Virchows Arch (2001) 438:435–441
DOI 10.1007/s004280000375

ORIGINAL ARTICLE

S. Müller · D. Neureiter · M. Stolte · C. Verbeke
P. Heuschmann · T. Kirchner · T. Aigner

Tenascin: a sensitive and specific diagnostic marker of minimal collagenous colitis

Received: 27 July 2000 / Accepted: 30 November 2000 / Published online: 2 March 2001

Abstract Collagenous colitis is a rare cause of chronic watery diarrhea. In this condition, endoscopic findings are usually normal. Currently, the diagnosis relies on the histological presence of thick subepithelial bands of collagen deposits and an inflammatory infiltrate within the mucosa. However, these subepithelial bands may be developed only focally and may be too subtle to allow a definitive diagnosis upon routine hematoxylin and eosin (HE) and van Gieson's stainings. Recently, we and others were able to show a prominent staining of tenascin and type-VI collagen in the subepithelial band-like structures. In this study, we tested the diagnostic value of tenascin staining and type-VI collagen immunolocalization for the identification of collagenous colitis and compared it with conventional histology and histochemical detection of collagens. The analysis was based on 434 biopsy specimens of collagenous colitis, other forms of colitis, and normal mucosa. We were able to show that the immunohistochemical detection of increased amounts of tenascin, selectively in the subepithelial zone, is a specific test for collagenous colitis, with a sensitivity superior to conventional histological and histochemical detection, especially in minimal collagenous colitis ($P<0.001$). Of note, tenascin staining also allows the diagnosis of collagenous colitis in biopsies obtained only from the rectum and sigmoid colon, thus avoiding the need for colonoscopic investigations. Tenascin immunostaining is a simple and safe tool to complement conventional histological diagnostics in clinically and histopathologically unclear cases of diarrhea.

Keywords Collagenous colitis · Tenascin · Colon · Mucosa · Immunohistochemistry

S. Müller · D. Neureiter · T. Kirchner · T. Aigner (✉)
Department of Pathology, University of Erlangen-Nürnberg,
Krankenhausstrasse 8-10, 91054 Erlangen, Germany
e-mail: Thomas.Aigner@patho.imed.uni-erlangen.de
Tel.: +49-9131-8522857, Fax: +49-9131-8524745

M. Stolte
Department of Pathology, Klinikum Bayreuth, Germany

C. Verbeke
Department of Pathology, Klinikum Mannheim,
University of Heidelberg, Germany

P. Heuschmann
Unit for Stroke Research,
Epidemiology and Public Health Medicine,
Department of Neurology, University of Erlangen-Nürnberg,
Germany

Introduction

Collagenous colitis is an uncommon diarrheal disease of unknown origin [20]. Clinically, laboratory findings, stool analyses, and radiographic and endoscopic findings are usually unremarkable [23]. Therefore, the diagnosis of this condition depends on the histological identification of the characteristic subepithelial collagenous bands accompanied by a largely detached surface epithelium and a slight to moderate inflammatory infiltrate within an otherwise grossly normal mucosa. Sometimes, the subepithelial collagen thickening is only focal, and the bands might not be pronounced enough to fulfill the classical diagnostic criterium of over 10-µm thickness in well-orientated sections [6, 10]. Furthermore, sequential biopsies of the whole colon are required, because sigmoid colon and rectum often fail to show a significantly thickened subepithelial collagenous plate [10, 15].

Recently, we were able to demonstrate a prominent prevalence of type-VI collagen and the glycoprotein tenascin within these band-like structures [1]. The results of our previously reported seven cases of pronounced collagenous colitis were recently confirmed in an additional seven cases, and a diagnostic usefulness of tenascin staining was suggested [2]. However, these studies were only based on a small series of cases and did not try to statistically evaluate the findings. Furthermore, no cases of minimal band formation were enclosed, and no evaluation of single biopsies was reported. In the present study, we investigated whether a distinct staining for tenascin is also found in less pronounced lesions and in less

affected areas and, thus, can be used as a sensitive and specific diagnostic test for collagenous colitis.

