Gastric and small intestinal traditional serrated adenomas: a detailed morphologic and immunohistochemical analysis

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ABSTRACT

Background/Aims: *Traditional serrated adenomas (TSAs), despite their low incidence in colorectum, may originate in other parts of the gastrointestinal (GI) tract, including stomach and small intestine. Malignant transformation for upper GI TSAs has recently been reported in the literature. Here, we present a series of gastric and small intestinal TSAs with the aim to characterize their morphologic and immunophenotypic features as well as their neoplastic potential in a compartmental manner using digitalized images.*

Materials and Methods: *The study comprised 12 GI polyps with TSA features—5 gastric and 7 small intestinal. The extent of the characteristic features of TSA, including eosinophilic cells, ectopic crypt foci (ECF), slit-like serration, foveolar epithelium, goblet cells, together with dysplastic/carcinomatous foci were assessed on digitalized H&E images and were used as reference for immunohistochemical analysis.*

Results: *All polyps in the cohort contained eosinophilic cells as the most extensive morphologic feature followed by ECF and slit-like serration in decreasing order. Serrated dysplasia was more common in gastric polyps, which more frequently showed neoplastic progression compared with the intestinal ones. CK20 was the most widely expressed marker with a preference to eosinophilic cells while ECFs were mostly negative. Ki67 showed the opposite pattern of CK20. MUC6 and MUC2 were selectively expressed in the basal zone and goblet cells, respectively.*

Conclusion: *Our results showed that the presence of eosinophilic cells with pencillate nuclei commonly accompanied by ECF and slit-like serration are the defining features of gastric and small intestinal TSAs. They frequently harbor neoplastic foci, particularly in gastric location where serrated dysplasia seems to be more common.*

Keywords: *Stomach, small intestine, dysplasia, neoplasia, traditional serrated adenoma*

INTRODUCTION

Since the introduction of the term "serrated adenoma" by Longacre and Fenoglio-Preiser in 1990, (1) serrated polyps have become increasingly popular among gastrointestinal pathologists. Up to 30% of colorectal carcinomas are considered to develop through serrated neoplasia pathway where sessile serrated lesion ("sessile serrated adenoma/polyp" in previous WHO classification) (2) and traditional serrated adenoma (TSA) are the potential precursor lesions. TSAs, the least common members of serrated polyps, represent less than 1% of all colorectal polyps (3). Their defining features have evolved over time, and currently, tubulovillous architecture, luminal slit-like serration, ectopic crypt foci (ECF) and epithelial cells with eosinophilic cytoplasm, and centrally placed pencillate nuclei are considered as characteristic (4-8). However, variations in the extent of these features may cause difficulty in the distinction of TSAs from other serrated polyps and conventional adenomas, particularly, tubulovillous adenomas. Immunohistochemical studies (9-11) performed to facilitate the diagnosis of TSAs in the colorectum showed widespread positivity with CK20 accompanied by aberrant CK7 expression related to BRAF mutation and serrated morphology while MUC gene expression pattern correlated with epithelial compartments: MUC5AC in gastric foveolar epithelium and MUC2 in goblet cells.

It is still controversial whether TSAs are inherently dysplastic or develop dysplasia later. While TSAs were previously considered as dysplastic ab initio, the current WHO classification (12) defines characteristic eosinophilic epithelial cells as senescent rather than dysplastic, although overt dysplasia can develop within these lesions. Despite initial conceptions, there is sufficient evidence in the literature that the bland-looking eosinophilic epithelial cells show low proliferative activity with Ki67 and are negative with p53, supporting their non-dysplastic nature (5,6).

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Differential diagnosis may be further complicated by the development of dysplasia, mainly the conventional adenomatous type but also the so-called serrated type.

Although initially identified in the colorectum, TSAs arising in the upper gastrointestinal (GI) tract, including the esophagus (13), stomach (14-22), duodenum (23-25), and also other GI sites, such as the pancreatic duct (26) and gallbladder (27) have recently been published as very rare case reports or small case series (28). Protuberant growth pattern, large polyp size, proximal location in the stomach, and ampullary preference in the small intestine are the features common to most of the reported TSAs. Furthermore, the majority of these cases harbor high-grade (HG) dysplasia and/or neoplasia suggesting aggressive behavior with rapid progression to invasive carcinoma (29). There are limited data concerning immunohistochemical and molecular features of the gastric and small intestinal TSAs, which may have different properties than their colorectal counterparts.

Here, we present a series of TSAs arising in unusual gastrointestinal locations, including the stomach and small intestine. We aimed to evaluate the histopathologic characteristics and neoplastic potential of these rare polyps in a detailed manner using digitalized images to make simultaneous comparisons of their morphologic and immunohistochemical features.

MATERIALS AND METHODS

Ethic statements

This study was approved by the institutional review board of Ankara University Medical School Division of Surgical Sciences, Department of Pathology (Decision Date: 13.05.2019). Written informed consent was obtained from patients who participated in the study.

