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Serrated adenoma of the stomach: A clinicopathologic, immunohistochemical, and molecular study of nine cases

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Summary. Gastric serrated adenoma is a recently recognized entity that has been rarely described and poorly characterized. To examine whether gastric serrated adenoma shares the same immunophenotypic and molecular features of its colorectal traditional serrated adenoma, the clinicopathologic features, expression of mucin proteins (MUC2, MUC5AC, CD10, MUC6) and mismatch repair protein (MLH1), and mutations of *BRAF* and *KRAS* genes were studied.

The nine serrated adenomas were obtained from five men and four women, with a mean age of 67 years. Seven (78%) serrated adenomas were located in the body of the stomach. The endoscopic findings were not sufficiently characteristic to diagnose serrated adenoma or serrated adenocarcinoma; however, most were elevated lesions. The initial biopsy material was available in all cases and the serrated features were evident in 6 cases diagnosed as adenoma. Among the nine cases, seven (78%) were associated with invasive adenocarcinoma within the serrated adenoma. MUC5AC was expressed in 6 serrated adenomas (67%). Expression of MUC5AC was observed in all tumors located in the lower third of the stomach. Focal MUC6 expression was observed in the basal part of two serrated adenomas. MLH1 expression was lost in two cases (22%). *KRAS* mutations were observed in three cases (33%) while *BRAF* mutations were not detected in any of the cases.

Gastric serrated adenoma does not completely share the same immunophenotypic and molecular features of its colorectal counterpart. Gastric serrated adenomas are frequently associated with adenocarcinoma. When serrated adenoma is encountered in a gastric biopsy specimen, the possibility of associated adenocarcinoma should be considered in the adjacent stomach.

Key words: Gastric, Serrated, Mucin, Adenoma, Adenocarcinoma, *BRAF, KRAS*

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Introduction

The World Health Organization (WHO) classification subdivides gastric adenomas into tubular, papillary, and papillary-tubular. Since Rubio et al. (Rubio, 2001) first reported these growths in the stomach, isolated cases of serrated adenoma have been described (Rubio and Lagergren, 2004; M'Sakni et al., 2007; Hasuo et al., 2009). Serrated adenomas often occur in male patients and are usually located in the upper third of the stomach presenting as a polypoid mass (Rubio, 2001; Rubio and Lagergren, 2004; M'Sakni et al., 2007; Hasuo et al., 2009). The gastric serrated adenoma has elongated fronds with lateral crenated, saw tooth-like notches as a result of scalloped epithelial indentations (Rubio, 2001). The serrated crypts are lined by overtly dysplastic epithelial cells containing abundant eosinophilic cytoplasm and stratified elongated penicillate nuclei. These microscopic features mimic traditional serrated adenoma found in the colorectum (Rubio, 2001; Rubio and Lagergren, 2004; Dong et al., 2005; M'Sakni et al., 2007; Kim et al., 2010).

The mucin phenotype in tumors of the gastrointestinal tract can be used to trace back to the cell of origin and can be classified into five phenotypes: gastric, gastrointestinal, intestinal, small intestinal, and unclassified (Winterford et al., 1999; Shiroshita et al., 2004). MUC2 is a goblet cell-type mucin predominantly expressed in the colon and small intestine. On the other hand, MUC5AC and MUC6 are gastric-type mucins expressed in the surface foveolar epithelium and deep antral/pyloric glands, respectively (Corfield et al., 2001; Byrd and Bresalier, 2004). CD10 is an intestinal marker for the striated border on the luminal surface of small intestinal absorptive cells (Shiroshita et al., 2004). Recently, mucin expression has been explored in the colonic serrated adenomas, with most being found to express colonic or gastric foveolar-type mucins (Hirono et al., 2004; Gibson et al., 2011). However, few studies have investigated the mucin phenotype in gastric serrated adenomas. A single case of gastric serrated adenoma reported to predominantly express gastric mucin phenotype (Hasuo et al., 2009).

In the colorectum, serrated polyps represent the histological expression of a molecular genetic paradigm of carcinogenesis that differs from that of the traditional adenoma–carcinoma sequence (Jass et al., 2002). Traditional serrated adenoma is a precursor of approximately 20% of all colorectal cancers and histologically shows nuclear atypia, pseudostratification, micropapillations of the surface epithelium, and the cells reveal abundant eosinophilic cytoplasm (Torlakovic et al., 2003). In the colorectum, a high frequency of *BRAF* mutation was reported and *KRAS* mutation may herald the onset of an aggressive phenotype in the neoplastic progression of traditional serrated adenomas (Yang et al., 2004; Lee et al., 2005; Kim et al., 2010).

Although diagnostic criteria, mucin phenotypes, and underlying genetic characteristics of traditional serrated adenoma in the colorectum were established, gastric serrated adenomas are far too rare to know whether this morphology reflects the underlying genetic alterations as it does in the colon (Fenoglio-Preiser et al., 2007). The objective of this study was to examine the clinicopathologic features, the relationship between serrated adenoma and associated carcinoma, expression of mucin phenotypes, and the presence or absence of *BRAF* and *KRAS* mutations in nine gastric serrated adenomas.

