Changes in Colonic Structure and Mucosal Inflammation

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5.1 Introduction

Diverticula are sac-like protrusions of the mucosal and submucosal layers through weak colonic wall areas ("locus minoris resistentiae"). These areas mainly include the points where intramural blood vessels, the perforating arteries ("vasa recta"), are brought into the mucosa to distribute blood by punching through the circular muscular layer. So defined, the existence of diverticula is a congenital or an acquired anomaly whose etiology has just begun to be understood but, because of its multifactorial condition, still has some unclear points. The study of changes in the structure of the colon and inflammation of the mucosa is the starting point for understanding the sequence of events that leads to the formation of diverticula and, consequently, to the setting of proper treatment of the pathology. In Western industrialized countries, the site most affected by diverticular disease is the left colon, but, in the Asian population, right-sided diverticulosis is more common. The incidence reported is in 17.5% of the general population, and it represents up to 42% of all endoscopic diagnosis, increasing steadily with age, reaching around 30% at 65 years, 50% in those over 75 years, and 71% in those aged ≥80 years [1]. No difference has been found in the sex distribution of diverticulosis [2]. Left-sided diverticulosis almost invariably involves the sigmoid colon and may extend proximally,

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but the involvement of the ascending colon and cecum occurs in fewer than 10% of cases. The extraperitoneal rectum is not affected [3]. Left-sided diverticulosis is also known as pulsion diverticulosis. The demographic profile of the typical patient with diverticulosis perfectly matches the natural history of diverticular disease. According to Laplace's law in organs with a distensible wall, it is commonly believed that high colonic pressure will develop tension in response to the elongation, thus leading to the development of diverticula at the weakest point of the colonic tissue. However, there is no validated theory to support these claims; even severe mechanical stress is a significant factor driving tissue remodeling [4, 5]. Patel et al. developed an experimental model on swine's descending colon based on simultaneous inflation and extension tests evaluating the result obtained using the Finite Element (FE) software. This approach simulates a physical phenomenon occurring during diverticula formations and reports the results with a computational model using a numerical mathematical technique to prove that the mechanical stress could be critical in diverticulum genesis and in the increase of the diverticulum's volume [6]. The model was designed keeping in mind the typical anisotropic nature of the colonic tissue, which in turn depends on its microscopic characteristics. Thus, the model has shown that the highest stress values are concentrated around the luminal side of the pouch's neck. The increase in stress increases with increasing pressure until it reaches two to three times the maximum values observed in a normal colon. A significant elevation of stress could occur in a colon with diverticulosis than in a normal colon, which implicates elevated stresses in this condition that are responsible for diverticular wall remodeling. In this manner, computational structural mechanics can investigate potential changes in stress distribution that could be introduced in the colonic tissue due to the presence of a pouch-like structure. More interesting, the analysis shows a correlation between stress elevation and size of the pouch. It is known that pouch size increases over time in diverticulosis and that mechanical stress is a significant factor driving biological tissue remodeling. These two elements would explain the overall pouch size increase in response to elevated stress values around the pouch, leading to a vicious cycle where the pouch size is further increased. The distance from the center of the pouch (zone of influence) increases with pressure, reaching a plateau value after a specific pressure elevation that correlates with the area of the pouch neck, suggesting that the size of the pouch neck is more important than the surface area of the pouch itself in pouches under high stress and with a greater zone of influence. Besides, a significant luminal pressure drop would be necessary to restore stress to an average level, explaining the low effectiveness of a high-fiber diet as a stand-alone treatment solution once pouches are developed. A diverticulum is expected to be more compliant than a normal tissue constituted by only the mucosal and submucosal layers. The mucosa has been reported to be extremely expansible, and the submucosa could withstand deformations four to five times greater than the muscular layer [7]. Notably, even if the colon is a collapsible tube with curves, the stress values would undoubtedly change, but the high-stress value observed at the neck of the pouch with a relative increase in pressure and pouch size will not change. Luminal pressure (pressure on the inner wall of the tissue with an external force equal to zero) values above 1.5 kPa lead to

permanent tissue damage. The computational simulations pushing this value to visualize the evolution of stress values and luminal pressure might explain the variation in diverticular shape and volume. Moreover, it might also try to explain tissue remodeling until a complication appears.