MAIN POINTS

- *Practicing pathologist should be aware of the existence of TSAs in gastrointestinal locations other than colon, particularly stomach and small intestine. This study is the second largest series of upper gastrointestinal TSAs.*
- *The study exhibits the morphologic and immunophenotypic features of upper gastrointestinal TSAs in a detailed manner.*
- *Eosinophilic cells with pencillate nuclei accompanied by ectopic crypt foci and slit-like serration are the defining features of gastric and small intestinal TSAs.*
- *Upper gastrointestinal TSAs frequently harbour neoplastic foci, so that the complete excision of the lesion is necessary.*

Cases

There were 12 polyps with TSA features retrieved from a total of 1,534 gastrointestinal epithelial polyps from sites other than colon, diagnosed between January 2008 and December 2017 in the Department of Pathology, Ankara University School of Medicine. The cohort comprised TSAs removed either endoscopically or surgically for malignancy. Data including patient age, gender, polyp location, polyp size, and clinical history were collected from electronic medical records. Histologic diagnostic criteria for TSA were based on the presence of tubulovillous appearance, complex crypt architecture with epithelial slit-like serration, ECF and characteristic epithelial cells with eosinophilic cytoplasm, and centrally placed pencillate nuclei, either focally or diffusely within each polyp. Both H&E and immunostained slides were scanned to obtain digitalized images using a digital scanner (3D Histech Pannoramic 250 flash3) along with Case Viewer software, allowing simultaneous comparisons on the screen.

Histopathologic examination

Morphologic compartments, including eosinophilic cells (epithelial cells with cytoplasmic eosinophilia and mid-zonal pencillate nuclei), ECF (abnormally developed small/abortive crypts with loss of orientation with respect to the muscularis mucosa, but oriented to the mucosal surface in the luminal end), slit-like serration (a jigsaw puzzle-like appearance of the epithelium with narrow slits leading to broad luminal fronds), gastric foveolar epithelium, and goblet cells were assessed on digitalized H&E images of each polyp for their extent presented as percentages. The presence, type (conventional adenomatous or serrated), and grade of dysplasia and neoplasia were also noted.

Immunohistochemical (IHC) examination

Primary antibodies, including CK7 (clone: OV-TL 1230, 1:200; Cell M, USA), CK20 (clone: Ks20.8, 1:200; Cell M, USA), MUC2 (clone: MRQ-18; Cell M, USA), MUC5AC (clone: NCL; Leica, USA), MUC6 (clone: MRQ-20; Cell M, USA), Ki67 (clone: 30-9; Ventana, USA), p53 (clone: Bp53-11; Ventana, USA), p16 (clone: EGH4; Ventana, USA), MLH-1 (clone: M1; Ventana, USA), MSH-2 (clone: G-219-1129; Cell M, USA), MSH-6 (clone: 44; Ventana, USA), and PMS-2 (clone: EPR.3947; Cell M, USA) were employed using streptavidin biotin complex immunodetection system on Ventana automatic immunostainer (BenchMark XT Staining Module, Ventana Medical Systems Inc; Tucson, AZ, USA). Two cases (case 7 and case 9) were excluded from IHC analysis due to the inadequate amount of tissue in the paraffin blocks.

Digitalized H&E images were used as a reference to determine the compartments for further evaluation on immunohistochemically stained images displayed simultaneously on the screen for comparative assessment. Accordingly, the expression of the above markers was evaluated in the following compartments: eosinophilic cells, ECF, gastric foveolar epithelium, goblet cells, basal zone, dysplastic, and carcinomatous foci. The extent of staining for cytoplasmic/membranous markers, including cytokeratins and mucin proteins, were assessed throughout the polyp and also in each compartment, separately, using an arbitrary scale (0: nil; 1: 1-25% of cells, 2: 26-50% of cells, 3: >50% of cells). Staining intensity was also assessed on an arbitrary scale of 0 to 3 (0: nil; 1: weak; 2: moderate; 3: strong), and a final IHC score (0 to 9) was calculated by multiplying the extent and intensity grades. Expression of nuclear Ki67, p53, and MSI proteins (MLH-1, MSH-2, MSH-6, and PMS-2) were evaluated in the compartments, including dysplastic and carcinomatous areas. Loss of MLH-1, MSH-2, MSH-6, and PMS2 proteins were noted when no lesional cells showed nuclear staining. The expression of cytoplasmic and/or nuclear p16 was interpreted as "low expression" or "high expression," which was patchy and weak in a randomly distributed fashion or strong in a continuous fashion, respectively.

Statistical Analysis

Categorical variables were compared by Fisher's exact test and Mann-Whitney U test. Correlations between continuous variables were analyzed by nonparametric Spearman's correlation test on SPSS11.5. A $p<0.05$ was considered significant.

