Serrated Adenoma of Appendix Synchronous with Invasive Adenocarcinoma of Transverse Colon: Both are Microsatellite Instability-Negative: Case Report

Transvers Kolonda Adenokarsinom ile Senkron Olarak Görülen Appendikste Serrat Adenom: İkisi de Mikrosatellit İnstabilite Negatif

Enver VARDAR,[a]
Güldidar BASMACI,[a]
Zehra ERKUL,[a]
Ahmet AYKAŞ,[a]
Senem ERSAVAŞ[a]

[a]Clinic of Pathology,
İzmir Training and Research Hospital,
İzmir

Geliş Tarihi/*Received:* 07.01.2015
Kabul Tarihi/*Accepted:* 06.10.2015

Yazışma Adresi/*Correspondence:*
Enver VARDAR
İzmir Training and Research Hospital,
Clinic of Pathology, İzmir,
TÜRKİYE/TURKEY
vardaren@gmail.com

ABSTRACT Appendix is a rare localization for serrated adenomas. Adenocarcinoma associated with serrated adenoma is a distinct type of colorectal neoplasm, accounting for 5.8% of all colorectal carcinoma cases. A 79-years-old male patient presented with three days of history of generalized abdominal pain, bloating and constipation. Due to the suspicion of intestinal perforation an explorative laparotomy was performed. Gross examination of the subtotal colectomy demonstrated a thickened ulcerated vegetative tumoral mass largest size 5 cm. In serial sections, moderately differentiated adenocarcinoma was seen in transverse colon, and incidentally, a serrated adenoma also was detected in serial sections of appendix. Ki67 was diffusely positive in lower half of the foeveolar structures. Immnohistochemically, MLH-1, PMS-2, MSH-6, MSH-2 were also positive and there was no microsatellite instability in this serrated adenoma of the appendix. In our case, microsatellite instability was not detected in serrated adenoma of the appendix and adenocarcinoma of the colon.

Key Words: Adenocarcinoma; appendiceal neoplasms; colorectal neoplasms

ÖZET Apendikste serrated adenom nadir olup, serrated adenom ile beraber olan adenokarsinom tüm kolorektal karsinomların %5,8'ini oluşturur. Üç gündür devam eden yaygın karın ağrısı, şişkinlik ve kabızlık şikayeti olan 79 yaşında erkek hastaya, intestinal perforasyon şüphesi ile eksploratif laparotomi uygulandı. Subtotal kolektomi materyalinin makroskobik incelenmesinde en büyük boyutu 5 cm olan ülserovejetan tümöral kitle saptandı. Seri kesitlerde transvers kolonda az diferansiye adenokarsinom izlendi ve appendikste insidental olarak serrated adenom tespit edildi. Ki-67 foveolar yapıların alt yarısında diffüz pozitifti. İmmünohistokimyasal olarak MLH-1, PMS-2, MSH-6, MSH-2'de pozitifti ve appendiksin serrated adenomunda mikrosatellit instabilite yoktu. Olgumuzda, apendiskteki serrat adenomunda ve kolon adenokarsinomunda mikrosatellit instabilitesi saptanmadı.

Anahtar Kelimeler: Adenokarsinom; apendiks neoplazileri; kolorektal neoplaziler

Turkiye Klinikleri J Gastroenterohepatol 2015;22(1):15-9

Appendix is a rare localization for serrated adenomas. Carcinoma associated with serrated adenoma is a distinct type of colorectal neoplasm, accounting for 5.8% of all colorectal carcinoma cases.[1] Thus, we reported this case for that a serrated adenoma was detected in the appendix of a subtotal colectomy specimen with colon cancer. The group of serrated polyps is classified into three lesions as; hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenomas.[2] Traditional serrated adenoma (TSA) is classified in the serrated polyps group. Traditional serrated adenomas are usually pedunculated, villiform, with the di-