Materials and methods

Case selection

Between January 2006 and July 2011, 13,840 patients were endoscopically (n=3,687) and surgically (n=9,497) treated for gastric adenoma or gastric carcinoma at Samsung Medical Center. Of these patients, nine (0.07%) gastric adenomas with at least a focal-serrated phenotype with or without associated invasive adenocarcinoma were identified and formed the basis of this study. Histology of the nine lesions was reviewed for the confirmative diagnosis and classified based on the presence of coexisting conventional tubular adenoma or tubular adenocarcinoma and the proportion of serrated adenoma/adenocarcinoma. The diagnosis of gastric serrated adenoma and serrated adenocarcinoma was based on histologic characteristics of traditional serrated adenoma and serrated adenocarcinoma of the colorectum (Makinen, 2007). Briefly, the diagnostic criteria included a serrated morphology with overtly dysplastic epithelial cells containing abundant eosinophilic cytoplasm and stratified elongated penicillate nuclei. Villous lesions of papillary projections with a fibrovascular core and serrated-like structure without overt dysplasia were excluded (Makinen, 2007). A massive invasion within the serrated adenoma with preservation of the serrated morphology was diagnosed as serrated adenocarcinoma. The size of adenomas/adenocarcinomas with serrated features was determined by measuring the lesion on a glass slide corresponding to the mapped lesion. Information regarding clinical history, follow-up data, endoscopic findings, relevant clinical investigations, treatment, and patient outcomes were obtained retrospectively from the review of medical records.

Immunohistochemical analysis

Immunohistochemical analyses were performed on 3 μm sections of formalin-fixed, paraffin-embedded tissue from all nine cases. Tissue sections on glass slides were deparaffinized in xylene, hydrated in descending concentrations of alcohol, and then washed with distilled water. The slides were washed three times in phosphate buffer, incubated with primary antibodies for MUC2 (Ccp58, 1:100, Novocastra, Newcastle, UK), MUC5AC (CLH2, 1:100, Novocastra), MUC6 (CLH5, 1:50, Novocastra), CD10 (56C6, 1:100, Novocastra), and MLH1 (clone G168-15, 1:100, BD Pharmingen, San Diego, CA, USA), and subsequently treated with secondary antibodies. All the reactions were performed using the Leica BOND-MAX™ System after antigen retrieval with the Bond epitope retrieval solution (Leica Microsystems, Wetzlar, Germany). For MUC2, MUC5AC, MUC6, and CD10, positive staining was defined as distinct membranous and cytoplasmic staining in more than 5% of the tumor cells, as previously described (Bartley et al., 2010).

For interpretation of immunohistochemistry, staining for MLH1 was considered assessable when nuclear staining was seen in either stromal or normal foveolar epithelial cells around the tumor. MLH1 expression was considered lost when no nuclear staining was identified within the nuclei of tumor cells. The two authors (MJK and KMK) interpreted the staining results, and there was good agreement (Kappa 100%) for the interpretation of MUC5AC, MUC2, and CD10. However, the interobserver agreement for MUC6 was moderate (Kappa 78%) because the staining was weak and

localized within the basal part of the tumors in two cases. In those 2 cases with disagreement, final scoring was determined by a consensus.

Molecular analysis of BRAF and KRAS genes

DNA was extracted from 0.1% methylene blue-stained, 4-μm-thick tissue sections of serrated adenomas and associated carcinomas. The tumor was separated from the adjacent normal tissue using light microscopic microdissection and 20-gauge needles. Molecular analyses of *BRAF* gene exon 15 and exons 2 and 3 of *KRAS* gene were conducted in all nine cases as previously described (Dong et al., 2005; Kim et al., 2010).

Results

The clinical, pathologic and molecular features of patients with gastric serrated adenomas are summarized in Table 1. The nine serrated adenomas were obtained from five men and four women, with a mean age of 67 years (range, 41 to 89 years). Seven (78%) tumors were removed from the body and two (22%) from the antrum. In one case (patient 9), there was a familial history of gastric cancer.

The endoscopic findings were not sufficiently characteristic to diagnose serrated adenoma or serrated adenocarcinoma; however, most of them were elevated lesions. Gross examination of the resected specimens showed elevated mass with lobulated surface (n=3), polypoid mass with nodular surface (n=4), and polypoid mass with infiltration (n=2).

The initial biopsy material was available for review in all nine cases. The pathologic diagnoses of these initial biopsies were tubular adenoma with low-grade dysplasia (n=2), tubular adenoma with high-grade dysplasia (n=2), villous adenoma with high-grade dysplasia (n=2), papillary adenocarcinoma (n=2) and tubular adenocarcinoma (n=1). In all six cases diagnosed as adenoma, serrated features were evident in the biopsy samples (Fig. 1). In 2 cases diagnosed as adenoma, endoscopic resection was performed. In the remaining 4 cases, gastrectomy was performed because the tumor size was large and clinically suspected as malignancy.

After review of the H&E slides obtained after treatment, the gastric serrated adenomas were classified into three subgroups: predominant serrated adenoma with minor portion of conventional tubular adenoma (Fig. 2); serrated adenoma in association with serrated adenocarcinoma (Fig. 3); and mixed serrated and tubular adenoma associated with serrated and tubular adenocarcinomas (Fig. 4).

In predominant serrated adenomas (patients 1 & 2), the tumors were located in the lower third of the stomach presenting as elevated lesions. The lesions were small and exhibited serrated adenoma with high-grade dysplasia and focal tubular adenoma with low-grade dysplasia. The serrated adenomas were located at the center of the lesion comprising more than 80% of the total tumor volume. The patients were treated by endoscopic submucosal dissection and the patients had no disease recurrence during follow-up periods.

The serrated adenoma in association with serrated adenocarcinoma was the most frequent histology found in 5 cases (patients 3, 4, 5, 6 and 7). The tumors occurred in the lower third and mid body of the stomach presenting as a polypoid mass. The serrated adenocarcinoma arose in the background of serrated adenomas with focal high-grade dysplasia. Serrated adenocarcinoma was the only component of invasive carcinoma and the patients had no lymph node metastasis or disease recurrence during follow-up.