RESULTS

Clinicopathologic features

The study cohort comprised 12 polyps with TSA features localized in the GI tract outside colon; 5 (41.6%) in the stomach and 7 (58.4%) in the small intestine. The male: female ratio was 2:1 and the mean age of the patients was 60 years, ranging between 21 and 87 years. In cases 7, 9, and 12, the exact polyp size could not be determined due to the forceps biopsy procedure. Mean diameter of the remaining polyps (n=9) was 25 mm ranging between 10-55mm. Small intestinal TSAs were mostly flat (5/7; 71.4%) while all gastric TSAs (5/5; 100%) were protuberant in nature (p=0.028), endoscopically. Demographic data, clinical history of the patients, and clinicopathologic features of the cohort are presented in Table 1.

Histopathologic findings

All polyps showed main characteristic features of TSA, including eosinophilic cells, ECF, and slit-like serration. Morphologic features of gastric TSAs (Figure 1, 2, 3, 4 and 5) and small intestinal TSAs (Figure 6, 7 and 8) are demonstrated separately. All TSAs in the cohort demonstrated (given in brackets as median and range, respectively), eosinophilic cells (50%; 40-90%) as the most extensive

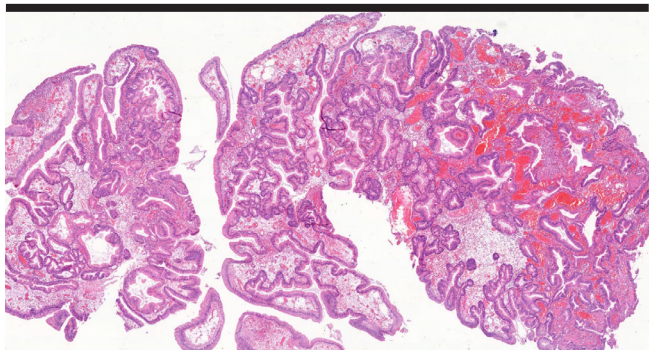

Figure 1. A gastric TSA; panaromic view with complex crypt architecture and villous surface (H&E, x20)

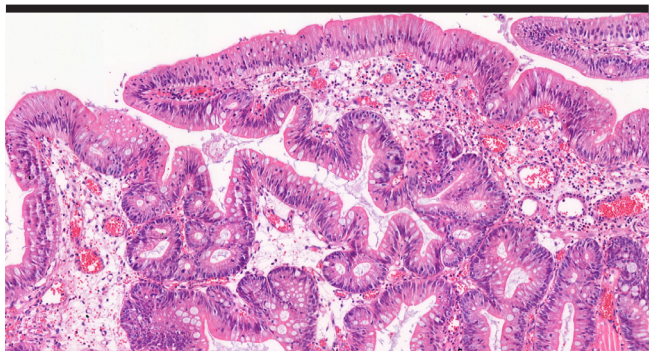

Figure 2. Ectopic crypts (H&E, x100)

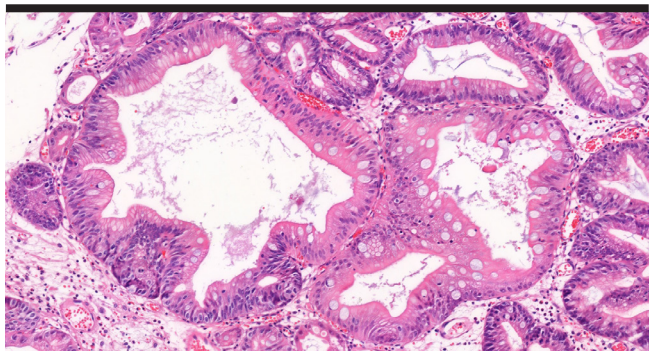

Figure 3. Eosinophilic cells with mid-zonal pencillate nuclei, ectopic crypts and scattered goblet cells (H&E, x100)

Table 1. Clinicopathologic characteristics of TSAs in the cohort.

Case no	Sex	Age	Polyp location	Specimen type	Growth pattern	Size (mm)	Malignant progression within TSA	Patient history
1	M	87	Stomach corpus	Polypectomy	Protuberant with stalk	10	Intramucosal carcinoma	Previous rectal adenocarcinoma + multiple colorectal tubular adenomas during follow-up
2	M	68	Stomach corpus	Gastrectomy	Protuberant with stalk	25	Intramucosal carcinoma	Synchronous grade3 gastric adenocarcinoma
3	F	53	Stomach corpus	Polypectomy	Protuberant no stalk	15	None	Concurrent multiple tubular adenomas in colorectum
4	M	69	Stomach pylorus	Polypectomy	Protuberant no stalk	35	Intramucosal carcinoma	None
5	F	45	Stomach antrum	Gastrectomy	Protuberant no stalk	25	Mucinous carcinoma	None
6	M	78	Duodenum ampulla	Polypectomy	Protuberant no stalk	20	Intramucosal carcinoma	Whipple's operation for adenocarcinoma of ampulla (focal signet ring cell) five months later + incidental gastric GIST
7	M	76	Duodenum	Forceps biopsy	Flat	3a	None	None
8	M	72	Duodenum	Endoscopic mucosal resection	Flat	55	None	None
9	M	54	Duodenum	Forceps biopsy (consult)	Flat	10a	None	None
10	F	22	Jejunum	Jejunectomy	Protuberant no stalk	35	Invasive carcinoma	Previous rectal adenocarcinoma
11	F	21	Jejunum	Jejunectomy	Flat	12	Invasive carcinoma	None
12	M	66	Terminal ileum	Forceps biopsy	Flat	8a	None	None

