Synchronous and Subsequent Lesions of Serrated Adenomas and Tubular Adenomas of the Colorectum

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Abstract

The characteristics of synchronous and subsequent lesions of serrated adenomas (SAs) of the colorectum are still unclear. This study aimed to clarify the characteristics of synchronous and subsequent lesions of SAs compared with tubular adenomas (TAs) of the colorectum. Patients were divided into 2 groups: SA (127 patients) and TA (158 patients) groups. The mean follow-up durations in the SA and TA groups were 39.7 months and 42.7 months, respectively. The number and clinical features of synchronous and subsequent lesions of both groups were examined. In the SA group, 19 (15%) patients had synchronous lesions, and 3 (2%) patients had subsequent lesions. In the TA group, 68 (43%) patients had synchronous lesions, and 14 (9%) patients had subsequent lesions. The frequencies of patient with synchronous and subsequent lesions in the SA group were significantly lower than those in the TA group ($p < 0.0001$ and $p = 0.02$, respectively). The most frequent synchronous lesion was SA (67%) in the SA group, and TA (95%) in the TA group. The most subsequent lesion was SA (62%) in the SA group, and TA (100%) in the TA group. The histology of the index polyp and synchronous and subsequent lesions tended to be identical. No invasive colorectal carcinomas were observed in either group. Our data suggest that the colonic tumorigenesis potential of patient with SA may differ from that of patient with TA.

Key Words: Serrated adenoma, Tubular adenoma, Synchronous lesion, Subsequent lesion

Introduction

Serrated adenomas (SAs) of the colorectum are recognized as a distinct form of neoplasia, histologically defined by the presence of hyperplastic and adenomatous features as proposed by Longacre and Fenoglio-Preiser in 1990 [1]. Histological diagnosis of SA is made by the observation of a serrated glandular pattern, the presence of goblet cell immaturity and upper zone mitoses, prominence of nucleoli, and the absence of a thickened collagen table. SAs harbor malignant potential, and high-grade dysplasia has been observed in 11% of SAs [1, 2].

Recently, the clinical and molecular differences between SAs and conventional tubular adenomas (TAs) have been detected. Clinically, SAs are located predominantly in the sigmoid colon and rectum, and incidences of high-grade dysplasia differ between SAs and TAs [3]. Genetically, SAs have frequent mutations of *p53*, K-*ras*, and B-*raf*, and methylations of *hMLH1*, *p16*, and *IGFBP7* [4]. However, researches on synchronous and subsequent lesions of SA are quite few. To our knowledge, there is only one study on the issue at present [5]. Thus, characteristics of those lesions are still unclear. The purpose of this study was to clarify the characteristics of synchronous and subsequent lesions of SAs, compared to those of TAs.

Patients and Methods

This is a retrospective study, and patients described in this paper were diagnosed from their first colonoscopy by polypectomy or endoscopic mucosal resection (EMR) via endoscope report files and pathology database files collected between January 2003 and December 2008 in Hiroshima University Hospital (Hiroshima, Japan). The cases that fulfilled the following criteria were selected in this study and were classified into the SA and TA groups: (1) underwent complete colonoscopy, (2) polyp(s) was resected by polypectomy or EMR for full evaluation, (3) diagnosed as SA and/or TA at the initial colonoscopic examination, (4) followed-up after at least one year and had at least one follow-up colonoscopy, (5) if only one SA or TA was present, the polyp was regarded as an index polyp, (6) if synchronous SA and/or TA were present, the largest polyp was regarded as the index polyp, and (7) excluded patients with polyposis syndrome such as

familial adenomatous polyposis and hyperplastic/serrated polyposis (HSP), those after colectomy, and those with advanced colorectal cancer (CRC) because of the followed surgical treatment. The diagnosis of all SAs and TAs was confirmed by a pathologist (K.A.). The location of the lesion was divided into proximal (from the cecum to the splenic flexure) and distal (from the descending colon to the rectum).

We identified 127 patients in the SA group and 158 randomly selected, age and sex-matched patients, were enrolled in the TA group. The mean follow-up duration was 39.7 months (13-58 months) in the SA group, and 42.7 months (14-62 months) in the TA group. We investigated the number and clinicopathologic features of synchronous and subsequent lesions in both groups.

Statistical analysis was evaluated by the chi-square test. $p < 0.05$ was considered to be significant.

Results

In the SA group, the male/female ratio was 86/41, and the mean age at the first diagnosis was 63.4 (range 36-91). In the TA group, the male/female ratio was 116/42, and the mean age at the first diagnosis was 65.3 (range 38-88) (Table 1, Figure 1).

In the SA group, 19 (15%) patients had synchronous lesions, and 3 (2%) patients had subsequent lesions in the follow-up period (Table 1). In the TA group, 68 (43%) patients had synchronous lesions, and 14 (9%) patients had subsequent lesions in the follow-up period. The frequencies of patients with synchronous and subsequent lesions in the SA group were significantly lower than those in the TA group ($p < 0.0001$ and $p = 0.02$ by chi-square test, respectively).