Table 1. Clinicopathologic findings in nine patients with gastric serrated adenoma.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age / Gender	72 / M	61 / M	89 / M	65 / F	77 / M	72 / M	72 / F	41 / F	54 / F
Associated lesion	TA	TA	SADC	SADC	SADC, TA	SADC	SADC	TA, SADC, TADC	TA,SADC, TADC
Size of serrated adenoma	2.2cm	1.5cm	5cm	5.2cm	3cm	4.2cm	5.5cm	4cm	8cm
Total mass size	2.6cm	1.6cm	5cm	5.2cm	3.2cm	4.2cm	5.5cm	9.5cm	13cm
Gross type	Elevated	Elevated	Polypoid	Polypoid	Elevated	Polypoid	Polypoid	Polypoid and infiltrative	Polypoid and infiltrative
Location	mid body	antrum	low body	low body	mid body	antrum	mid body	low body	low body, antrum
h of invasion	-	-	T1a (SM)	T2a (PM)	T1a (MM)	T1a (MM)	T1a (MM)	T4a (serosa)	T1a (SM)
LN status	-	-	N0 (0/28)	N0 (0/16)	N0 (0/25)	N0 (0/27)	N0 (0/29)	N3 (16/36)	N1 (2/21)
Family history	-	-	-	-	-	-	-	-	+
KRAS mutation	wild	exon 2 G12D	wild	wild	exon 2 G12A	wild	wild	wild	exon 3 G60G, Q61K
BRAF mutation	wild	wild	wild	wild	wild	wild	wild	wild	wild
MLH1 expression	preserved	preserved	lost	lost	preserved	preserved	preserved	preserved	preserved

M, Male; F, Female; HGD, serrated adenoma, high grade dysplasia; SADC, serrated adenocarcinoma; TA, tubular adenoma; SA, Serrated adenoma; TADC, tubular adenocarcinoma; SM, submucosa; PM, proper muscle; MM, muscularis mucosa; LN, Lymph node; Family history, family history of gastric cancer.

Mixed serrated and tubular adenoma associated with serrated and tubular adenocarcinomas were observed in two cases (patients 8 and 9). Grossly, the tumors were both polypoid and infiltrative. Microscopically, the serrated adenocarcinomas arising in the background serrated adenomas were observed in the polypoid portion. Lymph node metastases were observed in all two cases and one patient showed liver metastasis during follow-up.

Immunohistochemical results of MUC2, MUC5AC, MUC6, and CD10 are summarized in Table 2 and Fig. 5. MUC5AC showed moderate to strong and diffuse cytoplasmic staining in 6 (67%) serrated adenomas and in 5 (71%) serrated adenocarcinomas. Weak and focal MUC6 positivity was observed in 2 serrated adenomas (22%) (patients no. 1 and 3), where the positivity was localized in the basal part of serrated adenomas. The serrated adenocarcinoma portion of patient 3 did not express any MUC6 protein in the basal part. MUC2 and CD10 were negative in all gastric serrated adenomas. MUC5AC was not observed in the background conventional adenoma or tubular adenocarcinoma. Interestingly, six serrated adenomas with MUC5AC expression were found in the lower third of the stomach, whereas the other three cases without MUC5AC expression were located at the body of the stomach.

Expression of MLH1 was preserved in 7 (78%) gastric serrated adenomas and two cases (22%) lost MLH1 expression (Table 1).

Mutations of *KRAS* gene were identified in 3 serrated neoplasms (33%); a serrated adenoma with high-grade dysplasia and in two serrated adenomas associated with adenocarcinoma (Fig. 6). However, *BRAF* mutation was not detected in any of the cases.