[a]Datum represents the likely measurable minimum size of the polyp because of forceps biopsy procedure.

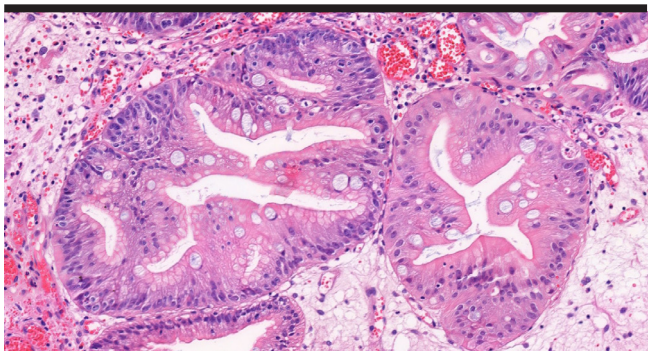

Figure 4. Slit-like serration and gastric foveolar epithelium (H&E, x200).

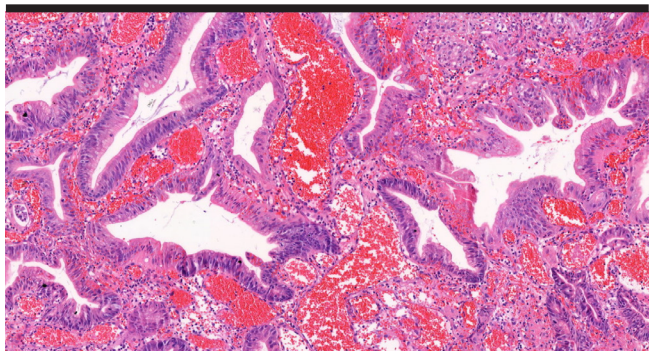

Figure 5. Dysplastic area and abrupt transition from eosinophilic cells to HG dysplasia (H&E, x100).

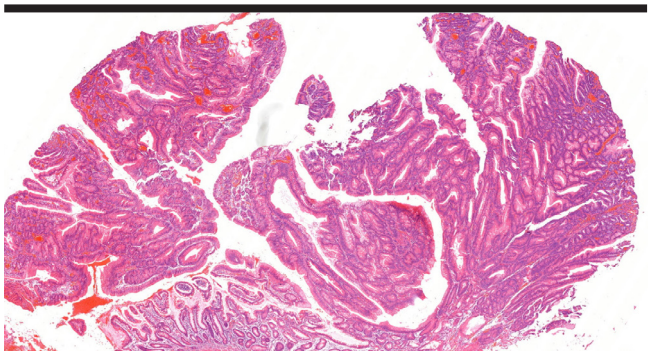

Figure 6. A small intestinal TSA; panaromic view with complex crypt architecture and villous surface (H&E, x17)

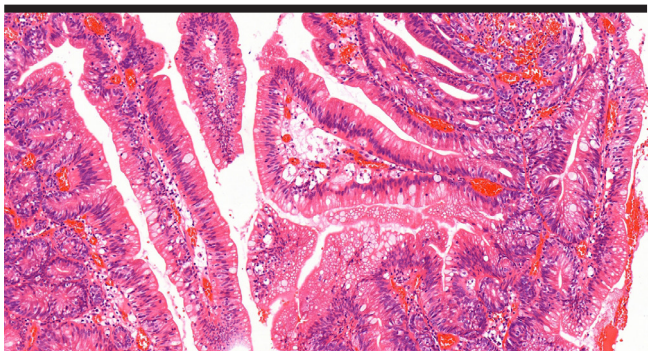

Figure 7. Eosinophilic cells with mid-zonal pencillate nuclei and numerous ectopic crypts in a small intestinal TSA (H&E, x130)

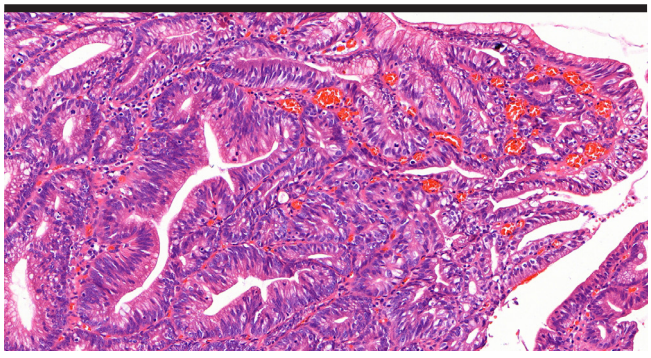

Figure 8. Neoplastic cells with severe cytologic atypia in a small intestinal TSA (H&E, x400).

morphologic feature followed by ECF (32.5%; 20-80%) and slit-like serration (30%; 20-50%), in decreasing order. However, gastric foveolar epithelium (10%; 0-60%) and goblet cells (25%; 0-70%) were mostly focal or absent.