As for synchronous lesions, a total of 87 and 196 lesions were detected in the SA group and the TA group, respectively (Table 2). Interestingly, the most frequent synchronous lesion was SA (67%) in the SA group, and TA (95%) in the TA group. Thus, the histology of the index polyp and synchronous lesions was identical in the most patients. No invasive colorectal carcinomas were observed in either group.

As for subsequent lesions, a total of 8 and 22 lesions were detected in the SA group and the TA group, respectively (Table 3). No invasive CRCs were observed in either group. The most frequent subsequent lesion was SA (62%) in the SA group, and TA

(100%) in the TA group. Thus, similar to synchronous lesions, the histology of the index polyp and subsequent lesions was identical in the most patients.

The locations of synchronous and subsequent lesions of both groups are indicated in Table 4. The distribution pattern did not differ significantly between SA and TA groups.

Discussion

In the present study, we showed that the colonic tumorigenesis potential of patient with SA may differ from that of patient with TA. The frequencies of synchronous and subsequent lesions in the SA group were significantly lower than those in the TA group. In addition to this, the most frequent synchronous and subsequent lesions were SAs in the SA group, and TAs in the TA group.

The frequency of SAs has been reported to be 1-2.4% of all colorectal polyps, indicating that SAs are rare polyps in the colorectum [1, 6]. However, 22.6% of rectosigmoid polyps originally diagnosed as hyperplastic polyps (HPs) demonstrated features of SAs on reanalysis [8]. In a recent study, the proportion of SAs among all index polyps was 10% [7]. It has been also reported that serrated adenocarcinoma arising from SA has been reported to account for at least 5.8% of CRCs [5]. These data suggest that SAs may not be rare lesions, but that SAs may be lesions of significant importance.

The grade of malignant potential of SAs is of great interest. To evaluate the malignant potential, examination of the incidence of malignant lesions including high-grade dysplasia and carcinoma in SAs is one method. Song et al [8] compared clinicopathologic features of 124 SAs from 116 patients and 419 TAs from 200 randomly selected patients. The incidence of malignant lesions including high-grade dysplasia and carcinoma in SA was found to be lower than in TA (3.2% vs 9.3%, $P<0.05$). Iwabuchi et al [3] reported that the percentage of concomitant carcinoma in cases of SA was significantly lower than in TA. These data suggest that SAs may be premalignant lesions but have a lower malignant potential than TAs.

Examining of synchronous and subsequent lesions of SA compared with those of TA is another method to evaluate the malignant potential of SA. However, there are few reports on characteristics of synchronous and subsequent lesions of SAs compared with

those of TAs. To our knowledge, there is only one study on the issue at present. Lazarus et al [5] reported that synchronous lesions identified at the index colonoscopy were of the same histological type as the index polyp (87% of the SA group, 94% of the TA group), and subsequent lesions were also the same histological type as the index polyp (75% of the SA group, 70% of the TA group), which is similar to our results. These findings suggest that the genetic and environmental factors determining the predominant type of polyp may influence the histology of colorectal polyps. In addition, the same authors reported that the frequencies of synchronous and subsequent lesions in the SA group were significantly lower than those in the TA group, which is also similar to our results.

Serrated lesions of the colorectum are subclassified primarily into 3 subtypes: hyperplastic polyp, traditional serrated adenoma (TSA) and sessile serrated adenoma/polyp (SSA/P). SSA/P has architectural features that include dilatation of base of the crypts, often with crypts that seem to grow parallel to the muscularis mucosa and result in T- or L-shaped crypts. TSA also has serration but a uniform population of dysplastic epithelial cells that are columnar cells with eosinophilic cytoplasm, and have a villiform configuration and appear protuberant rather than sessile [4]. In the present study, SA included both TSA and SSA/P. Although differences in clinicopathologic and molecular characteristics between these lesions have been reported, histologic diagnosis of these lesions is still confused among pathologists at present. There are some differences in diagnosis of TSA, SSA/P and hyperplastic polyp among pathologists. In addition to this, the number of lesions examined in the present study was relatively limited. Therefore, we did not subclassified the SA in the present study. Of course, further examinations with subclassification of SA may be needed to clarify the differences between TSA and SSA/P.

It has been suggested that left- and right-sided colorectal cancers differ in their associated genetic alterations in neoplastic transformation, based on studies in Western countries. For example, microsatellite instability (MSI)-positive cancers are preferentially found in right-sided colon cancers and in older women. Previous study has indicated a higher incidence of CpG island methylator phenotype (CIMP)-positive tumors in right-sided colon cancers compared with left-sided colon cancers. On the other hand, chromosomal instability (CIN) is said to characterize left-sided colorectal cancers. These findings have provided further evidence for the existence of at least two

mechanisms of colorectal cancer pathogenesis. One group (CIMP+/MSI+) occurs predominantly in the right side of the colon, and the other (CIN) occurs predominantly in the left side of the colon.

