatation and horizontal crypts, respectively (table 3). Each histopathologic parameter had a high negative predictive value.

**Clinical and Endoscopic Features of TSA and SSA**

The clinical and endoscopic features of TSA and SSA are summarized in table 4. The age of patients with TSA or SSA ranged from 24 to 88 years, with a mean of 59.6 years. The male:female ratio of TSA and SSA was 2:1 and 2.7:1, respectively. There was no significant difference in gender, age, BMI, and past history and family history of polyp or colorectal cancer between TSA and SSA.

The maximum diameter of TSA ranged from 2 to 45 mm, with a mean of 9.8 mm, and the maximum diameter of SSA ranged from 3 to 40 mm, with a mean of 12.6 mm. SSA size was significantly larger than TSA (p = 0.005). Endoscopically, flat type was more common in SSA than in TSA (50.0 vs. 29.8%; p = 0.006). TSA was commonly located in the sigmoid colon (105/420, 25%) and rectum (149/420, 35.5%), and SSA was commonly located in the ascending colon (13/56, 23.2%), sigmoid colon (11/56, 19.6%), and rectum (11/56, 19.6%). SSA was more frequently located in the proximal colorectum than TSA.

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**Table 2. Pathologic features of TSA and SSA**

<table>
<thead>
<tr>
<th>Pathologic finding</th>
<th>Cases</th>
<th>TSA (n = 420)</th>
<th>SSA (n = 56)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association with adenoma</td>
<td>101</td>
<td>93 (22.1%)</td>
<td>8 (14.3%)</td>
<td>0.177</td>
</tr>
<tr>
<td>Association with carcinoma</td>
<td>4</td>
<td>3 (0.7%)</td>
<td>1 (1.8%)</td>
<td>0.390</td>
</tr>
<tr>
<td>Dysplasia</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Absent</td>
<td>6</td>
<td>0 (0%)</td>
<td>6 (10.7%)</td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td>458</td>
<td>410 (97.6%)</td>
<td>48 (85.7%)</td>
<td></td>
</tr>
<tr>
<td>High grade</td>
<td>12</td>
<td>10 (2.4%)</td>
<td>2 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Amount of serration</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>20–50%</td>
<td>104</td>
<td>81 (19.3%)</td>
<td>23 (41.1%)</td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>372</td>
<td>339 (80.7%)</td>
<td>33 (58.9%)</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic cytoplasm</td>
<td>408</td>
<td>364 (86.7%)</td>
<td>44 (80%)</td>
<td>0.182</td>
</tr>
<tr>
<td>Crypt branching</td>
<td>179</td>
<td>117 (27.9%)</td>
<td>40 (71.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Crypt dilatation</td>
<td>169</td>
<td>93 (22.1%)</td>
<td>51 (91.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Horizontal crypts</td>
<td>39</td>
<td>11 (2.6%)</td>
<td>24 (42.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dystrophic goblet cells</td>
<td>181</td>
<td>137 (32.6%)</td>
<td>18 (32.1%)</td>
<td>0.987</td>
</tr>
</tbody>
</table>

**Table 3. Accuracy of pathologic parameters in the diagnosis of SSA (% values)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilic cytoplasm</td>
<td>78.6</td>
<td>13.3</td>
<td>10.8</td>
<td>82.4</td>
</tr>
<tr>
<td>Crypt branching</td>
<td>71.4</td>
<td>71.1</td>
<td>25.5</td>
<td>95.0</td>
</tr>
<tr>
<td>Crypt dilatation</td>
<td>91.1</td>
<td>77.9</td>
<td>35.4</td>
<td>98.5</td>
</tr>
<tr>
<td>Horizontal crypts</td>
<td>42.9</td>
<td>97.4</td>
<td>68.6</td>
<td>92.7</td>
</tr>
<tr>
<td>Dystrophic goblet cells</td>
<td>32.1</td>
<td>67.4</td>
<td>11</td>
<td>88.2</td>
</tr>
</tbody>
</table>

PPV = Positive predictive value; NPV = negative predictive value.

**Table 4. Clinical features of TSA and SSA**

<table>
<thead>
<tr>
<th>Demographic findings</th>
<th>TSA (n = 420)</th>
<th>SSA (n = 56)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.5 ± 10.9</td>
<td>60.3 ± 12.5</td>
<td>0.447</td>
</tr>
<tr>
<td>Males</td>
<td>284 (68%)</td>
<td>41 (73%)</td>
<td>0.398</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.8 ± 6.8</td>
<td>24.1 ± 2.7</td>
<td>0.826</td>
</tr>
<tr>
<td>Past history of polyp</td>
<td>93 (34.3%)</td>
<td>21 (43.8%)</td>
<td>0.209</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>56 (14.1%)</td>
<td>3 (5.5%)</td>
<td>0.075</td>
</tr>
<tr>
<td>Family history of polyp</td>
<td>11 (7.1%)</td>
<td>1 (2.4%)</td>
<td>0.272</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>20 (9.7%)</td>
<td>3 (7.5%)</td>
<td>0.667</td>
</tr>
</tbody>
</table>

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Traditional and Sessile Serrated Adenomas
(51.8 vs. 31.9%; p = 0.012) (table 5). There was no significant difference in the incidence of coexisting adenoma and carcinoma in other foci between the two groups (data not shown).