doi: 10.5336/gastro.2015-43449

mension less than 1.5 cm, present features of dysplasia as enlargement, variable nuclear size and shape, nuclear hyperchromasia, and irregular nuclear polarity and have eosinophilic cytoplasm with serration. The grade of dysplasia seen in TSA is assessed same as in other parts of the gastrointestinal tract. TSA may invade to give serrated carcinoma. TSA is most frequently seen in colorectum. Although very few case reports and case series have been reported in the literature, appendix is still a rare site for TSA.[3] 35% of colorectal carcinomas occur via serrated pathway. [4] In one series, 53% of serrated adenomas showed microsatellit instability (MSI), mostly of the low level (MSI-L) type.[5] The high p53 mutation rate and significant dysplasia in 13-37% of serrated adenomas were detected.[6] In this report we mention a serrated adenoma of appendix in a subtotal colectomy specimen which was performed for colon carcinoma and perforation.

CASE REPORT

A 79-years-old male patient presented to emergency room with three days of history of generalized abdominal pain, bloating and constipation. Nausea and vomiting also accompanied to these symptoms. Patient's medical history included right hemiplegia history of 25 years. Physical examination of the patient revealed generalized abdominal tenderness and distention at the presentation, blood analysis of the patient were in normal limits.

A computed tomography (CT) scan of the abdomen/pelvis demonstrated an advanced dilatation in colonic segments, especially in the transverse colon, up to 110 mm, thickening of intestinal wall, free fluid and air collection around liver and pelvis. History, physical exam, laboratory findings and imaging studies lead to the diagnosis of intestinal perforation and an explorative laparotomy was performed. Abdominal exploration revealed two perforation sites, distal part of the sigmoid colon and in ascending colon. Thus, a subtotal colectomy extending to 10 cm proximal to ileoceacal valve was performed. Pathological examination of the specimen demonstrated an area of 5x4cm with mucosal irregularity and thickened ulcerated vegetative tumoral mass, and the distance of the tumor to distal margin was 14 cm.

In hematoxylene and eosine sections, tubular, cribriform, and solid areas were seen and the diagnosis consisted with moderately differentiated adenocarcinoma of the colorectum (Figure 1). Immunohistochemically, MLH-1 (CLONE: ES05, Novocastra, 1/100 dilution), MSH-2 (Clone 25D12, 1/100 dilution), PMS-2 (Clone M0R4G, 1/100 dilution) and MSH-6 (Clone 25D12, 1/100 dilution), CK20 (Clone PW31, 1/100 dilution) and Ki67 (Clone MM1, 1/100 dilution) primary antibodies were used. The positive control was nuclear staining in normal mucosa and/or lymphocytic infiltration. The tumor cells and stromal cells were immunohistochemically positive for MLH-1, PMS-2, MSH-6, MSH-2 and negative for EGFR. No MSI was observed in colon adenocarcinoma. p53 positivity rate and Ki67 proliferation index were 35% and 30%, respectively. In addition to the invasive adenocarcinoma located in transverse colon, incidentally, a serrated adenoma was detected in routine serial sections of appendix lumina of the specimen (Figure 2). Completely normal glandular structure and lamina propria were seen in another serial section taken from different level in Figure 2. Distorted villous architecture, glands showing saw tooth lumina in more than half of the glands and cytologic features consisted with low-grade dysplasia. Ki67 was focally positive in upper half of the foeveola and crypt; on the other hand, p53 was positive in some foveolar pit and crypts. Immnohistochemically, MLH-1, PMS-2, MSH-6, MSH-2 were also positive and there was no MSI in this TSA of the appendix. CK20 was positive

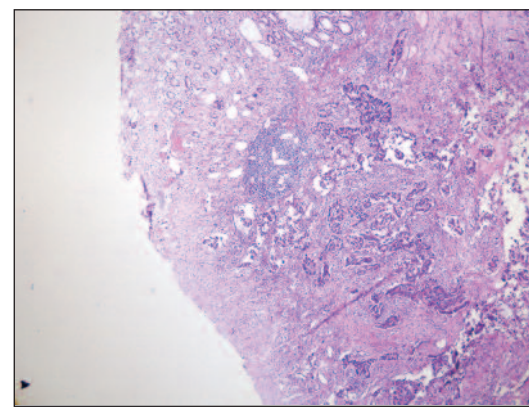

FIGURE 1: Abundant desmoplastic reaction within classical adenocarcinoma and normal colonic mucosa (top) were seeen (HE, x20).

