

Colonic Chicken Skin Mucosa: An Endoscopic and Histological Abnormality Adjacent to Colonic Neoplasms

Burton A. Shatz, M.D., Leonard B. Weinstock, M.D., Erik P. Thyssen, M.D., Imaad Mujeeb, M.D., and Katherine DeSchryver, M.D.

Departments of Medicine and Pathology, Barnes-Jewish Hospital, Washington University Medical Center, St. Louis; and West Central Pathologists, St. Louis, Missouri

Objectives: We recently described an endoscopic finding of pale yellow-speckled mucosa adjacent to colonic neoplasms. This resembled the appearance of chicken skin and was named chicken skin mucosa (CSM). CSM differs from previously reported gastrointestinal xanthelasmas in that this entity always occurs in association with colonic neoplasms. The prevalence, endoscopic characteristics, clinical significance, and possible etiology were investigated. **Methods:** Eight hundred fifty-two consecutive colonoscopies were prospectively evaluated for the presence of CSM associated with either cancer or adenomas ≥ 1 cm. Electron microscopy and histopathology using hematoxylin and eosin, mucicarmine, and oil red O stains were performed. Twelve consecutive colon cancer resection specimens were prospectively examined to determine the presence of histologic CSM. **Results:** CSM was adjacent to eight of 10 distal colorectal cancers, one of four proximal colon cancers, 16 of 42 distal adenomas, and three of 44 proximal adenomas. Four of seven resected distal cancers demonstrated histological evidence of CSM. Biopsies of the CSM revealed that lipid-filled macrophages in the lamina propria were responsible for this endoscopic appearance. Electron microscopy showed that the surface epithelial cells had small intestine-like microvilli. CSM was not seen with other colonic conditions and was not associated with the laxative preparation. In four instances, identification of the CSM alerted the endoscopist to the presence of polyps in locations difficult to visualize. **Conclusions:** CSM is an endoscopic entity that occurs as a result of fat accumulation in macrophages in the lamina propria of the mucosa adjacent to colonic neoplasms. Small intestine-like microvilli were present in CSM and the pathophysiological implications remain to be elucidated. (Am J Gastroenterol 1998;93:623-627. © 1998 by Am. Coll. of Gastroenterology)

INTRODUCTION

Mucosal abnormalities adjacent to gastrointestinal neoplasms including the colon have been reported previously (1-8). We recently described an endoscopic finding adjacent to colorectal neoplasms and named it chicken skin mucosa (CSM) for its resemblance to chicken skin (7). The histopathology of this pale yellow-speckled colonic mucosa was shown to be an aggregation of lipid-filled macrophages in the lamina propria. This entity appears to be different from previously reported cases of gastrointestinal xanthelasmas in that it only occurs in association with colonic neoplasms (8-21). The prevalence, endoscopic characteristics, clinical significance, and possible etiology of CSM were prospectively investigated in a group of patients undergoing colonoscopy. A series of colon cancer resection specimens were also evaluated for the prevalence of histologic CSM.

MATERIALS AND METHODS

Patients

Eight hundred fifty-two consecutive colonoscopies performed by the authors (B. S., L. W., and E. T.) during a 7-month period were prospectively evaluated for the presence of CSM associated with either cancer or adenomas ≥ 1 cm in diameter. The indications for colonoscopy in the 852 cases included surveillance for colonic neoplasia in patients with a history of polyps or cancer in the past, polyps identified by screening flexible sigmoidoscopy, rectal bleeding, anemia, abnormal digital rectal examination, occult blood in stool, and a family history of colon cancer. None of the patients had inflammatory bowel disease, diverticulitis, or lipid storage diseases. In the first 10 patients with CSM, the fasting serum triglyceride and cholesterol levels measured within a year of colonoscopy were compared to 10 consecutive patients with similar-sized colonic lesions who did not have CSM. These data were obtained from the patient's office records.

Methods

Olympus 1TL100 videocolonoscopes were used (Olympus Corp., Lake Success, NY). The laxative preparations employed included bisacodyl plus magnesium citrate, oral

sodium phosphosoda, and the PEG-3500 solution. Polyp size was determined by comparison to an open biopsy forceps.

