Colonic Adenomatous Polyps Involving Submucosal Lymphoglandular Complexes

A Diagnostic Pitfall

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Abstract: Lymphoglandular complexes (LGCs) are lymphoid nodules containing intestinal mucosa, present in close apposition to muscularis mucosae or submucosa. Rarely, colorectal adenomas involve submucosal LGCs, simulating invasive adenocarcinoma with associated submucosal lymphoid aggregates, and presenting a diagnostic pitfall. We aimed to identify distinctive histologic features between submucosal LGCs and true invasion. Seven adenomas (tubular/tubulovillous adenomas [n = 6], including 4 with high-grade dysplasia and 1 with focal intramucosal adenocarcinoma, and sessile serrated adenoma [n = 1]) were in the right (n = 5) and left colon (n = 2). Seven adenocarcinomas were in the right (n = 3), left (n = 2), and rectum/rectosigmoid colon (n = 2). Adenomatous glands involving submucosal LGCs were invested in lamina propria, showed continuity with surface adenoma, were well rounded and contained within lymphoid tissue, and predominantly lacked classic features of "pseudoinvasion." One case showed a herniation pattern carrying muscularis mucosae. Adenocarcinomas had at least one of the following features: infiltrating single cells/small clusters (n = 5), poorly formed, fused, and irregular glands (n = 2), solid tumor nests (n = 1), desmoplastic reaction (n = 5), intraluminal necrosis (n = 3), or lymphovascular invasion (n = 1). In contrast, no adenoma had these features. Adenocarcinomas showed no herniation, but connection to surface tumor (n = 5) was seen. Five invasive adenocarcinomas extended into the submucosa beyond the lymphoid aggregate. In conclusion, adenomas involving LGCs are a rare, clinicopathologically distinct form of pseudoinvasion that mimics invasive adenocarcinoma; histologic features that distinguish them are a well-rounded contour contained within the lymphoid tissue, and lack of infiltrating single cells/small clusters, poorly formed, fused, and irregular glands, solid tumor nests, desmoplastic reaction, and lymphovascular invasion.

Key Words: colorectal adenoma, lymphoglandular complex, pseudoinvasion, colorectal carcinoma mimicker, misplaced epithelium

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Distinction between colorectal adenoma and invasive adenocarcinoma in the colorectal polyp is very important clinically because they carry significantly different risks of local recurrence and regional lymph node metastasis.[1,2] Colonic adenomas sometimes show misplaced epithelium into the submucosa, also known as "pseudoinvasion," causing diagnostic challenge; histologic features that help distinguish between "pseudoinvasion" and true submucosal invasion have been described.[2–5]

The intestinal mucosa-associated lymphoid tissue is distributed as lymphoid nodules or aggregates in close apposition to the muscularis mucosae, either below it in the upper part of the submucosa, above it in the lamina propria, or lying between its muscle fibers or filling gaps in it.[6,7] The lymphoid nodules have an intimate relationship with the surface epithelium, which has led to their designation as "lymphoglandular complexes" (LGCs).[6,7] At times, the mucosa of LGCs is known to protrude through gaps in the muscularis mucosae into the submucosa, accompanied by prominent lymphoid nodules.[6]

Investigation of LGCs in the intestinal tissues commenced in 1926 by Dukes and Bussey.[8] With considerable further investigation, LGCs are now known to be a normal structure in human intestines.[6,7] They are recognized as being sites of antigen processing.[6,7,9] B and T lymphocytes, dendritic cells, macrophages, and lymphocytes with surface HLA-DR antigen expression as well as columnar absorptive cells and M (membranous) cells are all found within them.[7,10] M cells are capable of transporting antigenic macromolecules from the lumen to the underlying lymphocytes, thus serving as an important afferent limb of the immune system.[10] The frequency of LGCs increases from proximal to distal colon and it is highest in rectum.[6,7] Normal colon has significantly fewer LGCs than colons affected by intrinsic disease such as carcinoma, ulcerative colitis, Crohn disease, and diverticulitis, etc.[6,7,11,12]