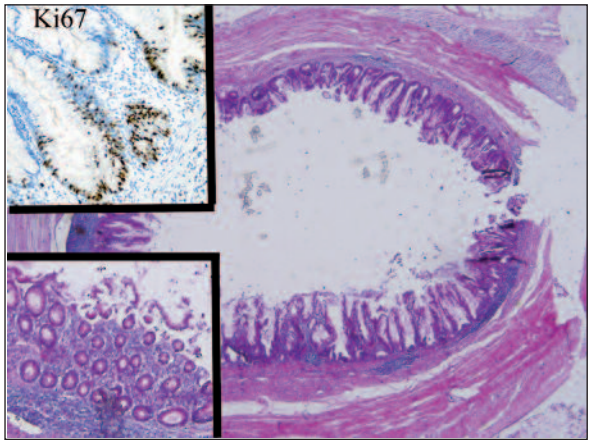

FIGURE 2: Serrated adenoma located in whole mucosal surface circumferentially and please compare with normal colon glands (lower left inset) (HE, x20). Prominent Ki67 nuclear positivity was seen in crypts (Ki67-immunohistochemistry).

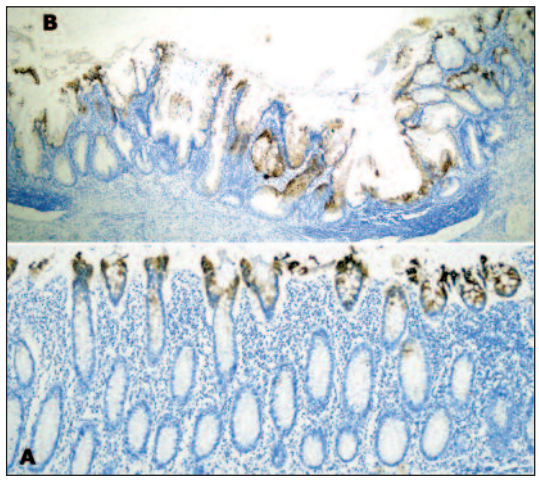

FIGURE 3: CK20 staining pattern in normal colon mucosa and serrated adenoma. Only superficial positivity in the image **(A)** and full thickness staining were seen in lower half of the image **(B)**. (Cytokeratin20-immunohistochemistry).

in full-thickness lamina propria contrary to the superficial positivity of the normal mucosal areas (Figure 3). As a result, MSI status of both adenocarcinoma and serrated adenoma were identical and negative.

DISCUSSION

The review of the literature confirmed that only one case of serrated adenoma of the appendix had been reported until Rubio's paper published in 2004 about serrated adenomas of the appendix.[7,8] In his report, Rubio mentioned serrated adenomas and explained them as "adenomas with saw tooth-like dysplastic epithelium found in more than 50% of basal crypts." He also pointed that serrated and villous adenomas of the appendix are highly aggressive lesions, compared to adenomas of the colon and rectum.[8] Another report about serrated adenomas in appendix in the literature belongs to Longacre and Fenoglio-Preise.[9] In their report, 110 cases of mixed hyperplastic adenomatous polyp of the colon and rectum were mentioned and 12 of them were detected in the cecum-appendix.[9] In their report it was mentioned that half (53.6%) of serrated adenomas were located in the rectosigmoid area, but that they were more evenly distributed in the caecum and ascending and transverse colon, with a prevalence of 10.9%, 13.6%, and 10.9%, respectively.[9] However, the number of lesions seen in only appendix was not clear in the report. In a subsequent report by Williams et al. 42 benign epithelial neoplasms of the appendix had been reported, but none of these 42 cases was classified as serrated adenoma.[10] Later, Carr et al. classified benign tumors of the appendix.[11] 25 of 42 cases had an undulating architecture, but not named as "serrated adenomas".[11] The first detailed report on serrated polyps of appendix belongs to Rubio, in which 10 serrated adenomas were reported among the 38 epithelial tumors of the appendix.[8]