5.2 Muscle Thickening and Mucosal Inflammation

Morson [8] demonstrated a marked abnormal muscle thickening in colonic diverticulosis without inflammation, and Golder reported occasional neutrophils and plasma cells and a diffuse lymphocytic infiltrate mainly localized to the luminal side of the lamina propria, findings consistent with a chronic inactive inflammatory infiltrate, a natural defense mechanism of a normal large bowel mucosa [9]. It was suggested that thickening of the muscularis propria is caused by two factors: (1) aging or more extended periods of low dietary fiber intake and (2) high intraluminal pressure. The muscle thickening might be associated with rigidity or decreased strength of the colonic wall in diverticulosis.

5.3 Mesenchymal Alteration

The etiology and pathogenesis of diverticular disease are multifactorial. Various aspects can also be understood at the time of macroscopic evaluation (Figs. 5.1 and 5.2) of colectomy samples removed for diverticular disease: a considerable thickening of the muscular layer, peri-diverticular fibrosis, which means an increase in elastin content together with elastosis [10], and increased intraluminal pressure within the sigmoid colon of persons with diverticulosis during periods of

Fig. 5.1 Cut section: thickening of the colonic wall near a diverticulum

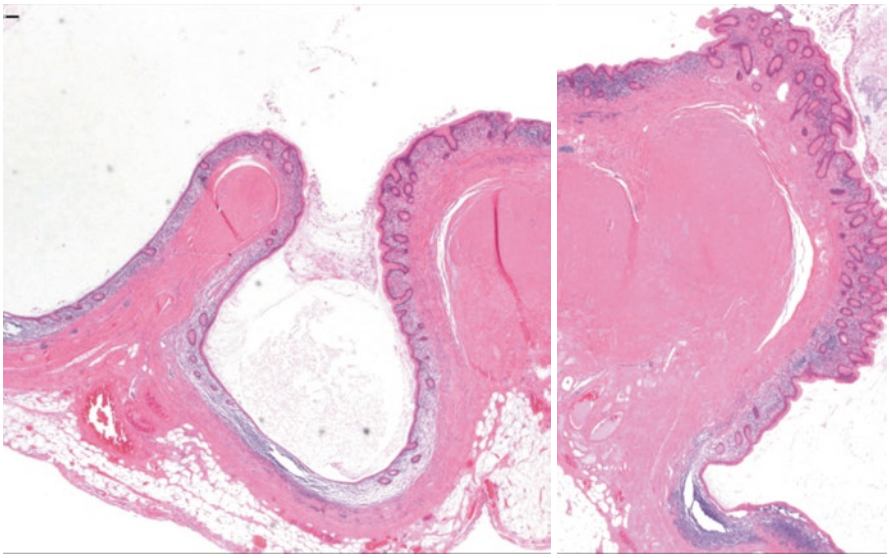

Fig. 5.2 Diverticula (hematoxilin & eosin-stained section)

peak contraction, resulted in pressures of up to 90 mmHg, a value nine times higher than those in normal colons [11], demonstrated by the increase in thickness of the circular and longitudinal muscular layers together with a progressive increase in the thickness of collagen and elastin tissues of the colon wall [12]. The latter feature is related to the deficiency in dietary fiber consumption and genetic factors [13]. Collagen is the most abundant protein in mammals, and one of its primary functions is to maintain the structural integrity of connective tissues [14]. The mechanical properties of the colon wall depend not only on the individual components of its various layers but also on the relationships they contract with each other. Whiteway and Morson [10] observed that the elastin content of the taenia coli in patients with diverticular disease is twofold higher than that in controls. The elastin was documentable between the muscle cells, warping the typical fascicular pattern of the taenia coli. This variation of the viscoelastic properties of the colon is related to the decrease in the integrity of the connective tissue, as reported by Watters et al., which is responsible for a reduction in tensile strength in the colonic wall with age, particularly in the distal colon. An extracellular matrix provides the maintenance of the integrity and flexibility of the colonic wall with its components such as collagen, elastin, and proteoglycans [15], which are, however, subject to rehash due to age. Thus, pathological aging changes in the colonic wall could be secondary to a decline in the structural and mechanical integrity of the various layers of the large bowel wall [15]. Given that the development of colonic diverticulosis, as known, is a function of age and declining colonic wall mechanical strength, the latter should be addressed partly due to changes in the collagen structure [16].