Rarely, colorectal adenomatous polyps may have dysplastic epithelium involving LGCs; this can simulate invasive adenocarcinoma when the LGCs are located in the submucosa. This unique form of pseudoinvasion represents a diagnostic challenge in separating adenoma from invasive adenocarcinoma with prominent submucosal lymphoid aggregates (LAs), but has not been well described in the literature. We aimed to describe the clinical and pathologic findings of 7 colonic adenomatous polyps

TABLE 1. Clinical Findings of Colonic Adenomas Involving Submucosal LGCs and T1 ADACs With Associated Submucosal LAs

Case	Age (y)/Sex	Location	Gross	Size (cm)	Procedure	Follow-up (mo)
Adenoma involving submucosal LGCs						
Case 1	64/M	Right	Sessile	NA	Resection	NA
Case 2	56/F	Ileocecal valve	Sessile	4.5	Resection	Further resection for residual polyp; AWOD (24)
Case 3	61/M	Sigmoid	Sessile	1.0	Polypectomy	AWOD (91)
Case 4	71/F	Right	Sessile	4.0	Resection	NA
Case 5	54/F	Descending	Sessile	1.2	Polypectomy	AWOD (14)
Case 6	66/F	Cecum	Sessile	2.3	Resection	AWOD (6)
Case 7	63/M	Ascending	Sessile	0.7	Polypectomy	AWDO (1)
T1 ADCA with associated submucosal LAs						
Case 8	52/F	Transverse	Flat	1.7	Resection; s/p polypectomy	AWOD (70)
Case 9	73/F	Sigmoid	Flat	1.0	Polypectomy	NA
Case 10	55/F	Rectum	Sessile	NA	Polypectomy	NA
Case 11	66/F	Proximal transverse	Sessile	1.7	Polypectomy	Resection (pT1N0); AWOD (14)
Case 12	79/F	Cecum/proximal ascending	Flat	NA	Polypectomy	NA
Case 13	62/M	Rectosigmoid	Flat	2.2	Polypectomy	AWOD (12)
Case 14	69/F	Sigmoid	Flat	1.8	Polypectomy	AWOD (24)

TNM stages by 7th AJCC/TNM staging manual.
ADCA indicates adenocarcinoma; AWOD, alive without disease; F, female; M, male; NA, not available.

involving submucosal LGCs. We also collected 7 invasive adenocarcinomas invading into submucosa (pT1) with associated prominent submucosal LAs as a control group. The morphologic findings were compared between the 2 groups in order to identify distinctive histologic features that differentiate between invasive adenocarcinoma with prominent associated submucosal LAs and dysplasia involving LGCs.

MATERIALS AND METHODS

Patients

Seven colonic adenomatous polyps involving submucosal LGCs were collected from the consultation files of the Mayo Clinic, Rochester, MN (2007 to 2018). The cases included 3 polypectomies and 4 surgical resections. In addition, 7 colorectal adenocarcinomas invading into submucosa with associated submucosal LAs (all pT1; 6 polypectomies and 1 surgical resection) were retrieved from the surgical pathology archives of the Mayo Clinic, Rochester, MN (2011 to 2018) to serve as a control group. Clinical information including patient's age and sex; procedure (polypectomy vs. surgical resection); tumor location, size, and endoscopic appearance of the polyp; and patients' outcome/survival were obtained from the medical records and pathology reports. The study was approved by the Mayo Clinic Rochester Institutional Review Board.

Pathologic Examination

Hemotoxylin and eosin–stained sections were reviewed on each case. Adenomatous polyps were evaluated and classified into tubular (<25% villous component), tubulovillous (25% to 75% villous component), villous adenoma (>75% villous component), and sessile serrated adenoma. Dysplasia was classified as low grade or high grade. Crowded glands lined by cells with enlarged, hyperchromatic, and pseudostratified nuclei with inconspicuous nucleoli were considered to represent low-grade dysplasia; loss of nuclear polarity, cribriform or fused glands, and rounded nuclei with nucleolar prominence, and open chromatin were considered to represent high-grade dysplasia.[2] Each case was reviewed by at least 3 of 5 pathologists (H.E.L., T.M., T.T.W., V.S.C., and M.S.T.) and a consensus diagnosis was obtained. Cases were evaluated for classic features of pseudoinvasion, characterized by the presence of lobules of "misplaced" adenomatous epithelium and lamina propria in the submucosa, in association with fibrosis/fibroinflammatory tissue, granulation tissue, hemorrhage, hemosiderin deposits, cystically dilated glands, and acellular pools of mucin.[2]