Materials and methods

Clinical cases

The cases investigated are listed in Table 1. Neoplastic lesions were not included in this study, since they can easily be differentiated from collagenous colitis on clinical, endoscopical, and histological grounds. Colorectal bioptic specimens from 188 patients taken from 1995 to 1998 were drawn from the files of the Institute of Pathology at the University of Erlangen-Nürnberg, Bayreuth, and Mannheim, Germany. The diagnoses were made by one pathologist and confirmed independently by at least a second pathologist of the group using pathological criteria described by Lazenby and colleagues [12].

Tissue preparation and histochemistry

Immediately after the endoscopic procedure, the biopsies were fixed in buffered 5% formalin and embedded in paraffin. For histopathologic evaluation, 3-µm paraffin sections were stained with hematoxylin and eosin (HE) and van Gieson's elastin (EvG) in order to visualize the collagenous bands.

Primary antibodies

Polyclonal antibodies against collagen type VI were kindly provided by Dr. Timpl (Max Planck Institute for Biochemistry, Munich, Germany) [19]. The monoclonal anti-tenascin antibodies (clone TN2) were purchased from Dakopatts (Denmark).

Immunohistochemistry

The immunohistochemical studies were performed using the streptavidin–biotin technique (Biogenex, Mainz, Germany), combined with alkaline phosphatase as the detection enzyme and 3-hydroxy-2-naphtylacid 2,4-dimethylanilid as the color substrate. The sections were pretreated with protease XXIV [0.02 mg/ml; phosphate-buffered saline (PBS), pH 7.3, for 60 min at 37°C]. For control experiments, primary or secondary antibodies were omitted and replaced with PBS or non-immune serum. Only a very low percentage of biopsies (2 of 434) could not be evaluated using the technique, because they were not suitable for immunodetection, presumably due to overfixation.

Evaluation and quantification of the subepithelial staining

Semiquantitative evaluation of HE, EvG, tenascin, and collagen type-VI stainings was performed by two pathologists, independently. Quantification was done using direct measurement of the most pronounced staining in three different intercryptal spaces of one biopsy using an Olympus microscope and an objective micrometer.

Statistical analysis

Data were processed using the statistical package for social scientist advanced statistics software, version 7.5.2 (Chicago, Ill.). Categorical data were compared using the McNemar test [14]. The Wilcoxon test was used for all two-group comparisons of continuous variables. A statistically significant difference was regarded as $P<0.05$. Numerical data are quoted as means [95% confidence interval (CI)]. Cases in which certain stainings were not available were not used for statistical analysis (missing values). For determination of sensitivity, we agreed to combine all (strong and weak) positive results as one variable.

Results

All specimens were analyzed independently for the presence of staining in the subepithelial and the intercryptal matrix in the EvG and the type-VI collagen and tenascin immunostainings. The evaluation criteria are given in Table 2, and the results are listed in Table 3. The diagnostic criteria of collagenous colitis published by Lazenby [11, 12] – though present to a various extent in the specimens – were on purpose not taken into account for the present study. Thus, alterations of the surface epithelium and inflammatory infiltrates were ignored in order to test the immunohistochemical staining for tenascin as an independent diagnostic factor. HE staining was also semiquantitatively evaluated for visible subepithelial band formation.

Any staining of tenascin in the intercryptal mucosal matrix was classified as positive (+) and excluded the (safe) diagnosis of collagenous colitis. This criterion was not applicable for type-VI collagen immunostaining, because type-VI collagen occurred to a variable degree in the normal intercryptal matrix. An obvious increase in

Table 1 The investigated cases. All diagnoses were made according to conventional pathological criteria. Cases of collagenous colitis were identified upon measurement of the subepithelial collagen deposits in at least one of the specimens. In "minimal" collagenous colitis, these deposits were only seen in part of the specimens (see Table 2) and did not form "pronounced" bands easily visible in routine hematoxylin and eosin or van Gieson's-elastin (EvG) stains

Diagnosis (clinico-pathological)	No. of specimens	No. of patients	Age range (years)	Gender male:female
Normal mucosa	78	47	19–87	23:24
Collagenous colitis (pronounced band formation)	106	41	38–86	9:32
Collagenous colitis (minimal)	83	29	21–76	10:19
Ulcerative colitis[b]	58	16	11–63	6:10
Crohn's disease[b]	29	13	19–57	5:8
Infectious colitis	10	6	17–77	0:6
Lymphocytic colitis	34	10	53:74	3:7
Pseudomembranous colitis	12	7	57–87	4:3
Ischemic colitis	7	7	48–87	2:5
(Postirradiation) fibrosis	6	5	64–82	1:4
"Chronic unspecific colitis"[a]	11	8	23–81	3:5

[a] Cases of normal colonic architecture but increased stromal lymphoplasmacellular infiltrates
[b] From active and inactive disease stages

intercryptal type-VI collagen staining was only visible in interstitial fibrosis due to radiation therapy.