5.3.1 Decrease of Collagen I and Increase of Collagen III

Notably, collagen is the most abundant extracellular matrix protein, which is implied in the mechanical stability of the connective tissue and is responsible for the tensile strength of tissues. Fibrillar collagens are synthesized as precursors (procollagens) containing different extra domains known as pro-peptides. After extracellular cleavage of both ends, collagen molecules are assembled into collagen fibers, where covalent cross-links form between the adjacent collagen molecules. The most important types are collagen I, found in mature tissues, and collagen III; collagen I is the critical structural component of several tissues. It is expressed in almost all connective tissues, and it is the predominant component of the interstitial membrane. It is also responsible for forming mature tissues, whereas collagen III, a homotrimer consisting of only one collagen alpha chain, shows less mechanical strength [17]. Mature collagen type I was significantly lower in the diverticulitis group, whereas immature collagen type III was higher than in controls. Therefore, the collagen ratio (I/III) was significantly lower in the diverticulitis group. The amount of collagen and its structure is regulated mainly by matrix metalloproteinases (MMPs). These are a family of enzymes, zinc-containing neural endopeptidases, which are structurally related neutral proteinases that use either disulfides or calcium ions to stabilize the enzyme's structure. MMPs are secreted as inactive zymogens with structural pro-forms; the activation of these zymogens requires double proteolytic cleavage of the pro-domain at the N-terminal of the MMP. They have crucial roles in many physiological situations [18]. MMP activity is regulated by interactions with members of the tissue inhibitor of matrix metalloproteinase (TIMP) family, generating an inactive MMP/TIMP complex. Remarkably, TIMPs may also play a role in the activation process of MMPs by binding to the hemopexin-like domains of adjacent MMPs, thus favoring a reciprocal activation. Moreover, TIMPs are secreted in proenzyme forms requiring extracellular activation from various cell types, including macrophages, T cells, and myofibroblasts, stimulated by cytokines and other factors [19]. MMPs can virtually degrade all extracellular matrix components. Thus, MMPs directly determine the synthesis, deposition, and remodeling of collagen types I and III in all tissues [20]. Among the MMPs, MMP-1 and MMP-3 are the principal enzymes that can cleave fibrillar type I, II, and III collagens. MMP-1 cleaves both ECM and non-ECM substrates such as collagen, gelatin, laminin, complement C1q, IL-1β, and TNF-α, suggesting a crucial role in inflammatory and fibrotic responses. The MMP-3 enzyme degrades collagen types II, III, IV, IX, and X, proteoglycans, fibronectin, laminin, and elastin. MMP-3 can also activate other MMPs such as MMP-1, MMP-7, and MMP-9, rendering MMP-3 crucial to connective tissue remodeling [21]. Stumpf et al. found a statistically significant reduction in the expression of MMP-1 in the diverticulitis group. Downregulation of MMP-1 may be necessary for the development of diverticulitis because proteases act not only in proteolysis, inflammation, and invasion but also in angiogenesis and even growth [22]. MMP-1 and MMP-3 are abundant in granulation tissues of gastrointestinal ulcers [23]. A considerable number of polymorphonuclear leukocytes, immune-positive for MMP-9, were observed throughout the

intestinal wall of Crohn's disease, implying its role in connective tissue remodeling. MMP-3 is markedly overexpressed at inflamed sites in patients with ulcerative colitis or Crohn's disease, whereas TIMP-1 remains unaltered, suggesting that excess MMP-3 might be responsible for loss of mucosal integrity in these conditions [24]. Mimura et al. demonstrated an increasing trend in the amount of collagen in both uncomplicated and complicated diverticulosis than in controls. Both TIMP-1 and TIMP-2 were significantly higher in the muscular layer of complicated diverticulosis than in controls [25]. The finding that the mRNA of TIMP-1 was higher, with a decreasing trend in such order, in complicated diverticulosis, uncomplicated diverticulosis, and controls, might suggest that the expression of their mRNA is related to the clinical course of diverticula. Macrophage-like and fibroblast-like cells (TIMP-1- and TIMP-2-positive cells) were frequently encountered around the blood vessel areas in the muscular layer and serosa. This suggests that these cells could be sources of TIMPs in this disease. They could infiltrate the inflamed areas where extracellular matrix deposition was required for tissue remodeling, thus affecting the turnover of the extracellular matrix and creating a predisposition that has formation of colonic diverticula as an outcome. It is a prolonged process, usually taking 40 years, undergoing periods of exacerbation and remission of inflammation. Thus, it could involve extensive MMP-driven remodeling of the connective tissue and possibly chronic inflammation, causing an increase in TIMPs and facilitating the excess deposit of the extracellular matrix in the pathogenesis of diverticular disease.