A LGC was defined as colonic epithelium in a lymphoid nodule or aggregate in close apposition to the muscularis mucosae or submucosa. In all cases, the following histologic features was recorded: Continuity of neoplastic glands in the submucosal LGCs (for adenoma cases) or in the submucosal LAs (for adenocarcinoma controls) with the overlying surface lesion; presence of lamina propria surrounding neoplastic glands within the LGCs or LAs; degree of glandular dysplasia within the LGCs or LAs; presence of solid tumor cell nests; presence of infiltrating single cells/small clusters; presence of poorly formed, fused, and/or irregular glands; presence of intraluminal neutrophils/necrosis; presence of associated desmoplastic response within the LGCs or LAs; and presence of lymphovascular invasion. The number of submucosal LGC foci involved by dysplasia and submucosal LAs involved by invasive adenocarcinoma was recorded in each specimen.

RESULTS

Clinical Characteristics

In the cases of adenomas involving submucosal LGCs (n = 7), 3 (43%) were male with a median age of 61 years (range, 54 to 71 years). Five (71%) polyps were located in right colon and 2 (29%) in left colon. All were sessile with sizes ranging from 0.7 to 4.5 cm (median, 1.8 cm). Four polyps were surgically resected (including 1

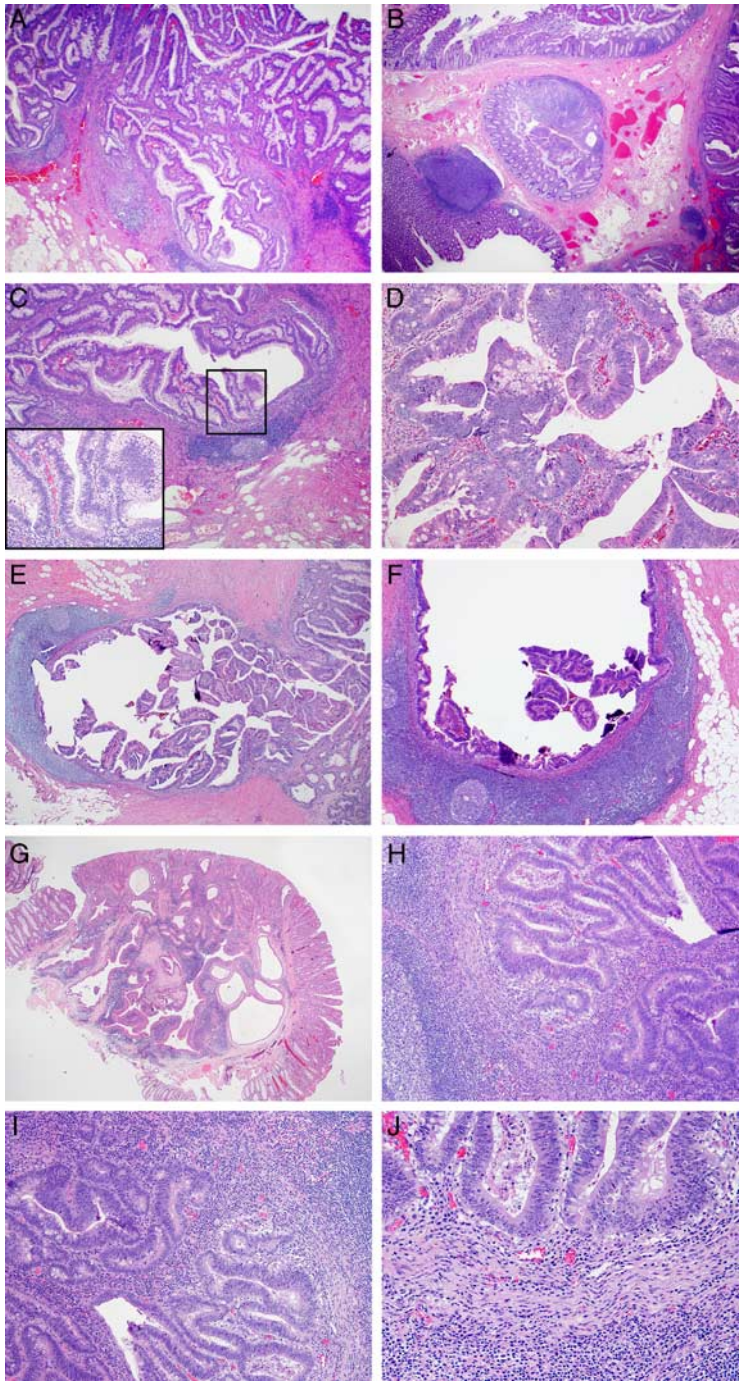

FIGURE 1. Colonic adenomatous polyps involving LGCs. A, The adenomatous glands in the submucosal LGCs show continuity with overlying surface adenoma. B, The adenomatous glands within a submucosal LGC are accompanied by lamina propria and the submucosal LGC is well rounded in contour. The degree of glandular dysplasia within the submucosal LGCs was low grade (C; the inset depicting adenomatous glands with low-grade dysplasia surrounded by lamina propria) in all but 2 with focal high-grade dysplasia (D). E and F, One case showed a "herniation" pattern, featuring large mucosal protrusion deep into submucosa. E, Note the connection between adenomatous glands in surface and