### Discussion

With recent advances in molecular and morphologic characterizations of the serrated neoplasia pathway, the concept of serrated polyps has also rapidly evolved [14–16]. Accurate diagnosis of these serrated polyps is important not only for pathologists but also for endoscopists in order to optimize patient management. However, since the concept of SSA has only been recently emphasized, and SSA can lack cytologic dysplasia [14], its diagnosis is not familiar to many general pathologists and may be confused with HP. Glatz et al. [17] tested the variability of 168 Western pathologists in the diagnosis of HP, TSA, and SSA using an Internet-based quiz. The proportion of correct diagnoses for SSA (55%) and TSA (44%) was lower than for TA (90%) and HP (80%) [17]. In the present study, the proportion of correct diagnoses for SSA (46.9%) was lower than for TSA (56.9%). The proportion of correct diagnoses for SSA in this study was lower than that of Glatz because this study was performed using serrated polyps diagnosed 2–4 years earlier than Glatz, and the diagnostic criteria of serrated polyps was not widespread at that time.

For accurate diagnosis of SSA, a well-oriented and abundant tissue section is essential because the most diagnostic histologic features are present at the base of the crypts. In this study, overall architectural features (branching, cystic dilatation, and horizontal alignment of the basal crypt) were meaningful in the differential diagnosis of SSA from TSA, but cytologic features (eosinophilic cytoplasm and dystrophic goblet cells) were not. The most sensitive and specific parameters for the identification of SSA were crypt dilation and horizontal crypt, respectively. These findings are in accordance with previous reports [4, 18]. Recently, Torlakovic et al. [19] evaluated colonic crypt development and cellular compartmentalization in individual crypts of serrated polyps to differentiate SSA from TSA. They found that ectopic crypt formation (ECF) defined by the location of ectopic crypts with bases not seated adjacent to the muscularis mucosae was nearly exclusive to TSA and was found in all cases while the presence of cytologic atypia and eosinophilia of the cytoplasm were characteristic but not limited to TSA. No evidence of ECF, but nevertheless abnormal distribution of proliferation zone was characteristic of SSA [19]. Although we cannot test their concept in this study, we thought that their findings may help in exploring the genetic and molecular basis for differences between SSA and TSA. Differences in molecular pathogeneses of TSA and SSA can give light to differentiation between them. Mäkinen [20] pointed out that SSA is most often a right-sided lesion characterized by BRAF mutations, whereas TSA is most often left-sided with Kras mutations. BRAF and Kras mutations are mutually exclusive; so if this is true, it further supports that SSA and TSA are indeed biologically different [19].

SSA was regarded as a rare lesion. Previous reports have estimated a prevalence of only 2% [21]. Spring et al. [22] recently reported that SSA comprised 9% of all identified polyps, whereas MHAP comprised only 1.7% and TSA comprised <1%. This high detection rate may be facilitated by the use of magnification chromoendoscopy. In this study, we cannot estimate prevalence or incidence of SSA because we did not include polyps previously diagnosed as HP. It was reported that SSA could often be confused not only with TSA but also with HP [17]. SSA accounted for 8.3 and 18% of polyps, which were previously diagnosed as HP in Japan and Western countries [11, 23]. Actually, HP was seldom removed by polypectomy or biopsy. Further studies including HP are necessary in order to confirm the clinicopathologic differences between TSA and SSA.

In this study, SSA shows a predilection for large size, flat type, and proximal location. SSA was distributed comparatively equally in the distal and proximal colorectum, whereas TSA was predominantly located in the distal colorectum, which is consistent with previous reports [6, 8, 24]. The male:female ratio in SSA was higher than that of a previous report [22]. Frequency of high-grade

<table>
<thead>
<tr>
<th>Table 5. Endoscopic features of TSA and SSA</th>
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<tbody>
<tr>
<td><strong>Endoscopic finding</strong></td>
</tr>
<tr>
<td>Size, mm</td>
</tr>
<tr>
<td>Type</td>
</tr>
<tr>
<td>Polyoid</td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td>Distal</td>
</tr>
</tbody>
</table>

<sup>a</sup> Above splenic flexure level.
dysplasia and carcinoma between TSA and SSA was not significantly different. Oka et al. [8] divided SA into superficial and polypoid types by macroscopic appearance and reported that high-grade dysplasia and carcinoma in situ arising in superficial SA was more frequent than those arising in polypoid SA.

In summary, in order to determine surveillance guidelines or to perform prospective studies for SA, awareness of the unified histologic criteria for TSA and SSA is necessary. Location and endoscopic features of polyps with abnormal crypt morphology in histologic findings could be helpful for the diagnosis and classification of SA in this study. Although a number of pathologists designed definition for SA, TSA, and SSA, considerable confusion continues to exist. Clinicians and pathologists should pay special attention to diagnosis and classification until their natural history and molecular basis are more clearly defined. The current findings may help in the differentiation of TSA and SSA.

References