Serrated adenomas are more important precursors of invasive cancer than their observed very low prevalence.[9] Yao et al. reported a patient with six synchronous advanced colonic "serrated adenocarcinoma", all of which were associated with juxtalesional serrated adenoma.[12] Jass and Smith reported five cases where serrated glandular architecture was observed in carcinoma, but information about a serrated adenomatous component was not included.[13] Jeevaratnam et al. reported familial colorectal cancer cases associated with hyperplastic polyposis, but the serrated adenomatous origin of the carcinomas was not shown in any of these cases.[14] Bengoechea et al. reported a case of colorectal carcinoma associated with hyperplastic polyposis, but they could not detect juxtalesional adenoma/serrated adenomas.[15] Five cases of ser-

rated adenoma with a carcinomatous component have been reported by Hiyama et al. but four of these showed only minimal and disputable submucosal invasion and there was only one with definite invasion limited to submucosa.[16] Mäkinen et al. reported 27 (5.8%) adenocarcinoma with an immediately adjacent serrated adenoma could be found in a consecutive series of 466 colorectal cancers.[1]

Serrated polyps of the colorectum are accepted as precursors in the serrated pathway for colorectal carcinogenesis.[17] They may also be seen in appendix with invasive cancer, and they are probable precursor lesions of those tumors. Studies have been inconsistent about the association between serrated neoplasia in the appendix and concomitant colorectal neoplasms.[18,19] Immunohistochemical staining results of this case may help additional findings about the association of serrated lesion and adenocarcinoma and neoplastic evolution mechanisms based on the positivity MLH1, PMS2, MSH2 and msh6 consisted with negativity of MSI pathway.

There is increasing evidence to support the hypothesis that a hyperplastic polyp-serrated adenoma-carcinoma sequence exists, similar to the well-established adenoma-carcinoma sequence. MSI seems to play an important role in the development of these neoplasms: both hyperplastic dysplastic areas of serrated polyps and in synchronous cancers.[1] Small sessile serrated adenoma/polyp (SSA/P) with cytological dysplasia, on the other hand, in some cases (i.e., in the case of lesions developing into MSI carcinomas) represents the development of MSI in the lesion and hence is creating a lesion with a propensity to develop into carcinoma with high frequency and rapidity. These lesions are not adenomatous polyposis coli (APC) mutated and probably require considerably more aggressive follow-up than conventional adenomas.[17] An immunohistochemical analysis of proliferation and maturation in serrated lesions has pointed out that a more likely diagnostic abnormality in TSA is the presence of small ectopic crypts created by apparent loss of anchoring of the crypt bases to the muscularis mucosae.[20] These ectopic crypts demonstrated strong CK20 staining in the luminal portions and Ki67 staining in the deeper aspects. Similar staining pattern was present in our case.

The prognosis of carcinomas associated with serrated adenomas did not differ from the other adenocarcinoma, but distal cancers with serrated adenoma tended to be more aggressive than proximal ones.[1]

In conclusion, according to some studies, a relationship between serrated polyps and concomitant colonic carcinomas is concerned as seen in our case about appendix. We also have found no microsatellite instability in appendicieal serrated adenoma and in colonic adenocarcinoma similar to previous cases.