cystic glandular structures associated with lymphoid tissue in the submucosa. F, The herniating glands are rimmed by muscularis mucosae, which are surrounded by submucosal lymphoid tissue. G, The LGC rarely contained cystically dilated glands. H–I, This adenoma shows fibrosis associated with dysplastic glands within a submucosal LGC. I, A tubulovillous adenoma with low-grade dysplasia shows mucosal glands protruding into submucosa associated with lymphoid tissue, and the protruded glands have low-grade dysplasia and are accompanied by lamina propria. J, The stroma surrounding the glands focally shows fibrosis with associated inflammation. The fibrosis depicted here is more layered than typical desmoplasia and lacks the typical loose/edematous appearance of desmoplasia commonly seen in invasive adenocarcinoma. The fibrosis also appears to surround lamina propria and does not appear directly intermingled with the dysplastic glands.

TABLE 2. Histologic Findings of Colonic Adenomas Involving Submucosal LGCs and T1 ADACs With Associated Submucosal LAs

	Adenoma With Submucosal LGCs						
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**
Pathologic diagnosis of the polyp	TVA w/ADCA (pTis)	TVA w/ L&HGD	TA w/ L&HGD	TA w/HGD	TA w/ L&HGD	TVA w/ LGD	SSA
No. submucosal LGCs or Las	2	1	1	1	> 3	> 3	1
Continuity with surface adenomatous glands	+	+	+	+	+	+	+
Accompanying lamina propria	+	+	+	+	+	+	+
Rounded contour contained in lymphoid tissue	+	+	+	+	+	+	+
Glandular dysplasia in lymphoid tissue	LGD	LGD w/ focal HGD	LGD	LGD w/ focal HGD	LGD	LGD	No dysplasia
Solid tumor nest formation	−	−	−	−	−	−	−
Single cell/small clusters	−	−	−	−	−	−	−
Poorly formed, fused, irregular glands	−	−	−	−	−	−	−
Intraluminal neutrophils/necrosis	−	−	−	+	−	−	−
Associated desmoplastic reaction	−	−	−	−	−	−	−
Lymphovascular invasion	−	−	−	−	−	−	−
Fibrosis/fibroinflammatory tissue	−	−	+	−	−	−	−
Cystically dilated glands	−	+	+	−	−	+	−
Extruded mucin	+	−	−	−	−	−	−
Herniation pattern	−	+	−	−	−	−	−

T stage by 8th AJCC/TNM staging manual.