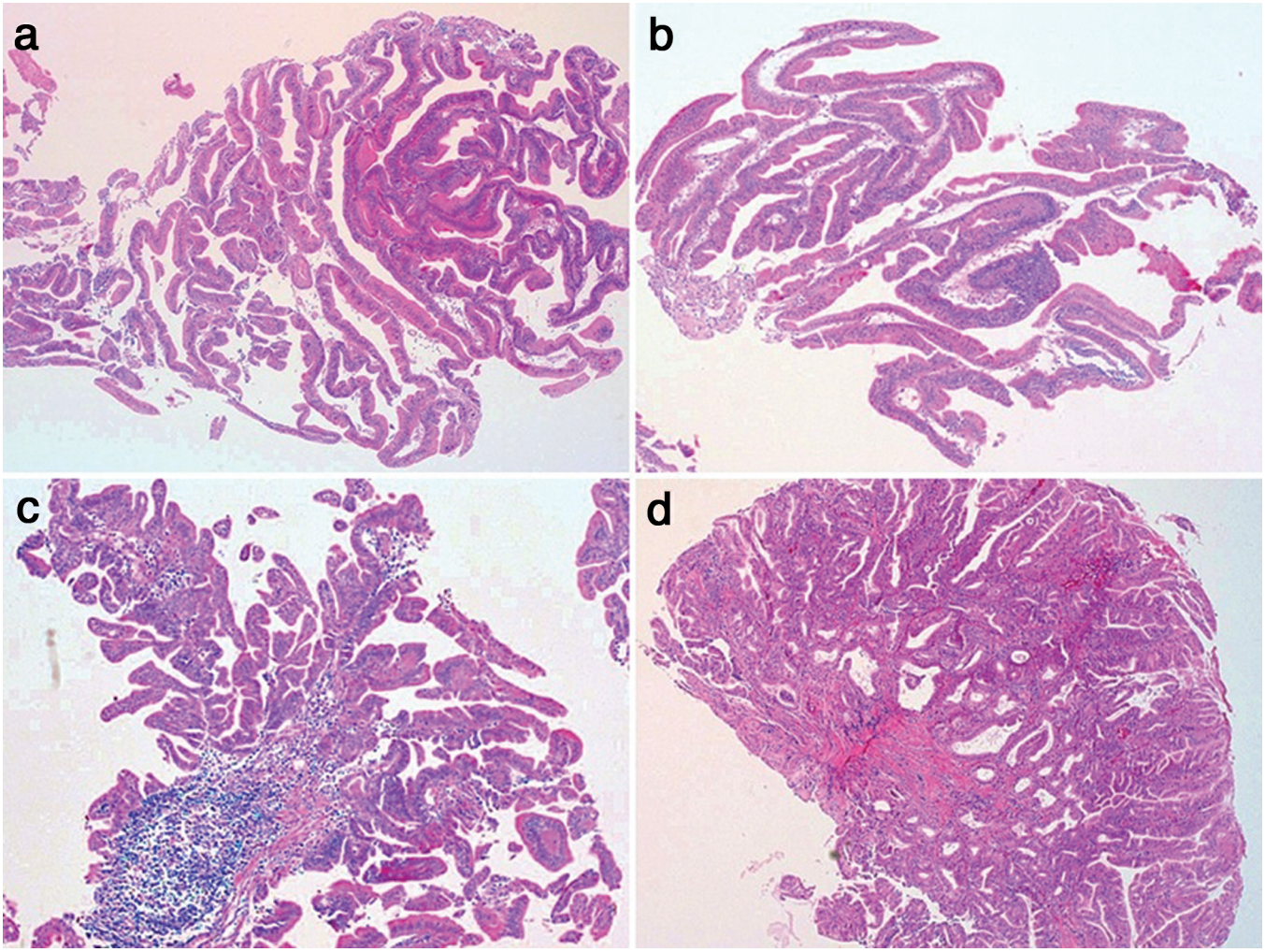

Fig. 1. Serrated adenomas recognized in biopsy specimens. Histologically, neoplastic glands show serrated morphology with overtly dysplastic epithelial cells containing abundant eosinophilic cytoplasm and stratified elongated penicillate nuclei. **a.** Patient 1. **b.** Patient 9. **c.** Patient 2. **d.** Patient 7. x 100

Discussion

To examine clinicopathologic, immunophenotypic and molecular features of gastric serrated adenomas, we investigated 9 gastric serrated adenomas. We found that 78% of gastric serrated adenomas were associated with invasive adenocarcinoma and mutations of *KRAS* gene were detected in 33% of cases.

A review of previous publications indicates that gastric serrated adenoma is a recently described