In terms of neoplastic progression, HG dysplasia was present in eight (66.6%) cases (3/5 gastric + 5/7 intestinal) and carcinomatous foci were found in seven (58.3%) cases (4/5 gastric + 3/7 intestinal). Majority of the cases (9/12; 75%) showed adenomatous dysplasia, while the remaining three (25%) had serrated dysplasia. Though not significant, serrated dysplasia, invariably HG, was more common in gastric compared with intestinal TSAs (40% vs 14.3%, respectively). Adenocarcinoma was present in seven (58.3%) cases. Gastric TSAs (4/5; 80%) were more likely to show neoplastic progression compared with small intestinal TSAs (3/7; 42.9%) (p>0.05). Regardless of the location, carcinoma was significantly more frequent in protuberant TSAs (6 of 7; 85.7%) compared with the flat variant (1 of 5; 20%) (p=0.01).

Immunohistochemical findings

CK 20 was the most widely expressed marker in TSAs with the preference to eosinophilic cell compartment, while ectopic crypts were mostly negative. Ki67 (Figure 9) showed the opposite pattern of CK20 (Figure 10); ectopic crypts showed high proliferative activity as opposed to eosinophilic cells, which were scarcely positive with Ki67. MUC6 (Figure 11) and MUC2 (Figure 12) were selectively expressed in the basal zone and goblet cell compartments, respectively, with occasional positivity in other compartments. With regard to the polyp site, CK7 (p=0.003) and MUC5AC (p=0.049) were more commonly expressed by gastric TSAs, while MUC2 (p=0.055) was more common in intestinal TSAs. The results of IHC compartmental analysis for both gastric and small intestinal TSAs are demonstrated in Table 2.

Dysplasia and carcinoma compartments revealed CK7+/CK20+ profile in all gastric TSAs except one, while three of five intestinal TSAs showed CK7-/CK20+ profile. These compartments showed high expression of Ki67 and p53 together with mismatch repair (MMR) proteins, which were diffusely expressed in all except for two cases—combined loss of MLH1 and PMS2 was present in case 2 and combined loss of MSH2 and MSH6 was seen in case 10. p16 was "highly expressed" in all cases except for a gastric TSA (case 2), which contained serrated dysplasia and intramucosal carcinoma (Figure 13), distinctly negative for p16. Expressions of p53 and p16 in neoplastic foci are shown in Figure 14 and Figure 15, respectively.

Correlation analysis showed that CK7 and MUC5AC were positively correlated in eosinophilic cell (r:0.906**, p:0.000), ECF (r:0.712*, p:0.021), and gastric foveolar epithelial (r:0.828**, p:0.003) compartments. Positive correlation was also observed between CK7 and MUC6 in the basal zone (r:0.715*, p:0.020) and ECF (r:0.712*, p:0.021) compartments.

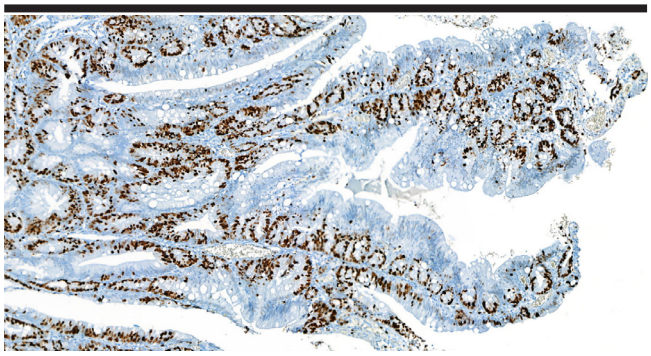

Figure 9. Ki67 emphasizes the high proliferation rate in ectopic crypts compared with eosinophilic cells, which are scarcely positive (IHC, x81).

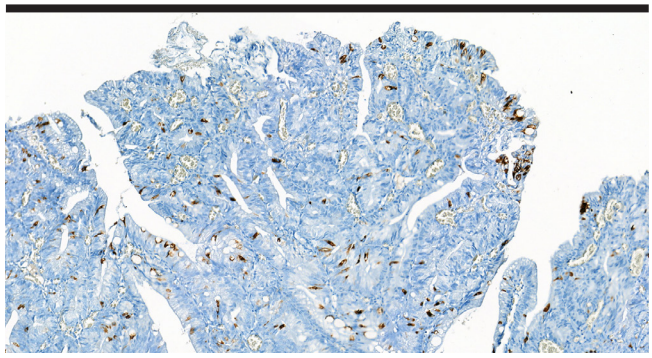

Figure 12. MUC2 highlights goblet cell compartment (IHC, x105).