*Case 12 showed microsatellite instability with MLH1 and PMS2 loss. Granulation tissue, hemorrhage/hemosiderin-laden macrophages, and inflamed/ruptures cyst are all absent in all cases.

+ indicates present; −, absent; ADCA, adenocarcinoma; HGD, high-grade dysplasia; inv, invasion; LGD, low-grade dysplasia; MD, moderately differentiated; PD, poorly differentiated; SM, submucosa; SSA, sessile serrated adenoma; TA, tubular adenoma; TVA, tubulovillous adenoma; w/, with; WD, well differentiated.

polyp further surgically resected after the initial resection, which showed residual tumor; this further resected specimen was not reviewed at our institution) and 3 underwent polypectomy. In contrast, the control group of T1 adenocarcinoma with associated submucosal LAs (n = 7) was composed of 6 females (86%) and 1 male (14%) with a median age of 66 years (range, 52 to 79 years). Three (43%) cases were located in right colon, 2 (29%) in left colon, and 2 (29%) in rectum/rectosigmoid colon. Two were sessile and 5 were flat grossly/endoscopically. The sizes ranged from 1.0 to 2.2 cm (median, 1.7 cm). Six tumors underwent polypectomy and 1 was surgically resected after an initial polypectomy (polypectomy specimen not reviewed at our institution) (Table 1).

Pathologic Features

The group of adenomatous polyps involving submucosal LGCs consisted of tubular/tubulovillous adenomas with low-grade dysplasia (n = 1), low-grade and high-grade dysplasia (n = 3), high-grade dysplasia (n = 1); high-grade dysplasia with focal intramucosal adenocarcinoma (pTis; n = 1); and sessile serrated adenoma (n = 1). Four cases showed a single LGC involved by adenomatous epithelium and 3 showed multiple LGCs involved by adenoma. In all cases, there was continuity of adenomatous glands in the submucosal LGCs with overlying surface adenoma and the adenomatous glands were accompanied by lamina propria surrounding them within the submucosal LGCs. All submucosal lesions were well rounded and contained within the lymphoid tissue. The degree of glandular dysplasia within the submucosal LGCs was low grade in all but 2 with focal high-grade dysplasia. The case with sessile serrated adenoma did not show epithelial dysplasia. None had infiltrating single cells/small clusters, poorly formed, fused, and irregular glands, solid tumor nest formation, desmoplastic reaction, or lymphovascular invasion. Only 1 case showed focal intraluminal neutrophils and/or necrotic debris found in the focus of high-grade dysplasia. Three cases had cystically dilated glands, 1 case had focal acellular mucin, and 1 case had submucosal fibrosis/fibroinflammatory tissue, but other classic features of pseudoinvasion were predominantly absent; none had granulation tissue, hemorrhage, hemosiderin deposits, or inflamed/ruptured cysts (Fig. 1 and Table 2). Of note, however, 1 case showed a herniation pattern featuring dysplastic glands invested in lymphoid tissue and pushing into the submucosa, but clearly surrounded by a rim of muscularis mucosae (Figs. 1E, F).

The control group of T1 adenocarcinomas with associated submucosal LAs were histologically classified into invasive well differentiated (n = 1), moderately differentiated (n = 5), and poorly differentiated (n = 1) adenocarcinoma. All adenocarcinomas also contained foci of high-grade dysplasia. All showed submucosal invasion (pT1) with the submucosal carcinoma component being surrounded by LAs at least focally. In 5 cases, the invasive adenocarcinoma extended into the submucosa beyond the LAs (Figs. 2A, B). Four cases showed 1 submucosal LAs involved by adenocarcinoma and 3 had multiple LAs involved by adenocarcinoma. Five cases showed continuity of dysplastic glands in the submucosal LAs with the overlying surface dysplasia; these included 2 cases where the submucosal tumor focally contained lamina propria, but also contained other areas definitely lacking lamina propria. All invasive adenocarcinomas had at least