Normal colonic mucosa

Normal colonic mucosa results are shown in Fig. 1a–d. In normal colonic mucosa, a constant staining pattern identical to that described earlier [1] was found in all segments of the colon. Tenascin showed mostly a weak staining subepithelially and around the upper parts of the crypts (Fig. 1c, d). The borderline subepithelial staining of tenascin in five single biopsies (5 of 78) was always restricted to a single biopsy of one patient and never lead to the false-positive diagnosis of collagenous colitis (Table 2). Walls of larger submucosal arteries and the muscularis mucosa were positive for tenascin and could be used as an internal positive control.

In some samples, intracellular staining for tenascin was found in surface and crypt epithelial cells without any evident diagnostic relevance. Type-VI collagen (Fig. 1c) and EvG staining (Fig. 1b) were found subepithelially but also around the deeper parts of the crypts and the intercryptal matrix. Moreover, type-VI collagen could be detected in the vessel walls, in the perimysium, and in the perineurium.

Table 2 Histopathologic criteria used in this study. Only the pattern "++/–" was diagnostic for collagenous colitis in a single biopsy specimen. "+/–" was considered to be of borderline value and was only diagnostic if present in three independent biopsies of different colonic regions. The other patterns were considered to be negative. *()* Absolute values measured using quantitative microscopy [only performed for van Gieson's-elastin (EvG) and tenascin (Ten)]. *VI* type-VI collagen

	Subepithelial		
	EvG	VI	Ten
–	Thin layer (<5 µm)	Thin layer	No/thin layer(<5 µm)
+	Borderline (5–10 µm)	Borderline	Borderline (5–10 µm)
++	Pronounced (>10 µm)	Pronounced layer	Pronounced (>10 µm)
	Intercryptal		
–	Weak	Weak	No
+	Strong	Strong	Positive

Collagenous colitis

Collagenous colitis results are shown in Fig. 1e–m. In all cases of collagenous subepithelial bands ("pronounced collagenous colitis"), a strong staining with all three methods (tenascin, type-VI collagen, and EvG staining) was consistently seen in the subepithelial bands. An unremarkable staining pattern was seen in the intercryptal and in the rest of the mucosal matrix. Notably, virtually all biopsies (104 of 106), including those which failed to reveal histologically and histochemically an increased subepithelial collagen content, showed increased staining for tenascin. Thus, by using tenascin as a marker, only rare false-negative results were observed in single biopsies (2 of 106) and none if looking at two biopsies (0 of 41). In contrast, immunostaining for type-VI collagen was found to be less sensitive and much less specific than conventional histochemical staining ($P<0.001$).

Cases that were clinically suspect of representing collagenous colitis (chronic watery diarrhea, abdominal pain, and no significant abnormal laboratory or endoscopic findings) but histologically in most single biopsies not identifiable according to conventional criteria (subepithelial bands >10 µm), are specifically listed in Table 3 as "minimal" collagenous colitis. The firm diagnosis of collagenous colitis was, however, in all cases, possible due to at least one biopsy fulfilling the conventional diagnostic criteria of collagenous colitis. The staining for tenascin allowed the identification or suspicion of the condition in all but two single biopsies (81 of 83) and in all multiple biopsies of one patient (typical results are given

Table 3 The results in the investigated biopsies according to the evaluation criteria given in Table 2. *HE* hematoxylin and eosin; *EvG* van Gieson's-elastin; *VI* type-VI collagen; *Ten* tenascin