REFERENCES

1. Mäkinen MJ, George SM, Jernvall P, Mäkelä J, Vihko P, Karttunen TJ. Colorectal carcinoma associated with serrated adenoma--prevalence, histological features, and prognosis. J Pathol 2001;193(3):286-94.
2. Snover DC, Ahnen DJ, Burt RW, Odze RD. Serrated polyps of the colon and rectum and serrated polyposis. In: Bosman FT, Carnerio F, Hruban RH, Theise ND. World Health Organization Classification of Tumours. Lyon, France: IARC Press; 2010. p.160-5.
3. Yildirim U, Ozaydin I, Erdem H, Uzunlar AK. Intussusception of the appendix induced by sessile serrated adenoma: a case report. Turk Patoloji Derg 2012;28(3):290-2.
4. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. Histopathology 2007;50(1):113-30.
5. Iino H, Jass JR, Simms LA, Young J, Leggett B, Ajioka Y, et al. DNA microsatellite instability in hyperplastic polyps, serrated adenomas, and mixed polyps: a mild mutator pathway for colorectal cancer? J Clin Pathol 1999;52(1):5-9.
6. Yao T, Kouzuki T, Kajiwara M, Matsui N, Oya M, Tsuneyoshi M. 'Serrated' adenoma of the colorectum, with reference to its gastric differentiation and its malignant potential. J Pathol 1999;187(5):511-7.
7. Rudzki Z, Zazula M, Bialas M, Klimek M, Stachura J. Synchronous serrated adenoma of the appendix and high grade ovarian carcinoma: a case demonstrating different origin of the two neoplasms. Pol J Pathol 2002; 53(1):29-34.
8. Rubio CA. Serrated adenomas of the appendix. J Clin Pathol 2004;57(9):946-9.
9. Longacre T, Fenoglio-Presiser CM. Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. Am J Surg Pathol 1990;14(6):524-37.

10. Williams G, du Boulay C, Roche W. Benign epithelial neoplasms of the appendix: classification and clinical associations. Histopathology 1992;21(5):447-51.
11. Carr N, McCarthy W, Sobin L. Epithelial noncarcinoid tumors and tumor-like lesions of the appendix. A clinicopathologic study of 184 patients with a multivariate analysis of prognostic factors. Cancer 1995;75(3):757-68.
12. Yao T, Nishiyama K, Oya M, Kouzuki T, Kajiwara M, Tsuneyoshi M. Multiple `serrated adenocarcinomas' of the colon with a cell lineage common to metaplastic polyp and serrated adenoma. Case report of a new subtype of colonic adenocarcinoma with gastric differentiation. J Pathol 2000;190(4):444-9.
13. Jass JR, Smith M. Sialic acid and epithelial differentiation in colorectal polyps and cancer-a morphological, mucin and lectin histochemical study. Pathology 1992;24(4):233-42.
14. Jeevaratnam P, Cottier DS, Browett PJ, Van De Water NS, Pokos V, Jass JR. Familial giant hyperplastic polyposis predisposing to colorectal cancer: a new hereditary bowel cancer syndrome. J Pathol 1996;179(1):20-5.
15. Bengoechea O, Martínez-Peñuela JM, Larrínaga B, Valerdi J, Borda F. Hyperplastic polyposis of the colorectum and adenocarcinoma in a 24-year-old man. Am J Surg Pathol 1987;11(4):323-7.
16. Hiyama T, Yokozaki H, Shimamoto F, Haruma K, Yasui W, Kajiyama G, et al. Frequent p53 gene mutations in serrated adenomas of the colorectum. J Pathol 1998;186(2):131-9.
17. Snover DC. Update on the serrated pathway to colorectal carcinoma. Hum Pathol 2011;42(1):1-10.
18. Yantiss RK, Panczykowski A, Misdraji J, Hahn HP, Odze RD, Rennert H, et al. A comprehensive study ofnondysplastic and dysplastic serrated polyps of the vermiform appendix. Am J Surg Pathol 2007;31(11):1742-53.
19. Younes M, Katikaneni PR, Lechago J. Association between mucosal hyperplasia of the appendix andadenocarcinoma of the colon. Histopathology 1995;26(1):33-7.
20. Torlakovic EE, Gomez JD, Driman DK, Parfitt JR, Wang C, Benerjee T, et al. Sessile serrated adenoma (SSA) vs. traditional serrated adenoma (TSA). Am J Surg Pathol 2008; 32(1):21-9.