TABLE 2. *(continued)*

T1 ADCA With Associated Submucosal LAs						
Case 8	**Case 9**	**Case 10**	**Case 11**	**Case 12***	**Case 13**	**Case 14**
MD ADCA w/ SM inv	MD ADCA w/ SM inv	MD ADCA w/ SM inv	MD ADCA w/ SM inv	PD ADCA w/ SM inv	WD ADCA w/ SM inv	MD ADCA w/ SM inv
1	3	1	1	>3	>3	1
−	+	+	−	+	+	+
−	−	Focal	−	−	Focal	
+	−	−	+	−	−	−
HGD/ADCA	HGD/ADCA	HGD/ADCA	HGD/ADCA	HGD/ADCA	HGD/ADCA	HGD/ADCA
−	−	−	−	+	−	−
−	−	+	+	+	+	+
−	−	−	+	−	+	−
+	+	−	−	+	−	−
+	+	−	+	−	+	+
−	−	−	−	+	−	−
−	−	−	−	−	−	−
−	−	−	−	−	+	−
−	−	−	+	−	−	−
−	−	−	−	−	−	−

one of the following histologic features: infiltrating single cells/small clusters (n = 5; Fig. 2C), poorly formed, fused, and irregular glands (n = 2; Fig. 2D), solid tumor nest formation (n = 1), desmoplastic reaction (n = 5; Fig. 2E), intraluminal necrosis (n = 3; Fig. 2F), or lymphovascular invasion (n = 1). The adenocarcinomas lacked classic features of pseudoinvasion, with only 1 case containing focal acellular mucin pools and 1 showing cystic dilatation of glands in the LAs; none had granulation tissue, fibroinflammatory tissue, hemorrhage, hemosiderin deposits, or inflamed/ruptured cysts. The herniation pattern observed in 1 case of the adenoma group was absent in the adenocarcinoma group (Fig. 2 and Table 2).

Patient Survival

Survival data were available in 9 of total 14 cases including both adenoma cases and adenocarcinoma controls. Two patients underwent subsequent resection after polypectomy. All 9 patients were alive with no evidence of disease recurrence for the median follow-up of 14 months (range, 1 to 91 mo) (Table 1).

DISCUSSION

We herein describe the clinicopathologic features of 7 colonic adenomatous polyps involving submucosal LGCs, representing a unique form of pseudoinvasion, and presenting a potential diagnostic pitfall. They were found both in the right and left colon. All were grossly sessile. We compared the histologic findings to those of 7 colorectal T1 adenocarcinomas with associated submucosal LAs in order to reveal the distinctive histologic features between the 2 entities. The main distinctive features of adenoma involving LGCs are glands with well-rounded contours contained within the lymphoid tissue, the consistent presence of lamina propria in the LGC, and lack of infiltrating single cells/small clusters, poorly formed, fused, and irregular glands, solid tumor nest formation, desmoplastic reaction, and lymphovascular invasion. Furthermore, 1 case showed a "herniation pattern" featuring dysplastic glands invested in lymphoid tissue and pushing into the submucosa, but clearly surrounded by a rim of muscularis mucosae. In contrast, invasive adenocarcinomas with prominent associated submucosal LAs always lacked a "herniation pattern" and often lacked lamina propria and extended into the submucosa beyond the LA; all also had at least one of the following histologic features: infiltrating single cells/small clusters, poorly formed, fused, and irregular glands, solid tumor nest formation, desmoplastic reaction, intraluminal necrosis, or lymphovascular invasion.

It is well known that colorectal adenomas with pseudoinvasion can be distinguished from invasive adenocarcinoma by the presence of histologic findings suggestive of tissue injury associated with mucosal herniation.[2–5] The histologic findings include granulation tissue, fibroinflammatory reaction, hemorrhage with hemosiderin-laden macrophages, cystically dilated glands, inflamed/ruptured cyst, and extruded mucin in association with misplaced epithelium in submucosa.[2–5,13] These suggest that misplacement of epithelium occurs secondary to tissue damage from torsion or twisting of the polyp, or increased luminal pressure due to vigorous bowel contraction, followed by protrusion of glands through inherently weak regions of the muscularis mucosae to submucosa and subsequent hemorrhage and/or inflammation associated with necrosis and/or rupture of