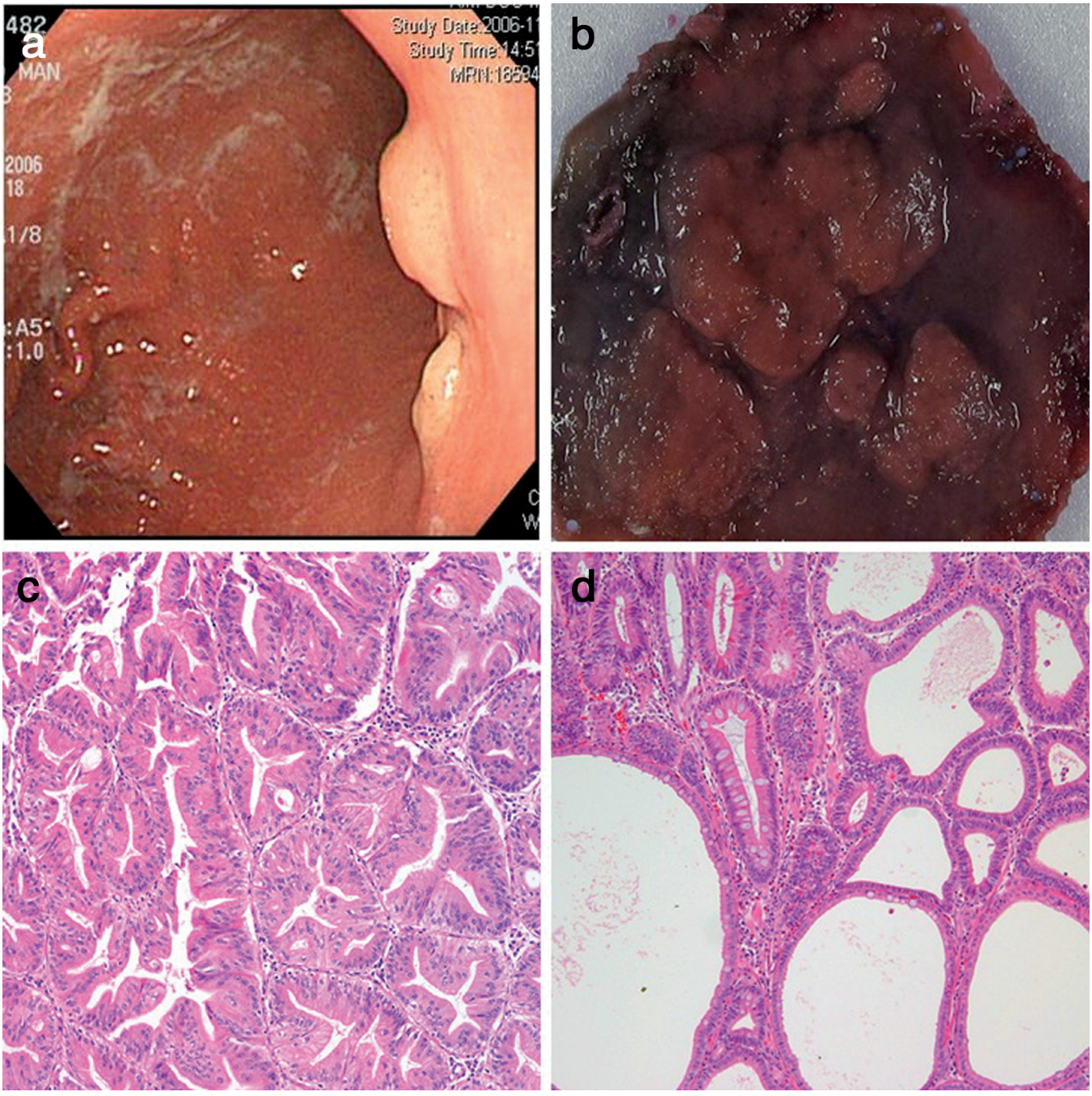

Fig. 2. Predominant serrated adenoma with a minor portion of conventional tubular adenoma. The endoscopic **(a)** and gross **(b)** findings show an elevated mass with a lobulated surface. The serrated adenoma with low-grade dysplasia has crowded dysplastic epithelial cell nests with serration. The cells have eosinophilic cytoplasm and stratified elongated penicillate nuclei **(c)**. The conventional tubular adenoma with low-grade dysplasia is located at the periphery of the lesion **(d)**. x 200

phenotype of gastric adenoma, characterized by a particular proclivity to evolve into invasive carcinoma (Rubio and Lagergren, 2004). More than half of the gastric serrated adenoma cases have shown malignant transformation (Rubio, 2001; Rubio and Lagergren, 2004; M'Sakni et al., 2007; Hasuo et al., 2009). Consistent with previous findings, we also recognized that a remarkably high frequency (78%) of gastric serrated adenomas was accompanied by invasive adenocarcinoma. In gastric conventional adenomas, malignant transformation or coexistence with cancers were found in 6.8% to 30% of cases (Kamiya et al.,