5.3.2 Cross-Linking Between Collagen Fibers

Collagen is known to have intermolecular and intramolecular cross-links, which stabilize and strengthen the tissue in which it is located. Two cross-linking pathways have been identified in collagen, one based on lysine aldehydes and the other on hydroxylysine aldehydes, producing allysine and hydroxylysine, respectively. The reaction of either type of aldehyde with the e-amino group of lysine or hydroxylysine results in the production of reducible intermolecular cross-links. Initially, all reactions produce a Schiff base-type cross-link, also known as an aldimine-type linkage. These intermediate forms are susceptible to cleavage by diluting acid. Hydroxyallysine-derived intermediate cross-links can also undergo a further spontaneous reaction to form a ketamine-type structure in vivo (known as the Amadori rearrangement). The ability of the intermediate cross-link to create the acid-stable ketamine depends on whether it is derived from allysine and hydroxylysine or from hydroxylysine and lysine. The first of these is unable to form the ketamine, whereas the second can do this. The ketamine-type cross-link is stable for weak acids. The number of acid-labile cross-links decreases with maturation of the tissue [26]. A healthy colon has both propulsive and storage functions and needs to withstand the extremes of pressure in the large bowel – equivalent to 100–150 mmHg [27]. The intrinsic strength of the bowel wall is believed to be independent of the submucosal layer. Wess et al. [16] found significantly different levels of mature cross-linked collagen in healthy colons from individuals over 60 years and in colons from subjects

of the same age showing diverticulosis. As the number of collagen cross-linkage increases, the corresponding tissue becomes stiffer [28]. These observations may explain the onset of high intraluminal pressures because of changes in the colonic wall in patients with diverticular disease. Early-onset diverticula have been reported in patients with connective tissue diseases such as Ehlers–Danlos syndrome and Marfan syndrome [29]. Despite this increased thickness of muscle coats, however, the colonic wall is reported to have a lowered resistance to distension in diverticulosis. Watters et al. [15] showed that both the tensile and the burst strength of the human colonic wall depend on the integrity of the submucosa. Thomson et al. [14, 30] showed that colonic submucosal structures undergo aging changes in both standard and diverticular colons. These changes include differences between the right and left sides of the colon as an increase in the number of fibrils and a decrease in the fibril diameter in the left colon compared with those in the right colon. Acid insolubility increases after 40 years—an exciting finding as colonic diverticulosis is rare before that age. This relationship was more strongly significant in the sigmoid colon, which is the predominant location for the development of colonic diverticula. These results also indicate that colonic collagen from subjects affected by colonic diverticulosis is less acid-soluble than that from healthy colons of those over 60 years ($p < 0\ 05$), suggesting that the collagen from colonic diverticulosis colons has a higher number of cross-links than that from the unaffected colonic tissue. The solubility of collagen in weak acids is known to decrease with advancing age in specific tissues, such as the skin, vascular adventitia, and chordae tendineae of the heart valves [28]. Thomson et al. have shown an increase in the collagen fibril numbers and decreased collagen fibril diameter in the left colon of patients with diverticular disease [14]. Colonic collagen is in a dynamic state, given that it is continuously produced and degraded. Aging is associated with increased cross-linking between collagen molecules, which results in decreased solubility in weak acids, increasing stiffness and resistance to enzymic digestion in vitro [26].