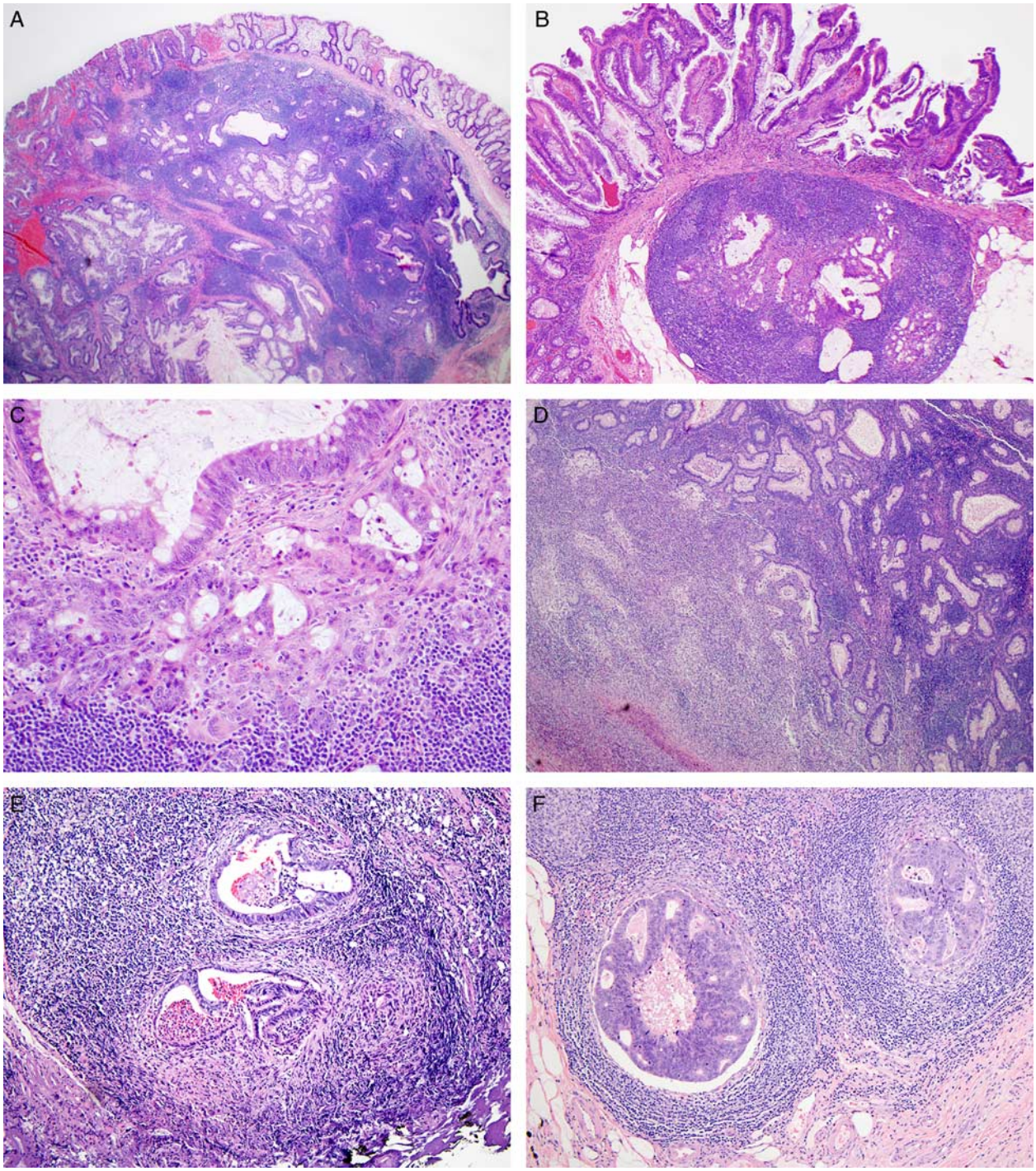

FIGURE 2. Colonic T1 adenocarcinoma (ADCA) involving submucosal LAs. This ADAC is partly surrounded by LAs and also extends into the submucosa beyond LAs (A, bottom left). B, In contrast, this ADAC is entirely surrounded by a LA. All invasive ADACs had at least one of the following histologic features: infiltrating single cells/small clusters (C), poorly formed, fused, and irregular glands (D), solid tumor nest formation (not shown), desmoplastic reaction (E), intraluminal necrosis (F), or lymphovascular invasion (not shown).