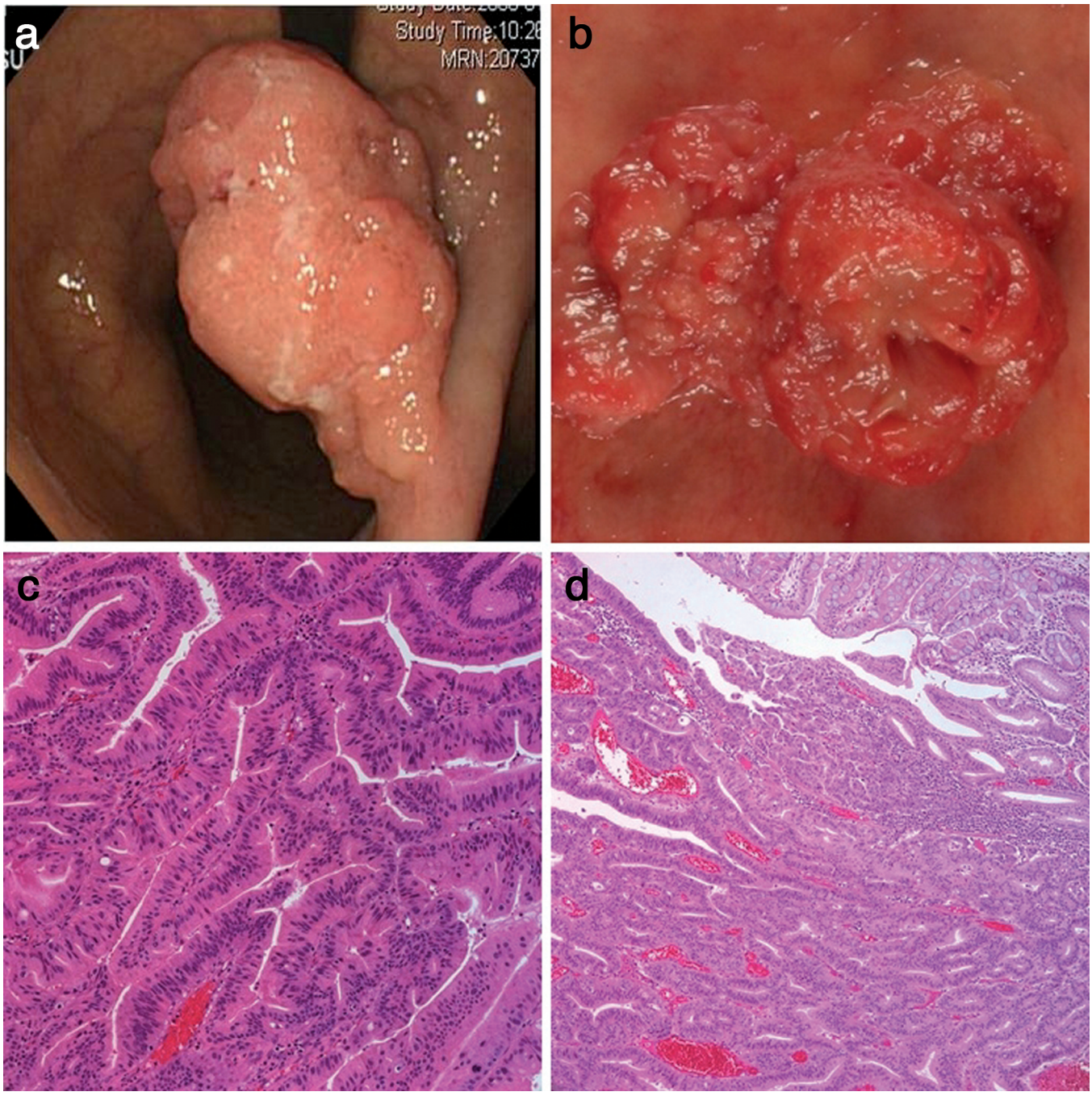

Fig. 3. Serrated adenoma associated with serrated adenocarcinoma. Endoscopic **(a)** and gross **(b)** examination shows a polypoid mass with a nodular surface. The serrated adenoma with high-grade dysplasia is a predominant component **(c).** The serrated adenocarcinoma **(d)** arose in the background of serrated adenomas with high-grade dysplasia. x 200

1982; Park et al., 2001; Jung et al., 2010). The high frequency of association with an invasive carcinoma in gastric serrated adenoma is intriguing. Although the high rates of accompanying carcinoma cannot confirm serrated adenomas as being precursor lesions to gastric cancer, these findings nevertheless cannot be ignored. Therefore, when serrated adenoma is diagnosed in a gastric biopsy specimen, the possibility of carcinomatous transformation within the serrated adenoma should be considered. In these circumstances, multiple biopsies are recommended, and if malignancy is suspected clinically, surgical management should be considered.

In the colorectal traditional serrated adenomas, mutations of *BRAF* and *KRAS* genes were observed in 33-62% and 24-29% of cases, respectively (O'Brien et al., 2006; Jass, 2007; Kim et al., 2010), and the risk of malignant transformation was approximately 10% and closely associated with *KRAS* mutations (Kim et al., 2010). In gastric serrated adenoma, *BRAF* and *KRAS* mutations have been investigated in a single case and turned out to be wild-type for both *BRAF* and *KRAS* genes (Hasuo et al., 2009). The present 9 cases did not exhibit any *BRAF* mutation either. However, *KRAS* mutations were identified in 33% (3/9); one mutation detected in high-grade serrated adenoma, and the other 2 mutations detected in serrated adenomas associated with adenocarcinoma. Considering that mutations of *BRAF* and *KRAS* genes were observed in 2.2% and 2.8% of gastric adenocarcinomas in the same ethnic background (Lee et al., 2003), the frequency of *KRAS* mutations found in this study was relatively high. In conventional gastric adenomas, no studies on mutations of *KRAS* or *BRAF* genes have been reported.

In this study on mismatch repair protein expression in gastric serrated adenomas, we found that 22% of cases lost expression of MLH1. In traditional serrated adenomas of the colorectum, loss of MLH1 expression is