Diagnosis	No.	HE			EvG				Ten				VI			
Subepithelial		++	+	–	++	+	++/+	–	++	+	++/+	–	++	+	++/+	–
Intercryptal					–	–	+	–/+	–	–	+	–/+	–	–	+	–/+
Normal mucosa	78			78			1	77		5		73		2		71
Collagenous colitis (pronounced)	106	82	21	3	75	19	4	5	100	4	2		28	49	2	26
Collagenous colitis (minimal)	83	31	36	16	35	25	1	20	62	19	1	1	13	26		40
Ulcerative colitis	58			58				58				58				58
Crohn's disease	29			29				29				28				21
Infectious colitis	10			10				10				10				10
Lymphocytic colitis	34			34				34				34				34
Pseudomembranous colitis	12			12				12				12				12
Ischemic colitis	7		4	3		2	1	4			3	4			3	4
Postirradiation colitis	6		3	3			4	2			3	3			2	4
Chronic unspecific inflammation	11			11				11				11			1	8

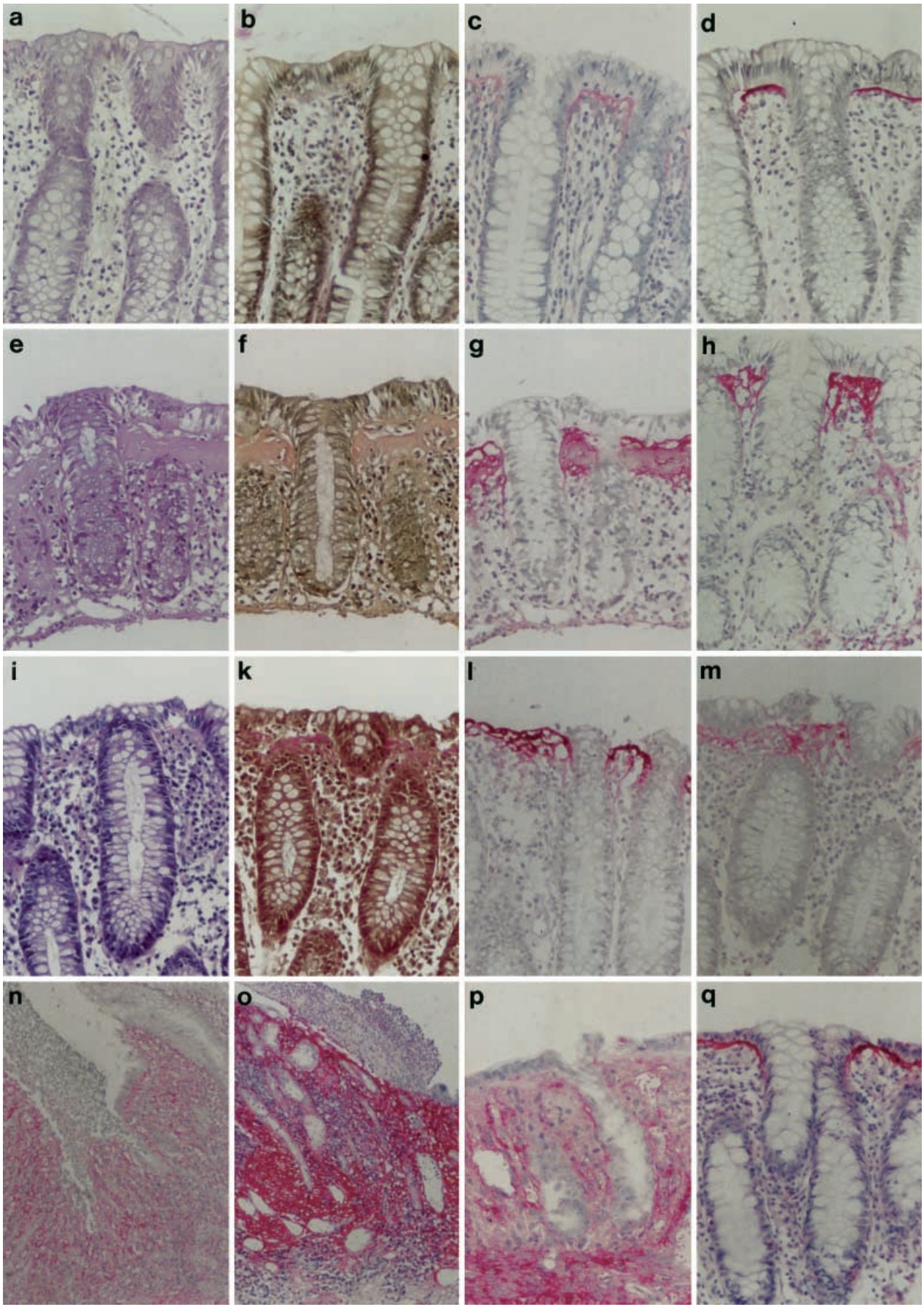
a
b
c
d
e
f
g
h
i
k
l
m
n
o
p
q

Table 4 Measurement and semiquantitative assessment of subepithelial deposition in pronounced and minimal collagenous colitis (cc) and in normal mucosa of different colonic segments. *EvG* van Gieson's-elastin; *Ten* tenascin

	Normal		"Pronounced" cc		"Minimal" cc	
	EvG	Ten	EvG	Ten	EvG	Ten
Colon – not rectosigmoid colon						