Biopsies of endoscopically detected CSM were stained with hematoxylin and eosin. In seven cases biopsies of mucosa 5 cm from the CSM were also stained with hematoxylin and eosin as controls. Three cases with CSM had frozen sections stained with oil red O. These three cases were also sectioned and stained with mucicarmine. Electron microscopy (EM) was performed in one case of CSM adjacent to a rectal cancer and two cases of CSM adjacent to benign sigmoid adenomas. Two patients who had 1-cm polyps without endoscopic evidence of CSM had biopsies adjacent to the polyps to determine whether histologic CSM was present.

Twelve consecutive colon cancer resection specimens were prospectively examined to determine the presence of histological CSM. This was defined as the presence of large, foamy macrophages in the superficial lamina propria. Only three of these 12 patients were included in the prospective endoscopic study and the pathologist (I. M.) was unaware of the identity of these patients. The other nine patients had colonoscopy by other gastroenterologists and therefore were not included in the prospective endoscopic study. The left-sided cancers were located in the rectum in six cases and in the sigmoid in one case. The right-sided cancers were located in the transverse colon in one case, the ascending colon in two cases, and the cecum in two cases. The mucosa 5 cm away from the tumor was also biopsied in each case and was examined for the presence of foamy macrophages.

Statistical analysis

The Fisher's exact test was used for a test of association of indications for colonoscopy and the occurrence of CSM. Two-sample *t* tests were used to determine the association of colonic location, polyp size, and lipid levels with the occurrence of CSM. The distributions of polyp size and triglyceride levels were skewed, so *t* tests were carried out on the natural logs of these two variables. The polyp size data were sufficiently nonnormal, so an additional nonparametric Wilcoxon 2-sample test was carried out to confirm that the *t* test did not give misleading information. Probabilities < 0.05 were considered significant. For analysis, the neoplasms were grouped into distal (rectum, sigmoid, and descending) and proximal (transverse, ascending, and cecum) locations.

RESULTS

In the prospective endoscopic study, 14 patients with colorectal cancer and 49 patients with 86 adenomas > 1 cm in diameter were identified. The 14 patients (nine men, five women) with cancer had a mean age of 69 yr. The 49 patients (27 men, 22 women) with adenomas had a mean age of 65 yr. The primary indication for colonoscopy in 41 of 49 patients with adenomas varied slightly from those with

CSM (N = 14) and those without (N = 27), and included history of polyps (two of 14 vs four of 27), history of cancer (two of 14 vs two of 27), polyp seen by screening flexible sigmoidoscopy (four of 14 vs 10 of 27), rectal bleeding (one of 14 vs five of 27), anemia (two of 14 vs three of 27), abnormal digital rectal examination (two of 14 vs none of 27), occult blood in stool (none of 14 vs one of 27), family history of cancer (none of 14 vs one of 27), abnormal barium enema (none of 14 vs one of 27), and diarrhea (one of 14 vs none of 27). There was no statistically significant association between the indications for colonoscopy and the presence or absence of CSM ($p = 0.54$). In eight of 49 patients there was more than one primary indication and therefore these patients could not be included in the statistical analysis of indications. There was no statistically significant difference between patients with or without CSM with respect to serum triglyceride levels (214.62 mg/dl vs 133.75 mg/dl; $p = 0.17$) or serum cholesterol levels (221 mg/dl vs 231.1 mg/dl; $p = 0.53$).

CSM is an area of 0.5 mm of pale yellow speckles adjacent to benign and malignant colonic neoplasms (Fig. 1). In the prospective endoscopic study, CSM was seen adjacent to eight of 10 distal colorectal cancers and one of four proximal colon cancers ($p = 0.611$). CSM was seen adjacent to 16 of 42 distal adenomas and three of 44 proximal adenomas ($p = 0.005$) (Table 1). CSM was adjacent to 11 of 77 sessile polyps and eight of nine pedunculated colonic polyps. The mean size (\pm SD) of polyps with CSM was 16.4 mm (\pm 7.3 mm) and the mean size (\pm SD) of polyps without CSM was 13.9 mm (\pm 7.5 mm) ($p = 0.48$ by *t* test; $p = 0.46$ by Wilcoxon test). During the course of the prospective endoscopic study, CSM was carefully searched for during all colonoscopies. Only on one occasion was CSM seen adjacent to a polyp < 1 cm (a 6-mm sigmoid adenoma) and it was not found in association with any other colonic condition. There was no association with the type of preparation used. CSM was seen in five cases during fiberoptic flexible sigmoidoscopy where only an enema had been administered. Three patients with CSM adjacent to adenomas had persistence of this mucosal change at the polypectomy site on follow-up colonoscopy 6, 12, and 16 months later. CSM was otherwise not seen without an adjacent