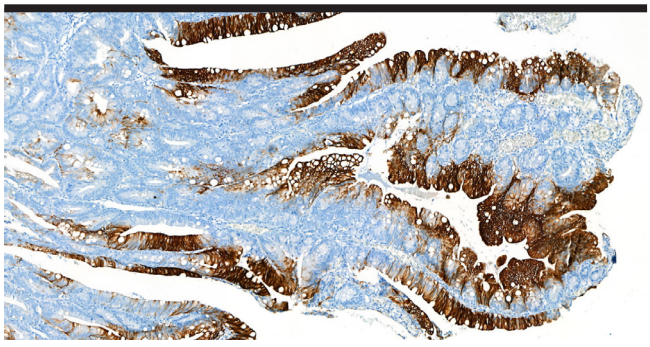

Figure 10. CK20 shows the opposite pattern of Ki67 with a high affinity to the eosinophilic cell compartment (IHC, x79).

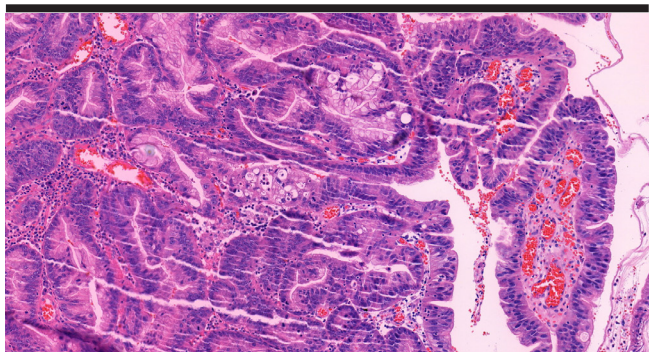

Figure 13. High-grade dysplastic foci harboring intramucosal carcinoma (H&E, x120).

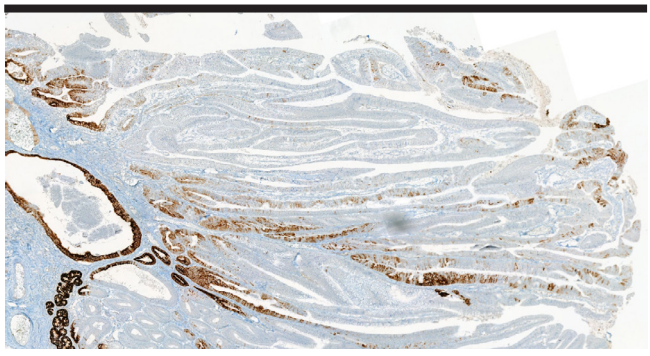

Figure 11. MUC6 is predominantly expressed in basal zone (IHC, x37).

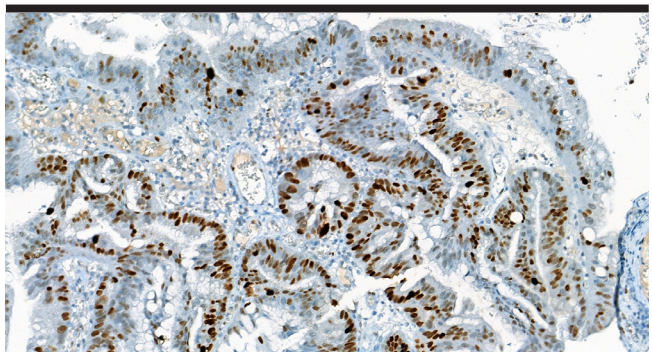

Figure 14. High expression of p53 in the dysplastic foci (IHC, x156).

DISCUSSION

A total of 74 TSAs located at sites other than colorectum, including esophagus, stomach, duodenum, pancreas, and gallbladder have been reported so far. Interestingly, 11 of these were case reports published by Rubio, who stressed the importance of pathologist's awareness of upper GI origin of TSAs as well as their neoplastic potential. Following the initial reports, two larger series by Rosty et al (23) and later by Kwon et al (22) comprising 13 duodenal and 9 gastric TSAs, respectively, were published. In some of these publications, polyps were defined as "serrated adenomas" (i.e., using the term without a prefix) without further specifying whether they were SSA/Ps or TSAs.