–	40 (97.6%)	39 (95.1%)	3 (3.8%)	0	12 (20.3%)	1 (1.7%)
+	1 (2.4%)	2 (4.9%)	12 (15.2%)	2 (2.5%)	19 (32.2%)	11 (18.3%)
++	0	0	64 (81.0%)	79 (97.5%)	28 (47.5%)	48 (80%)
Absolute levels (μm)	2.1+/–1.4	2.9+/–0.8	24.6+/–15.3	37.2+/–12.1	18.8+/–11.4	35.1+/–13.7
Sigmoid colon						
–	17 (100%)	15 (88.2%)	0	0	4 (26.7%)	0
+	0	2 (11.8%)	3 (33.3%)	1 (10%)	5 (33.3%)	5 (33.3%)
++	0	0	6 (66.6%)	9 (90%)	6 (40.0%)	10 (66.7%)
Absolute levels (μm)	2.2+/–1.3	4.3+/–3.1	18.5+/–7.3	29.8+/–12.5	15.4+/–9.4	43.0+/–23.4
Rectum						
–	20 (100%)	19 (95%)	2 (13.3%)	0	4 (57.1%)	0
+	0	1 (5%)	5 (33.3%)	1 (6.7%)	1 (14.3%)	3 (37.5%)
++	0	0	8 (53.3%)	14 (93.3%)	2 (28.6%)	5 (62.5%)
Absolute levels (μm)	2.1+/–1.5	3.4+/–1.6	19.7+/–13.2	31.7+/–17.2	11.2+/–9.7	27.3+/–12.2

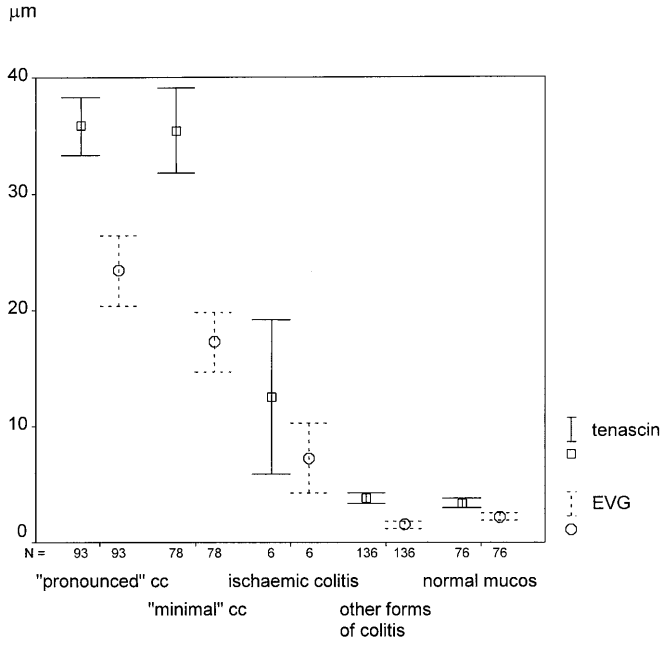

Fig. 2 Measurements (including confidential interval values) of subepithelial tenascin (immunostaining) and subepithelial total collagen (van Gieson's stain) in "pronounced" collagenous colitis, "minimal" collagenous, ischemic colitis, and other forms of colitis and normal mucosa. *cc* collagenous colitis