TABLE 1
Prevalence and Distribution of Chicken Skin Mucosa (CSM)
in Patients With Colonic Neoplasms

Location	Adenoma Group		Carcinoma Group	
	N	N With CSM	N	N With CSM
Rectum	10	4	5	5
Sigmoid	26	11	4	2
Colon				
Descending	6	1	1	1
Transverse	18	1	3	0
Ascending	23	2	1	1
Cecum	3	0	0	0
Total	86	19	14	9

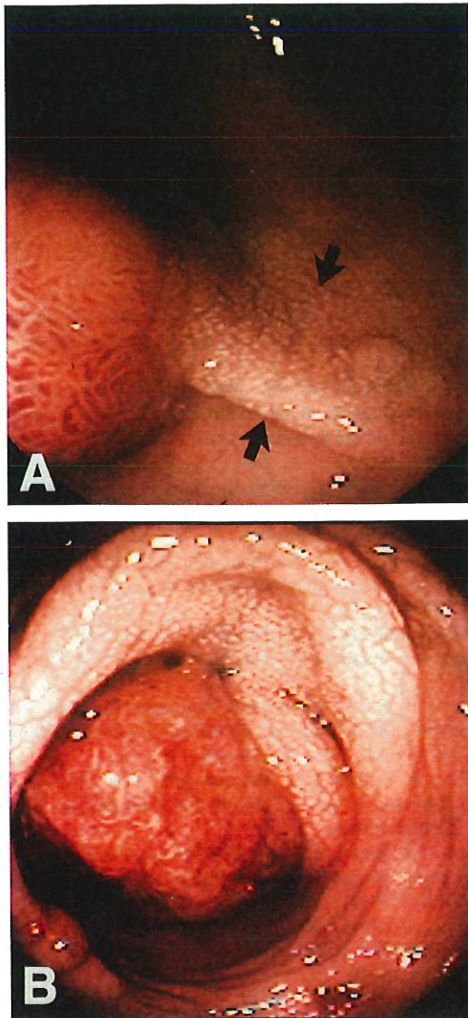


FIG. 1. (A) Sessile sigmoid adenoma with chicken skin mucosa adjacent to the polyp (arrows); and (B) rectal carcinoma with chicken skin mucosa.

neoplasm. The examiner was first alerted to the presence of four polyps only after first recognizing CSM. These polyps included a 2-cm flat adenoma with high grade dysplasia and three polyps that were hidden beyond a sharp angulation of the colon.

CSM stained with hematoxylin and eosin revealed foamy macrophages in the intercrypt spaces of the lamina propria (Fig. 2A). These findings were not present in control biopsies of mucosa 5 cm away from the neoplasms. The mucicarmine stains were negative, which excluded the presence of mucin within macrophages. Frozen sections stained with oil red O demonstrated that the foamy material in the macrophages was neutral fat. Fat was also seen in the epithelial intercellular spaces (Fig. 2B). In three cases of CSM, EM revealed multiple, long, thin microvilli on the apical cell surface that resembled small intestinal microvilli (Fig. 2C). Biopsies from the two patients with 1-cm polyps without endoscopic CSM did not have histological CSM.

In the surgical resection group, four of seven distal colon cancer resection specimens had foamy macrophages adjacent to the tumor but not 5 cm away. None of the other