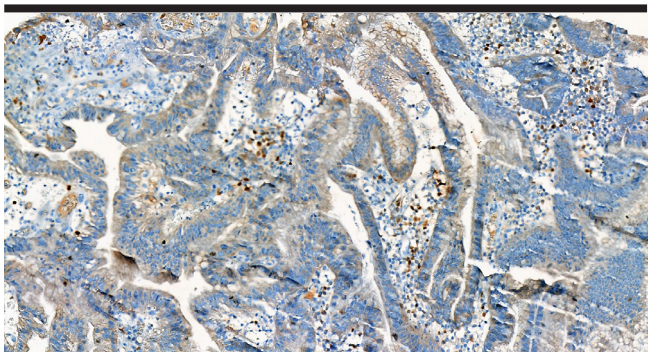

Figure 15. p16 is lost in the neoplastic compartment (IHC, x129).

Table 2. Immunohistochemical staining scores[a] in TSAs.

IHC markers	All TSAs	Gastric TSAs	Intestinal TSAs	p
CK7	0.5 (0-9)	4 (1-9)	0 (0-1)	0.003
CK20	3.5 (0-9)	6 (1-9)	3 (0-6)	0.268
MUC2	2 (0-4)	1 (0-4)	3 (0-4)	0.055
MUC5AC	1.5 (0-6)	6 (1-6)	0 (0-6)	0.048
MUC6	2 (0-6)	4 (0-6)	2 (0-6)	0.149

[a]Staining scores were achieved by multiplying intensity and extent of the markers and presented as median and range (brackets)

Table 3. Review of the literature on TSAs located outside the colon.

Localization	TSA (n)	Malignant progression (n)
Esophagus [13]	1	1
Stomach [14-22]	40 (5 - current series)	30 (4 - current series)
Small intestine [23-25, i, ii]	43 (7 from current series)	14 (3 from current series)
Pancreas [26]	1	1
Gallbladder [27]	1	1
Total n (%)	86	47 54.6%)

i.Srivastava A, Rege TA, Kim KM et al. (2000) Duodenal serrated adenomas: evidence for serrated carcinogenesis in the proximal small intestine. Mod Pathol 13: 103-6. Supplement USCAP 100th Annual Meeting. Abstract # 705.
ii. Taggart M, Rashid A, Estrella J et al. (2000) Serrated polyps of the extracolonic gastrointestinal tract. Histologic findings and genetic alterations. Mod Pathol 13: 212-4. Supplement USCAP 100th Annual Meeting. Abstract # 753.

However, the reported cases had similarities with TSAs of the colorectum. This study represents a significant number of TSAs in unusual GI sites comprising seven small intestinal and five gastric cases, examined meticulously for morphologic and immunophenotypic characteristics. Table 3 summarizes the published cases of TSAs with unusual locations, including our series.

Diagnosis of TSA is difficult on purely morphologic grounds, even in the colorectum. Tubulovillous architecture, ECF, slit-like serration and epithelial cells with eosinophilic cytoplasm, and centrally placed pencillate nuclei, in various combinations, have been favored as characteristic features of TSAs (30-32). In a very recent report, Hiromoto et al (9) based their inclusion criteria on the presence of all the above features in at least 50% of the polyp. In another study, at least two of the above features (except for tubulovillous architecture), one of which being present in >50% of the polyp, were considered as diagnostic for TSA (6). Due to the lack of consensus, we decided to look for all the currently available criteria and determine their extent within the polyps. With this approach, we found that the eosinophilic cell compartment was the most extensive feature with an average of 61.6% in our series, similar to previous reports (6,31,33,34), followed by slit-like serration and ECF in more than 30% of an individual polyp. Although ECF was proposed as the key diagnostic feature for TSA by Torlakovic et al (32) in their original proposal, colorectal TSAs with no ECFs (6, 35-37) and also other serrated or non-serrated polyps with ECFs (33,35) have been reported by others in the following years. Vayrynen et al (34) analyzed the prevalence of ECF in both conventional adenomas and serrated colorectal polyps, and suggested that the presence of numerous ECF favors the diagnosis of TSA. Our study also confirms that the coexistence of ECF, eosinophilic cells with pencillate nuclei, and slit-like serration should alert the pathologist for the possibility of a TSA, even when located in an unusual site.

In this study, digitalized images facilitated the evaluation of TSAs in a more detailed manner on the screen. Once the compartments were determined, H&E image of the compartment was uploaded on the screen next to the corresponding immunostained image. This approach allowed detailed simultaneous analysis of the cases for both morphologic and immunophenotypic features. The results of this analysis demonstrated that CK20 was the most extensively expressed marker in both intestinal and gastric TSAs, with a tendency to eosinophilic cell and dysplasia/carcinoma compartments, whereas CK7 was focal, with a tendency to gastric foveolar epithelium and dysplasia/carcinoma compartments and was restricted to gastric TSAs. Aberrant CK7 expression was associated