◀ **Fig. 1** Conventional hematoxylin and eosin (**a**, **e**, **i**) and van Gieson's staining (**b**, **f**, **k**) and tenascin immunostaining (**d**, **h**, **m–q**) of normal (**a–d**), "pronounced" (**e–h**), and "minimal" (**i–m**) collagenous colitis, colitis ulcerosa (**n** ulcerated area), Crohn's disease (**o** ulcerated area), ischemic colitis (**p**), and lymphocytic colitis (**q**). Original magnification **a–q** 70×

in Fig. 1i–m), whereas histochemistry and type-VI collagen immunostaining were much less conclusive ($P<0.001$). A firm diagnosis was possible in 76% (62 of 82) of all single biopsies and in all cases where two biopsies of different regions of the colon were available. This was also true for biopsies from the rectum and sigmoid colon, which allowed in all cases of collagenous colitis with minimal or pronounced band formation, a safe and specific diagnosis (70 of 70). None of the other cases (normal or other forms of colitis) were false-positive or suspicious of being collagenous colitis (119 of 119).

Other forms of colitis

Other forms of colitis are shown in Fig. 1n–g. None of the other investigated forms of colitis (Table 1 and Table 3) showed increased subepithelial deposition of tenascin and type-VI collagen. The only exception was ischemic colitis, which showed perilesional borderline subepithelial deposits in about half of the biopsies. However, all biopsies of ischemic colitis also showed a strongly positive signal for tenascin in the intercryptal matrix, which allowed easy differentiation from collagenous colitis (Table 2).

Quantification

In order to obtain quantitative data and to corroborate the qualitative evaluations, measurements of the subepithelial stainings were performed (Table 4; Fig. 2). This allowed the exact determination of thresholds as diagnostic criteria (Table 2). Notably, a rather broad zone of borderline positivity (ranging from 5–10 μm) was chosen in order to keep the distinction simple and to compensate for potential disorientation of specimens in routine histopathology.

Statistical evaluation

Statistical analysis was performed in order to confirm the significance of the obtained results. All three detection methods (tenascin, type-VI collagen, and EvG staining) were highly sensitive for detection of collagenous colitis (all sensitivities >93.3%). However, tenascin staining was the most sensitive technique for identifying less pronounced cases of collagenous colitis, which were not clearly identifiable using the other approaches (P<0.001; sensitivity for tenascin 95.2% vs sensitivity for EvG 75.6%). It also allowed sensitive and specific identification of minimal collagenous colitis if only biopsies from the sigmoid colon and/or the rectum were available (P<0.01 compared with EvG).

Discussion

The diagnosis of collagenous colitis depends on the histopathological identification of characteristic subepithelial matrix changes, which so far include the appearance of a pathognomonic subepithelial collagenous band with a thickness of more than 10 µm [6, 10]. These bands have been shown to consist mainly of different collagen types, such as VI, III, and I, but they also contain the glycoprotein tenascin [1, 8]. They are most likely derived from an abnormal matrix accumulation around the pericryptal fibroblast sheath [1, 9, 22].

Collagenous colitis is unrelated to other forms of inflammatory bowel disease, such as chronic ulcerative colitis and Crohn's disease, and it requires a different patient management [7, 20], although some evidence exists about transitions from collagenous colitis towards ulcerative colitis and from lymphocytic colitis to collagenous colitis. Hence, correct diagnosis is of clinical importance for identifying the cause of the clinical symptoms and to avoid inappropriate (over)treatment [18]. However, in cases that do not show pronounced subepithelial band formation, histological diagnosis is difficult and sometimes inconclusive. Thus, additional criteria, ancillary to conventional histology and histochemistry, are desirable in order to identify minimal collagenous colitis [20, 23] and to distinguish it from other forms of chronic colitis.