5.4 Nervous Alteration

Since the gut is regarded as the second brain, the search for nervous alteration or running change has a logical background. Short-lived recurrent abdominal pain is a common and debilitating symptom reported by a third of patients with symptomatic diverticular disease, suggesting that visceral hypersensitivity might play a role [31]. Patients with symptomatic diverticular disease demonstrate visceral hypersensitivity to rectal balloon distension because of peripheral sensitization, with both inflammatory and neurochemical factors playing a role [31]. This finding is associated with an increase in the expression of the inflammatory cytokines IL-6 and TNF-α and an upregulation of the neuropeptide receptor NK1. Prior inflammation, in the form of episodes of acute diverticulitis, is associated with a fourfold increase in the risk of reporting recurrent abdominal pain in patients with diverticulosis, with such patients also having inflammatory changes present in resection specimens [32]. An increase in substance P and galanin-secreting neurons in mucosal biopsies of

patients with prior episodes of acute diverticulitis has also been demonstrated [33]. This finding suggests that both inflammation and variation in neuropeptide secretions may be necessary for generating symptoms in patients with diverticulitis. Both these mechanisms may be responsible for peripheral sensitization leading to visceral hypersensitivity, as previous studies have separately demonstrated changes in inflammation, enteric nerves, and sensitization [31, 32], suggesting that patients with the symptomatic disease have distinct abnormalities in motor function and inflammatory and neural changes that differ from asymptomatic patients. Simpson et al. [33] focused on the structural and luminal changes in the condition, particularly the role of high-pressure colonic contractions. Similar amplitude contractions are also present in healthy volunteers but are not reported to be painful [34], suggesting that visceral hypersensitivity is an essential determinant of symptoms. Humes [35] demonstrated an increased expression of genes producing inflammatory proteins such as IL-6 and TNF-α in symptomatic than in asymptomatic patients. The increase in inflammatory gene expression and cell-to-cell interaction suggests that these patients have a low-grade inflammation associated with visceral hypersensitivity. In a normal gastrointestinal tract, vagal activity regulates exocrine function, promotes bowel motility, and initiates feedback signals to the central nervous system. The vagal signal is carried through the cholinergic and muscarinic pathways, whereas the sympathetic signal is carried through the adrenergic pathways [36]. The idea that chafing of vagal innervation leads to vagal hypersensitivity in the recipient organ may explain why baseline motility is normal in diverticular disease, but amplified colonic motility mimicking irritable bowel syndrome is seen postprandially. In this setting, dysfunctional bowel contractions are believed to contribute to gaps in tissue planes between muscle fibers, through which mucosal herniations are believed to occur. Notably, the heightened smooth muscle contractions in diverticular disease have been attributed to cholinergic receptor overexpression, and not excess vagal innervation [37]. Yun et al. [36] hypothesized that the vagal withdrawal of diverticulosis may represent a specific local manifestation of the aging-related global retreat of vagal innervation from recipient organs. This global phenomenon is likely to be an evolutionary maladaptation that has been unmasked by the rapid expansion of human lifespan during the last few centuries [38]. A loss of enteric neurons is a common histopathological feature within the spectrum of gastrointestinal neuromuscular pathology and diverticular disease (DD) [39]. In addition, Barrenschee et al. [40] reported a significant reduction in the myenteric neuronal number per 100 mm intestinal length and an average in neuronal number per ganglion in patients with DD. In contrast, Iwase et al. [41] observed a reduction in the number and size of myenteric ganglion cells per cm in both patients with asymptomatic diverticula and DD. In this case, the observed reduction might involve glial rather than neuronal cells. Immunohistochemistry shows a reduction in both the neuropil and the somata of myenteric neurons for GDNF family receptor alpha 1 (GFRα1) and REarranged during Transfection (RET), which provide evidence for the involvement of glial cells and neurons in the case of GFRα1. For RET, immunohistochemistry indicates only a reduction in myenteric neurons with its processes, given that RET is not expressed in glial cells. However,

a quantitation analysis exhibited a similar reduction in receptor expression in both diverticulosis and DD. This indicates that the reduced receptor expression is an early event within the pathogenic process, most likely provoked by an impaired glial cell line-derived neurotrophic factor (GDNF) system. GDNF is a potent neurotrophic factor for various neuronal cell populations in the central and peripheral nervous systems and in the enteric nervous system (ENS), which continues during the progression of the disease. Novel concepts consider that patients with DD exhibit disturbed intestinal motility patterns [34, 42], morphological alteration in the ENS (oligoneuronal hypoganglionosis) [41, 43], remodeling in the nerve tissue, and impaired neuromuscular communication and disturbed enteric neurotransmission [9, 44]. These alterations in patients with DD might lead to uncoordinated contractions and high pressure, thus producing and triggering the formation of diverticula. It is suggested that enteric neuromuscular changes may result from remodeling processes after acute inflammation since several neuropeptides, found to be increased after acute inflammation, were also increased in symptomatic but not in inflamed DD [33]. Thus, in the case of DD, a reduced GDNF expression could also be explained because of previous inflammation that damaged the ENS or the intestinal musculature. However, Barrenschee [40] demonstrated that downregulation of the components of the GDNF system already occurs in earlier stages of this illness, namely, in asymptomatic diverticulosis, where no inflammatory events could be observed before having strengthened the hypothesis that the disturbed GDNF system could be the primary trigger for the reduced neuronal number rather than for inflammatory processes.