herniated glands.[2–5,13] Also, it is known that pseudoinvasion commonly occurs in pedunculated polyps in left colon, likely because this region is prone to torsion or twisting.[2–5,13] Interestingly, adenomas involving submucosal LGCs in our series were found both in the right and left colon , and all were sessile rather than pedunculated. Also, they predominantly lacked classic histologic features usually associated with pseudoinvasion;

only 1 case showed submucosal fibrosis/fibroinflammatory tissue; 3 had cystically dilated glands; and 1 focal extruded mucin. We think the reason for this might be that LGCs probably occupy weak points of the muscularis mucosae and hence mucosal herniation/prolapse easily occurs through them, even without excessive pressure or mechanical forces. Consequently, tissue damage may not be very obvious under the microscope, yet misplacement of mucosa into the submucosa can still be seen. This would be particularly true when there is a large gap (break) of the muscularis mucosae occupied by an LGC, allowing adenomatous glands to protrude through it into the submucosa. The 1 case featuring a "herniation pattern" surrounded by a clear rim of muscularis mucosae but lacking associated tissue injury and reaction supports this theory. Thus, adenomas extending into submucosal LGCs appear to represent a distinct clinicopathologic variant of "pseudoinvasion" characterized by a sessile gross appearance, occurring at various colonic sites, and lacking the classic histologic findings suggestive of tissue injury associated with mucosal herniation.

The occurrence of the polyps in both the right and left colon is somewhat surprising given the relative abundance of LCGs in the left side compared with the right side. Of note, however, all polyps involving LCG were larger than 5 mm and almost all were equal or larger than 1 cm; it is possible that polyps must reach a certain size before this unique pattern of pseudoinvasion occurs. As most left-sided polyps are small hyperplastic polyps, this might account for some of the lack of preponderance of this phenomenon on the left side. It is also possible that this is a chance occurrence given the small number of cases and larger follow-up study might find an increased incidence on the left side.

The notion that LGCs appear to constitute weak points where mucosa herniates through to submucosa is supported by the literature. Colonic mucosal herniation into submucosa through gaps in muscularis mucosae associated with lymphoid nodules has been reported.[2,13–17] Dyson[16] and Clark[14,15] described it in ulcerative colitis and granulomatous ileocolitis. Zhou et al[17] reported a polyp with reactive glands associated with a lymphoid nodule in the submucosa as an inverted lymphoglandular polyp in descending colon. The mucosal herniation associated with LGCs has been also recognized in the setting of adenoma as conferring a diagnostic confusion in the limited literature.[2] However, detailed clinicopathologic features of such cases have not yet been examined.[2]

Limitations of this study include a small number of cases due to the rare nature of such lesions and limited follow-up of the patients due to the nature of the consultative practice. Identifying more such lesions will help better characterize them clinically and pathologically.

In summary, pathologists should recognize that epithelial dysplasia can involve submucosal LGCs in colonic adenomas, representing a clinicopathologically unique form of pseudoinvasion distinct from classic pseudoinvasion. This entity presents a potential diagnostic pitfall and should not be misinterpreted as invasive adenocarcinoma. Histologic features that support adenomatous involvement of LGC rather than invasive adenocarcinoma include glands with well-rounded contours contained within the lymphoid tissue, the consistent presence of lamina propria in the LGC, and lack of infiltrating single cells/small clusters, poorly formed, fused, and irregular glands, solid tumor nest formation, desmoplastic reaction, and lymphovascular invasion. Of note, 1 case in our study also showed a "herniation pattern" surrounded by a rim of muscularis mucosae.

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