In this study, the diagnostic value of conventional histology (HE staining) and histochemistry (EvG staining) was compared with that of immunostaining for collagen type-VI and tenascin. Based on a large series of cases, our results show that immunodetection of tenascin is a reliable diagnostic tool independent from other histopathological or clinical criteria. Tenascin staining was found superior to EvG staining and immunodetection of collagen type-VI, because tenascin allowed for the highlighting of subtle, network-like deposits in subepithelial localization. Especially in cases with borderline findings according to HE, EvG, and collagen-VI staining, immunohistochemistry for tenascin was found to be more sensitive than the other three methods (P<0.001) for the detection of minimal deposits in the characteristic subepithelial localization and to be of superior diagnostic significance for the discrimination between minimal collagenous colitis and normal mucosa. This is of importance, since clinical (radiographic and endoscopic) findings are negative or unspecific in collagenous colitis [20], and the gastrointestinal pathologist is sometimes confronted with biopsies showing near-normal or "unspecifically altered" mucosa. Also of note, biopsy specimens of the sigmoid colon and rectum allowed the definitive diagnosis of collagenous colitis (P<0.001). This is of diagnostic relevance, because to date, multiple sequential colonoscopic biopsies are required since HE and EvG staining usually reveal less significant subepithelial collagen thickening in the sigmoid colon and rectum than in the proximal colon [10, 15], an observation that could be confirmed with this study.

Tenascin staining revealed a specific histotopographic distribution pattern. Whereas tenascin deposits within the intercryptal matrix were found in other forms of colitis, selective subepithelial accumulation of tenascin was observed exclusively in collagenous colitis. This difference in histotopographic distribution of tenascin in collagenous colitis compared with other forms of colitis, including fibrosis of the lamina propria, e.g., due to radiation therapy, was statistically highly significant (P<0.001) and may therefore be used as a reliable diagnostic criterium. The only condition that showed borderline increased tenascin staining in subepithelial localization was ischemic colitis. However, this did not represent a differential diagnostic problem since concomitant intercryptal positivity for tenascin was always observed in ischemic lesions. Neoplastic and hyperplastic lesions of the colonic mucosa and carcinomas also show enhanced tenascin staining but not specifically beneath surface epithelium [5] (unpublished results).

Staining of tenascin is particularly suitable for routine testing as a good monoclonal antibody that works well for paraffin sections is commercially available. Only a low percentage of biopsies were – presumably due to overfixation – not suitable for immunodetection. Furthermore, colonic mucosa provides optimal internal positive (muscle and vasculature) and negative (intercryptal matrix) controls for tenascin immunohistochemistry [17].

Our findings also have implications for the understanding of the development of the disease. This study confirms, in a large series of cases, that a subepithelial increase of tenascin and type-VI collagen is characteristic and specific for collagenous colitis [1] and not found in other forms of colitis. Our results further show that subepithelial matrix accumulation is already found in minor lesions and is not a late-stage secondary phenomenon and not as focal as described previously. Thus, most areas seem to be substantially involved in alteration processes. This may explain the discrepancy between the severity of the clinical symptoms and the inconspicuousness and focal microscopic findings using HE and EvG stainings. The pathophysiological implications of subepithelial tenascin accumulation also in stages of discrete

band formation are unclear. Tenascin, a 100-kDa glycoprotein, shows a widespread distribution in fetal developing gut [3, 4, 13], whereas in the adult, it is restricted to the subepithelial area.

Tenascin is supposed to be positively involved in epithelial cell shedding and potential cell proliferation [3, 16, 17] and, in fact, the epithelium in collagenous colitis shows increased detachment and a regenerative phenotype also in areas lacking pronounced band formation. This might explain the cryptal atrophy found in collagenous colitis [21]. Overall, we were able to establish a highly sensitive and highly specific immunohistochemical detection criterion for collagenous colitis. Increased tenascin staining, thus, is suggested as a diagnostic criterion to be used in addition to epithelial alterations and inflammatory infiltration in equivocal cases of collagenous colitis.

Acknowledgments We thank Ms. D. Andrischevski and Ms. G. Herbig for expert technical and photographic assistance.