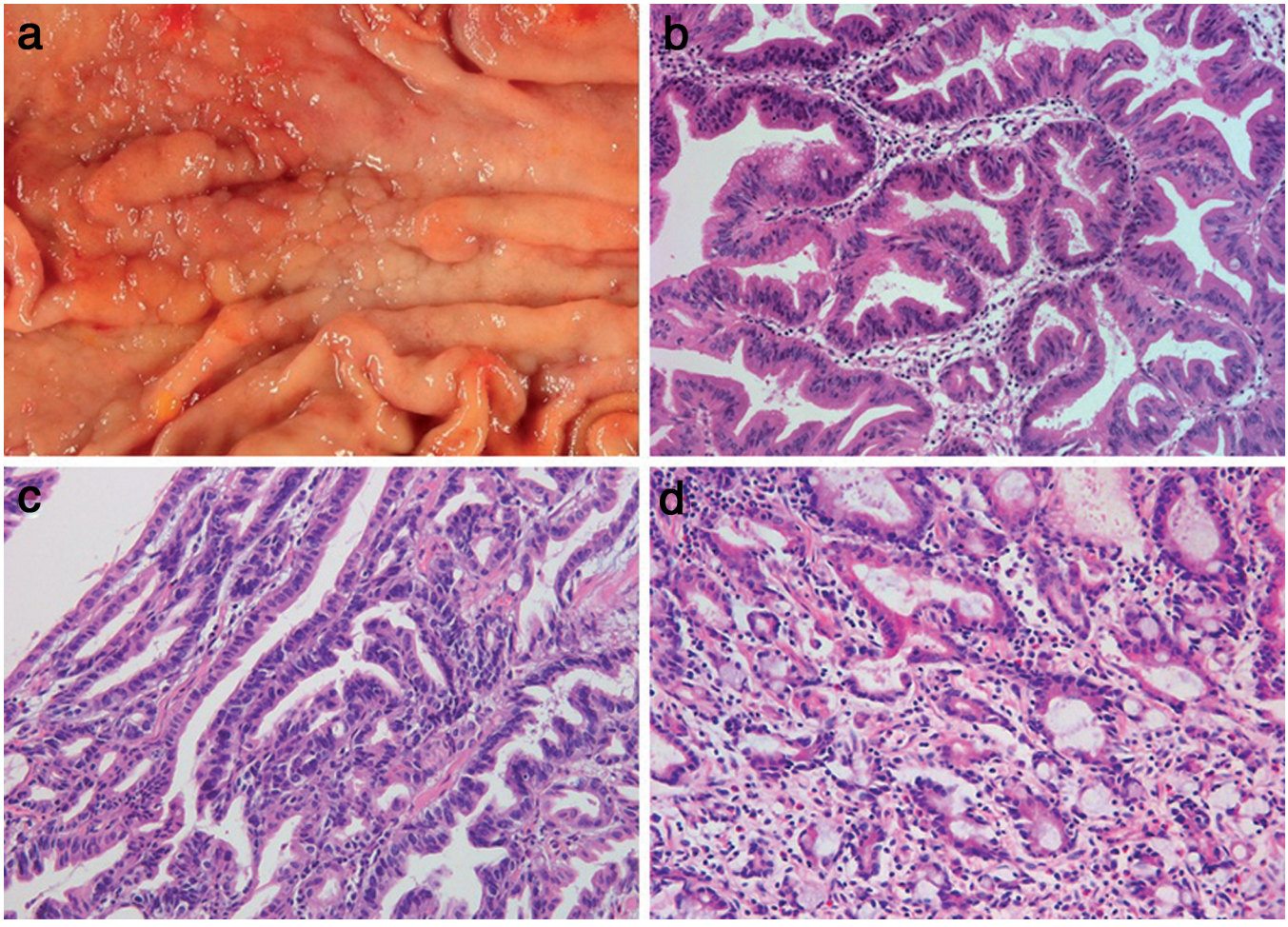

Fig. 4. Mixed serrated and tubular adenoma in association with mixed serrated and tubular adenocarcinomas. The gross examination shows an extensive irregular lesion with both polypoid and infiltrative portions **(a)**. The polypoid lesion is composed of serrated adenoma with low-grade dysplasia **(b)** and serrated adenocarcinoma **(c)**. The infiltrative lesion is composed of tubular adenocarcinoma **(d)**. x 200

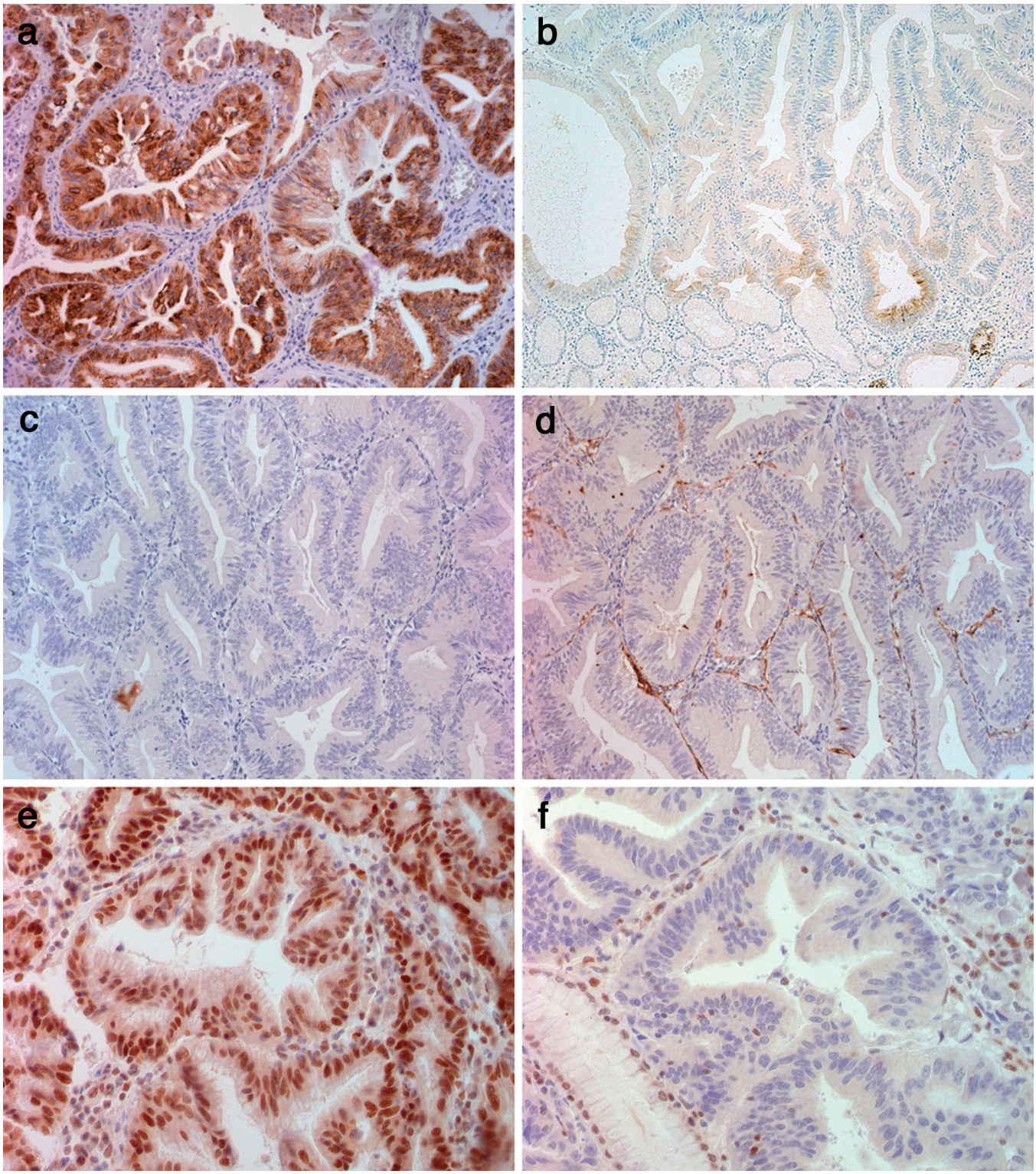

Fig. 5. Immunohistochemical stainings for **(a)** MUC5AC, **(b)** MUC6, **(c)** MUC2, **(d)** CD10, **(e)** MLH1 expression, and **(f)** loss of MLH1 expression in gastric serrated adenoma. x 200

rare (Snover et al., 2005). In the gastric counterpart, however, loss of MLH1 expression does not occur. In the stomach, loss of expression of MLH1 was detected rarely (3.1%) in the conventional adenomas, while a higher frequency (25.5%) was reported in the carcinomas (Kawaguchi et al., 2004). Although the examined number of cases is small, high frequency of MLH1 loss found in our gastric serrated adenomas also support their aggressiveness.