with serrated morphology in colorectal serrated lesions containing gastric foveolar epithelium (10,11). However, no such aberrant expression was present in small intestinal TSAs in our series, despite the presence of gastric foveolar epithelium. Ki67 showed the opposite pattern of CK20 and ectopic crypts showed high proliferative activity as opposed to eosinophilic cells, which were scarcely positive with Ki67. This peculiar pattern of TSA, presented by Torlakovich et al (32) in their detailed comparative analysis of serrated lesions, serves as a distinguishing feature in the colorectum, while no such information is present for other GI sites. However, it supports the view that eosinophilic cell compartment is non-proliferative and not dysplastic, but rather senescent. MUC gene expression, on the other hand, served useful in demonstrating intestinal and gastric differentiation using MUC2,and MUC 5AC and/or MUC6, respectively, in serrated lesions of the colorectum. TSAs in the present study showed a similar MUC gene expression pattern with MUC5AC in the foveolar epithelial compartment, predominantly in gastric TSAs, MUC2 in goblet cells, predominantly in small intestinal TSAs, and MUC6 in the basal zone with no site predilection.

The definition of TSA has some gray zones: (i) the epithelial lining is different from conventional adenoma despite the usage of the term "adenoma" in its name, (ii) characteristic epithelium with eosinophilic cytoplasm and mid-zonal pencillate nuclei are no longer considered as dysplastic but rather as senescent cells, however, overt dysplasia can develop in TSA, and (iii) TSA is a precursor lesion of colorectal carcinoma and belongs to the family of serrated polyps and should be regarded as a preneoplastic lesion in a similar manner as the conventional adenoma. Taken together, these make dysplasia in TSAs a controversial issue. With an emphasis on elongated penicillate nuclei of eosinophilic cells resembling adenomatous epithelium, TSAs were initially regarded as inherently dysplastic. However, recent evidence suggests that the reverse can be true (6). The counter thesis was first justified by Bettington et al, who stressed that eosinophilic cells showed no morphologic atypia, no mitotic activity/very low Ki67 proliferative index, and lack of p53 and ß-catenin staining with retained p16. Low expression of Ki67 in eosinophilic cells in contrast to the diffuse and strong p53 and Ki67 expression in dysplastic/carcinomatous foci in our series is in accordance with Bettington's thesis and support the idea that TSAs may not, at least initially, be dysplastic. Whether or not, inherently dysplastic, not all, but a substantial number of TSAs develop overt dysplasia (conventional adenomatous and/or serrated), which were alternatively called as "advanced TSAs" to highlight the high risk of (rapid) malignant progression (29,38). Both types of dysplasia were present in our cases—serrated dysplasia being more frequent in gastric TSAs, which showed higher neoplastic progression rate compared with intestinal TSAs. This finding is in accordance with the previous view regarding the occurrence of more rapid neoplastic transformation in dysplastic ("advanced") serrated polyps of the colorectum. Rubio, derived from previously published data, highlighted in his review that upper GI TSAs showed 53.4% neoplastic progression rate (ranging between 20-78%) (29). Therefore, we believe that the critical issue is to assign the presence of high-grade dysplasia rather than its subtype in the pathology report.

TSAs in our series showed high expression pattern of p16 in dysplastic and carcinomatous compartments, except for one case showing an abrupt loss of p16 in the area of serrated dysplasia. This observation was also reported by Bettington et al who associated the loss of p16 with BRAF mutations in the neoplastic areas of colorectal TSAs (6). Currently, we and others, do not know if similar association is present in gastric and small intestinal TSAs as there are very limited data on their molecular features (20,22,23).

Unlike SSA/Ps, colorectal TSAs and carcinomas arising in TSAs are known to be microsatellite stable (6,7). However, two of the TSAs in our study showed loss of MMR proteins; case 2, a 68-year-old male with a gastric TSA showing intramucosal carcinoma with an adjacent gastric adenocarcinoma, and case 10, a 22-year-old female with a jejunal TSA showing an invasive adenocarcinoma and a history of primary rectal adenocarcinoma. There is only one study in the literature looking at MSI in duodenal adenomas, including one TSA, which was microsatellite stable (39). The two cases discussed above may be MSI and may be members of Lynch families, though not confirmed by DNA fragment analysis and no such family history was available.

In conclusion, it is important for the practicing pathologist to be aware of the existence of TSAs in GI locations other than colon, particularly stomach and small intestine. The results of this study suggest that eosinophilic cells with centrally placed pencillate nuclei, slit-like serration, and ECF, each at least comprising more than 30% of the polyp are the major features for a diagnosis of TSA. Although they show significant similarities with their colorectal counterparts, it is of note that neoplas-

tic progression seems to be a more common feature for gastric TSAs. Therefore, the potential risk of rapid malignant transformation requiring complete excision of TSAs should also be mentioned in the pathology report. Further molecular analysis in correlation with the above findings would serve better to understand the biology of these rare polyps.

Ethics Committee Approval: This study was approved by the institutional review board of Ankara University Medical School Division of Surgical Sciences Department of Pathology (Decision date: May 13 2019).

Informed Consent: Written informed consent was obtained from patients who participated in the study.

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