References

1. Aigner T, Neureiter D, Müller S, Küspert G, Belke J, Kirchner T (1997) Extracellular matrix composition and gene expression in collagenous colitis. Gastroenterology 113:136–143
2. Anagnostopoulos I, Schuppan D, Riecken E-O, Gross UM, Stein H (1999) Tenascin labelling in coloretal biopsies: a useful marker in the diagnosis of collagenous colitis. Histopathology 34:425–431
3. Aufderheide E, Ekblom P (1988) Tenascin during gut development: appearance in the mesenchyme, shift in molecular forms and dependence on epithelial-mesenchymal interactions. J Cell Biol 107:2341–2349
4. Beaulieu JF, Jutras S, Kusakabe M, Perreault N (1993) Expression of tenascin in the developing human small intestine. Biochem Biophys Res Commun 192:1086–1092
5. Block JA, Inerot SE, Kimura JH (1992) Heterogeneity of keratan sulfate substituted on human chondrocytic large proteoglycans. J Biol Chem 11:7245–7252
6. Bogomoletz WV (1983) Collagenous colitis: a clinicopathological review. Surv Dig Dis 1:19–25
7. Bogomoletz WV (1994) Collagenous, microscopic and lymphocytic colitis. An evolving concept. Virchows Arch 424: 573–579
8. Flejou JF, Grimaud JA, Molas G, Baviera E, Potet F (1984) Collagenous colitis. Arch Pathol Lab Med 108:977–982
9. Hwang WS, Kelly JK, Shaffer EA, Hershfield NB (1986) Collagenous colitis: a disease of pericryptal fibroblast sheath? J Pathol 149:33–40
10. Jessurun J, Yardley JH, Giardello FM, Hamilton SR, Bayless TM (1987) Chronic colitis with thickening of the subepithelial collagen layer (collagenous colitis): histopathologic findings in 15 patients. Hum Pathol 18:839–848
11. Lazenby AJ, Yardley JH, Giardiello FM, Jessurun J, Bayless TM (1989) Lymphocytic ("microscopic") colitis – a comparative study with particular reference to collagenous colitis. Hum Pathol 20:18–28
12. Lazenby AJ, Yardley JH, Giardello FM, Bayless TM (1990) Pitfalls in the diagnosis of collagenous colitis: experience with 75 cases from a registry of collagenous colitis at the Johns Hopkins Hospital. Hum Pathol 21:905–910
13. Lohi J, Leivo I, Tani T, Kiviluoto T, Kivilaakso E, Burgeson RE, Virtanen I (1996) Laminins, tenascin and type VII collagen in colorectal mucosa. Histochem J 28:431–440
14. McNemar Q (1969) Psychological statistics. Willey, New York
15. Offner FA, Jao RV, Lewin KJ, Havelec L, Weinstein WM (1999) Collagenous colitis: a study of the distribution of morphological abnormalities and their histological detection. Hum Pathol 30:451–457
16. Probstmeier R, Martini R, Schachner M (1990) Expression of J1/tenascin in the crypt-villus unit of adult mouse small intestine: implications for its role in epithelial cell shedding. Development 109:313–321
17. Riedl SE, Faissner A, Schlag P, von Herbay A, Koretz K, Möller P (1992) Altered content and distribution of tenascin in colitis, colon adenoma, and colorectal carcinoma. Gastroenterology 103:400–406
18. Sloth H, Bisgaard C, Grove A (1991) Collagenous colitis: a prospective trial of prednisolone in six patients. J Intern Med 229:443–446
19. Specks U, Mayer U, Nischt R, Spissinger T, Mann K, Timpl R, Engel J, Chu M-L (1992) Structure of recombinant N-terminal globule of type VI collagen a3 chain and its binding to heparin and hyaluronan. EMBO J 11:4281–4290
20. Stampfl DA, Freidman LS (1991) Collagenous colitis – pathophysiological considerations. Dig Dis Sci 36:705–711
21. Stuber E, Von Freier A, Marinescu D, Folsch UR (1998) Involvement of OX40-OX40L interactions in the intestinal manifestations of the murine acute graft-versus-host disease. Gastroenterology 115:1205–1215
22. Widgren S, Jlidi R, Cox JN (1988) Collagenous colitis: histologic, morphometric, immunohistochemical and ultrastructural studies. Report of 21 cases. Virchows Arch 413:287–296
23. Zeroogian JM, Chopra S (1994) Collagenous colitis and lymphocytic colitis. Ann Rev Med 45:105–118