5.5 Mucosal Alteration and Markers of Histological Inflammation

Diverticula comprise mucosa pouches, surrounded by loose fibro fatty tissues in the subserosal layer or the adventitia of the colon. There is a residual strand instead of a fully formed muscularis mucosae, usually accompanied by an increase in the number and size of lymphoid follicles within the mucous lining [45], as a local response to fecal stasis, like that seen in the vermiform appendix or diversion proctocolitis [46]. The histology of diverticula is directly related to the degree of inflammation and injury to the mucosa [47]. Commonly, it has the histological feature of a normal colonic mucosa. However, most times, there is an increase in the lymphoplasmacytic mononuclear chronic cellular infiltrate in the lamina propria coupled with mucin depletion, cryptitis, architectural distortion, Paneth cell metaplasia, and formation of lymphoglandular complexes (Fig. 5.3). Erosions and ulcers (Fig. 5.4) can complete the histological picture, and fecal material escaping into the mucosa or subserosa may elicit a foreign body granuloma. The mucosal changes are usually confined to the diverticula but may extend to the ostia, whereas the surrounding mucosa, in most cases, is histologically normal. In severely shortened thick-walled segments of the bowel with diverticulosis, the redundant mucosa is bent into characteristic polypoid folds (Fig. 5.5). Microscopically, the folds show vascular

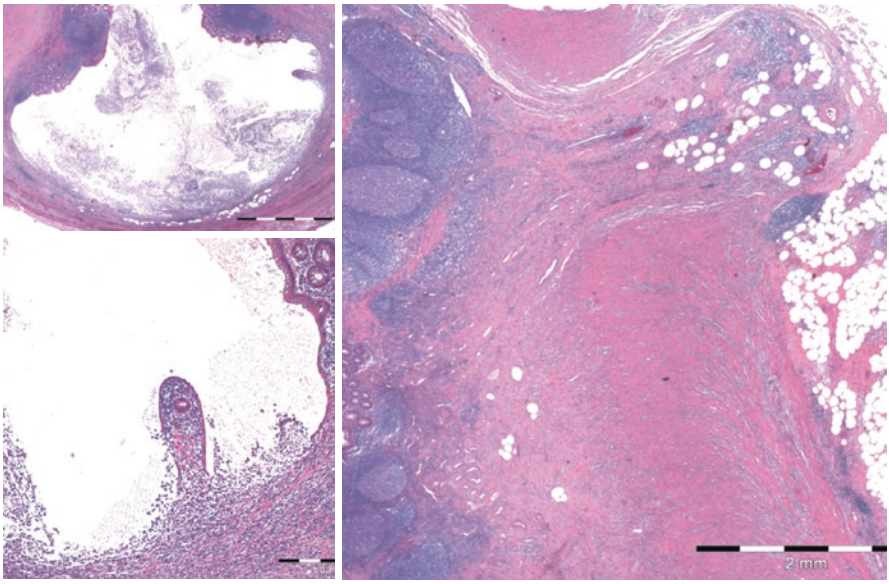

Fig. 5.3 Progressive damage of the epithelial lining and inflammatory reaction extending to the adjacent soft tissues