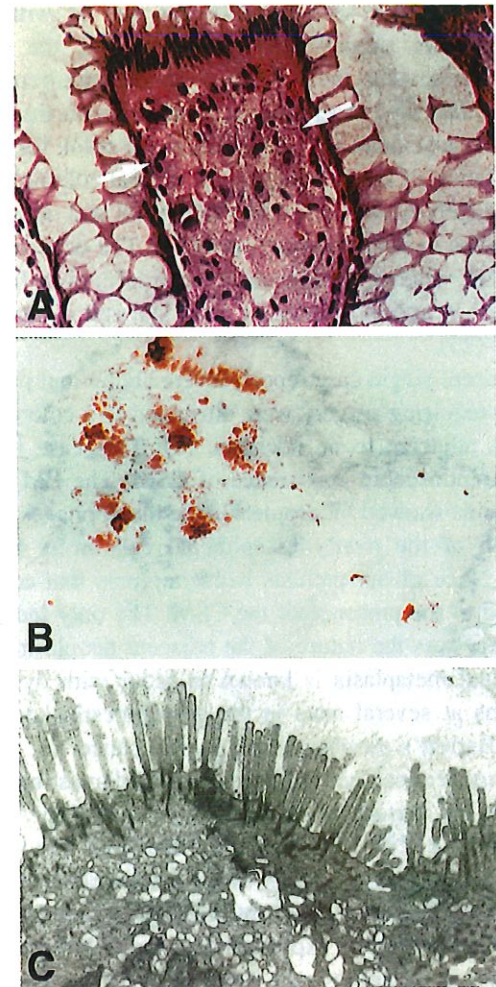


FIG. 2. (A) Histological appearance of chicken skin mucosa showing foamy macrophages expanding the intercrypt spaces (arrows) (hematoxylin and eosin, original magnification $\times 400$). (B) Oil red O fat stain demonstrating that the foamy macrophages and the overlying interepithelial spaces are filled with neutral fat $\times 400$. (C) Electron microscopic appearance of an epithelial cell of chicken skin mucosa with small intestine-like microvilli (Toluidine blue, original magnification $\times 4100$).

cancers had foamy macrophages adjacent to the tumor or 5 cm away. Three patients with histological CSM in the surgical resection group were recognized as having CSM in the prospective colonoscopy study.

DISCUSSION

Chicken skin mucosa is a common xanthoelasma-like abnormality found adjacent to colonic neoplasms. CSM is rarely seen adjacent to adenomas smaller than 1 cm and is not seen without an associated neoplasm. It is uncertain why this change is more commonly found in association with neoplasms of the distal colon than in the proximal colon.

CSM is characterized by fat accumulation in macrophages in the lamina propria. The fat accumulation may be the result of the breakdown of lipids within the colonocytes or adjacent tumor, which is then phagocytized by macrophages that migrate to the lamina propria. The small intes-

tine-like microvilli seen by EM and the fat within the epithelial cells suggest the possibility that the altered colonocytes develop the capacity to absorb intraluminal fat (22). The fat-filled macrophages accumulate in the lamina propria because there are no lacteals in the colon for further transportation of fat. In comparison, normal colonic enterocytes typically have short stubby microvilli and do not play a role in the systemic absorption of fat. The occurrence of lipid transportation by intestinal metaplasia was first described 30 yr ago in heterotopic intestinal epithelium in the stomach (23).

In a recent single case report, severe abdominal pain and diarrhea requiring surgery were attributed to a colonic xanthelasma adjacent to an adenoma (8). This case had the identical endoscopic appearance of CSM. The EM of this xanthelasma showed fat droplets in the macrophages but the microvilli of the overlying epithelial cells were not described. None of our patients had symptoms that could be attributed to the presence of the CSM. The only indication for surgery was the nature of the adjacent neoplasm.

Intestinal metaplasia is known to occur with dysplastic conditions at several sites in the gastrointestinal tract including Barrett's esophagus and gastric cancer (1, 2). Immunohistochemical methods have identified intestinal metaplasia on the surface of up to 95% of malignant colonic neoplasms (24-28). In two of these studies a few patients examined also had this change in the nonneoplastic mucosa adjacent to the cancer. Small-intestinal glycoprotein hydrolase enzyme activity is expressed in many colorectal carcinomas and in adenomas with an occurrence that correlates with the degree of dysplasia (26, 27). Intestinal metaplasia in areas of ulcerative colitis with dysplasia has also been reported with similar methods (2, 4-6). Intestinal metaplasia has been suggested to be part of the carcinogenic process in the setting of ulcerative colitis (5, 29). In the present study, CSM occurred frequently with large polyps (16 of 42 distal adenomas, mean size 1.6 cm) and was a common finding in distal colorectal carcinomas (80%). The degree of dysplasia compared to the prevalence of CSM was not determined. This would be an interesting study if a practical objective measure of dysplasia were to become available.

Endoscopic recognition of CSM in our experience was clinically valuable. It alerted our attention to the presence of lesions that otherwise may not have been detected. Recent reports have shown that colonoscopy has a 5% miss rate for significant colonic neoplasms (30, 31). Being aware of CSM could help endoscopists find flat lesions or polyps obscured by sharp angulations.

CSM is an endoscopic finding adjacent to colonic neoplasms resulting from fat accumulation in the lamina propria. CSM may be an endoscopic marker of colonic intestinal metaplasia. The pathophysiology and the role it may play in carcinogenesis remain to be elucidated.

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Reprint requests and correspondence: Burton A. Shatz, M.D., 10287 Clayton Road, St. Louis, MO 63124.

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