In the colorectum, traditional serrated adenomas frequently express MUC2, a goblet cell type mucin, and show bidirectional gastric differentiations of foveolar mucin (MUC5AC) and pyloric mucin (MUC6) (Hirono et al., 2004). In our study, MUC5AC expression was observed in 67% of serrated adenomas and in 71% of serrated adenocarcinomas, which is characteristically associated with gastric foveolar differentiation as previously reported (Hasuo et al., 2009).

Although traditional serrated adenomas of the colorectum much less express MUC6 than MUC5AC, the MUC6-positive cells are located in the lower part of crypts in colorectal serrated adenomas (Hirono et al., 2004). In the previously reported gastric serrated adenoma, MUC6 was demonstrated in the basal part (Hasuo et al., 2009). Unlike diffuse and strong positivity of MUC5AC, MUC6 expression was weak and localized in the basal part of gastric serrated adenomas. Moreover, serrated adenocarcinomas were negative for MUC6 expression. Therefore, we speculate that focal and rare expression of MUC6 is a coincidental finding shared by both gastric and colorectal serrated adenomas.

Interestingly, we found that six serrated adenomas with MUC5AC expression occurred in the lower third of the stomach, while the others without MUC5AC expression were located in the mid body, suggesting that specific mucin phenotypes may be related to the location of the tumor. The relationship between mucin expression and tumor location has been also described in traditional serrated adenomas of colorectum; MUC6 expression is frequently observed in right-sided colon compared with other locations (Gibson et al., 2011).

The diagnosis of gastric serrated adenoma has not been clearly defined. In the present study, gastric serrated adenoma was usually detected as an elevated lesion or polypoid mass. Pathologic examination revealed elongated fronds with saw-tooth-like notches due to scalloped epithelial indentations. As previously described in the colorectum, the cytoplasm of the cells was densely eosinophilic (Torlakovic et al., 2003). In differentiating gastric serrated adenoma from other non-dysplastic polyps with serrated features, evident serration, eosinophilic cytoplasm and overtly dysplastic stratified epithelial cells would increase diagnostic certainty.

In this study, out of 9 cases, our initial diagnoses were adenoma in 6 cases, in which 4 cases were diagnosed as adenocarcinoma in post-treatment specimens. High frequencies of malignant transformation and *KRAS* mutations found in our study suggest that gastric serrated adenoma is a precursor lesion of gastric mucin-phenotype adenocarcinoma with a high malignant potential. When serrated adenoma is

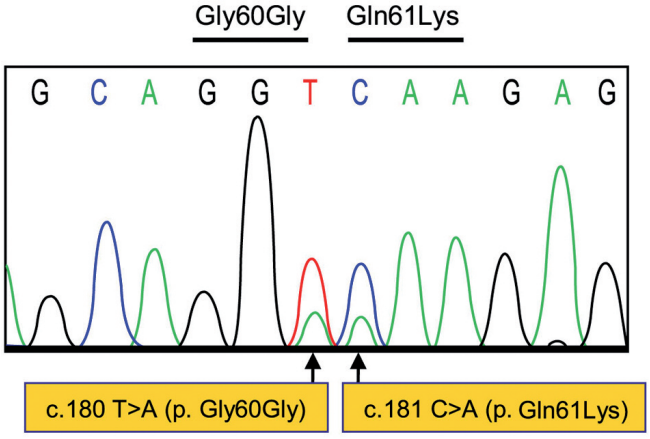

Fig. 6. Sequence chromatography revealed a missense point mutation (CAA>AAA) resulting in an amino acid exchange (Gln61Lys) and a nonsense point mutation (GGT>GGA) in exon 3 of the *KRAS* gene (Patient 9).

Table 2. Results of immunohistochemical staining for mucin proteins.

		MUC2	MUC 5AC	MUC6	CD10
Patient 1	SA	–	–	Basal +	–
	TA	–	–	–	–
Patient 2	SA	–	Diffuse +	–	–
	TA	–	–	–	–
Patient 3	SA	–	Diffuse +	Basal +	–
	SADC	–	Diffuse +	–	–
Patient 4	SA	–	Diffuse +	–	–
	SADC	–	Diffuse +	–	–
Patient 5	SA	–	–	–	–
	TA	–	–	–	–
	SADC	–	–	–	–
Patient 6	SA	–	Diffuse +	–	–
	SADC	–	Diffuse +	–	–
Patient 7	SA	–	–	–	–
	SADC	–	–	–	–
Patient 8	SA	–	Diffuse +	–	–
	SADC	–	Diffuse +	–	–
	TA	–	–	–	–
	TADC	–	–	–	–
Patient 9	SA	–	Diffuse +	–	–
	SADC	–	Diffuse +	–	–
	TA	–	–	–	–
	TADC	–	–	–	–

SA, serrated adenoma; SADC, serrated adenocarcinoma; TA, tubular adenoma; TADC, tubular adenocarcinoma; Diffuse+, diffusely positive; Basal+, positive in basal part of adenoma

encountered in a gastric biopsy specimen, it can serve as an indicator of carcinoma in the adjacent gastric mucosa.

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