There are several studies on genetic alterations of SAs: for example, presence of B-*raf* or K-*ras* mutations [9], extensive DNA methylations [10], and inactivation of hMLH1 or MGMT [10, 11]. We previously reported frequent *p53* mutations in SAs [12]. Recently, serrated pathway has been proposed as one of carcinogenetic pathways of the colorectum, and are divided into 2 categories: CIMP+/MSI+ cancer with B-*raf* mutation, and CIMP+/MSI- and B-*raf* mutation [4]. SSA/P is most often right-sided lesion characterized by B-*raf* mutation whereas TSA is most often left-sided with K-*ras* mutation [13]. The B-*raf* mutation is commonly seen in CIMP+/MSI- cancers (44%) although at a lower frequency than in CIMP+/MSI+ cancers (94%), and MSI+ cancers occur predominantly in the proximal colon. SSA/P is likely to be the principal precursors of MSI+ colorectal cancers [14].

We excluded patients with polyposis syndrome such as familial adenomatous polyposis and HSP in this study. HSP, however, is a distinctive entity. Definition of HSP is as follows; the presence of either (1) >30 HPs/SAs distributed throughout the colon, (2) more than 5 HPs/SAs proximal to the sigmoid colon, of which at least 2 polyps are >1 cm in size, and (3) any number of HPs/SAs located proximal to the sigmoid colon in a patient with a first degree relative with HSP [15]. In the case of HSP, Hyman et al [16] reported that 7 of these 13 (54%) patients with HSP developed CRC during the follow-up period. Rubio et al [17] summarized 30 publications about HSP in 1977-2005, that 51% (67/131) of the HSP patients had CRC at the time of diagnosis of HSP and/or during the follow-up period. This percentage is very high when compared with a recent study of 1,552 consecutive colorectal adenomas, where only 1.7% (27/1,552) showed invasive carcinoma [18], and which reported that the overall lifetime cumulative incidence of CRC in a population is only 5.5% [18, 19]. Several researchers have postulated that, in HSP patients, carcinomas may evolve through the HP-SA sequence [20, 21]. Although patients with SA seem not to be at high risk for CRC development, patients with HSP seem to be at very high risk for CRC development. The prevalence of HSP is still unclear, and the point should also be investigated.

In conclusion, our data suggest that the colonic tumorigenesis potential of patient with SA may differ from that of patient with TA. Large-scale, prospective study on the

synchronous and subsequent lesions of SAs and TAs of the colorectum should be performed to confirm the results.

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Figure Legends

Fig. 1. Colonoscopic and microscopic findings of serrated adenoma.
a Conventional colonoscopic finding. A sessile polyp is seen in the ascending colon. **b** Microscopic finding (HE staining, X40). Serrated pattern of the crypt is shown. **c** Microscopic finding (HE staining, X200). Pseudoinvasion of the tumor into the submucosa is observed. **d** Microscopic finding (HE staining, X400). The nuclei show atypia.

Table 1. Frequencies of patients with synchronous and subsequent lesions in the SA and TA groups

	SA group (N=127)	TA group (N=158)	*p* value
Male/female ratio	86/41	116/42	NS
Mean age (range) (y)	63.4 (36-91)	65.3 (38-88)	NS
No. of patients with synchronous lesions	19 (15%)	68 (43%)	< 0.0001
No. of patients with subsequent lesions	3 (2%)	14 (9%)	0.02

SA, serrated adenoma; TA, tubular adenoma; NS, not significant.

Table 2. Histology of synchronous lesions in the SA and TA groups

	SA (%)	TA (%)	HP (%)	Total (%)
SA group (N=19)	58 (67)	12 (14)	17 (19)	87 (100)
TA group (N=68)	0 (0)	187 (95)	9 (5)	196 (100)

SA, serrated adenoma; TA, tubular adenoma; HP, hyperplastic polyp.

Table 3. Histology of subsequent lesions in the SA and TA groups

	SA (%)	TA (%)	HP (%)	Total (%)
SA group (N=3)	5 (62)	3 (38)	0 (0)	8 (100)
TA group (N=14)	0 (0)	22 (100)	0 (0)	22 (100)

SA, serrated adenoma; TA, tubular adenoma; HP, hyperplastic polyp.

Table 4. locations of synchronous and subsequent lesions of SA and TA groups

	Proximal	Distal	*p* value
SA group			NS
SA	32	31	
TA	11	4	
HP	5	12	
TA group			NS
SA	0	0	
TA	106	103	
HP	5	4	

SA, serrated adenoma; TA, tubular adenoma; HP, hyperplastic polyp, NS, not significant.

Fig. 1