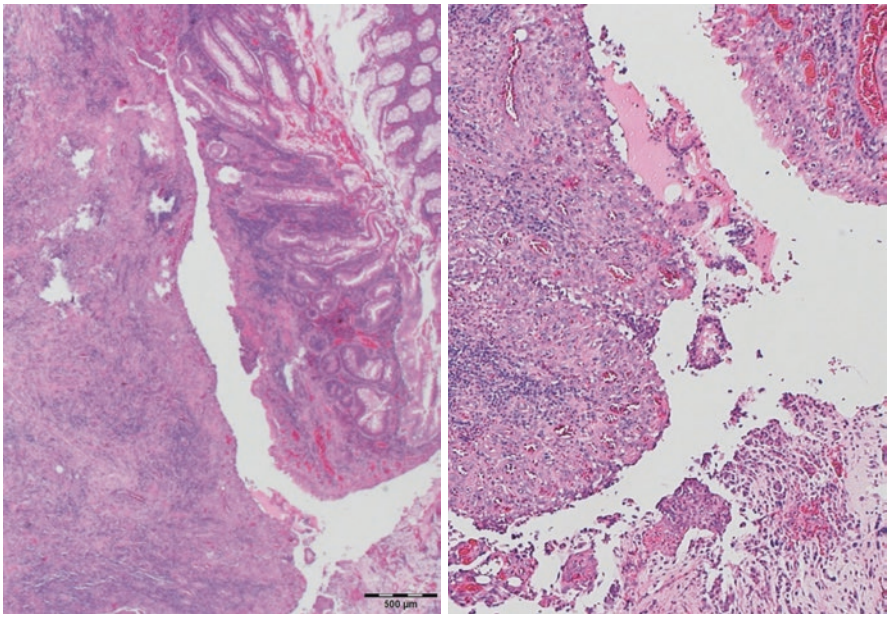

Fig. 5.4 Abscess in diverticular disease

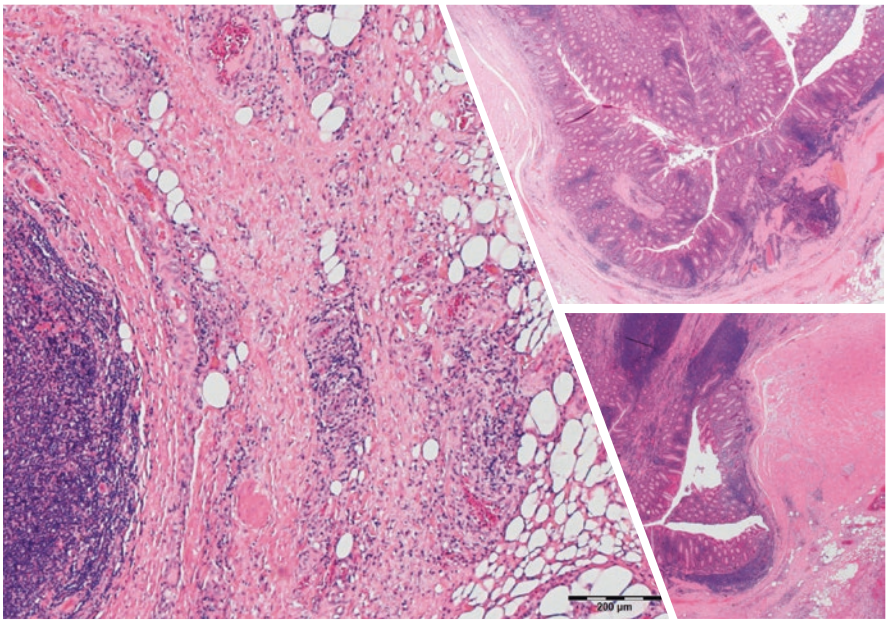

Fig. 5.5 Chronic diverticulitis, fibrosis, and mucosal polypoid fold

congestion, mucosal edema, and hemosiderin deposition, which follows acute bleeding [47]. The characteristic features of mucosal prolapse, including crypt hyperplasia, muscularization of the lamina propria, and superficial erosions, are commonly present [48]. In a small proportion of patients with sigmoid diverticulosis or diverticulitis (estimated to be from 0.3 to 1.3%), the mucosa between the diverticula of surgically removed diverticulitis specimens is grossly erythematous, granular, and friable. It thus resembles the colonic mucosa in a chronic inflammatory bowel disease [49]. Most patients (75–80%) with diverticulosis will remain asymptomatic throughout their lifetime. Diverticulitis is the most common cause of symptoms, affecting 10–25% of patients with diverticulosis [50]. Obstruction of the neck of a diverticulum with fecal matter is believed to cause distension of the diverticulum responsible for the compression of the vasa recta deployed on the convexity of the pouch, resulting in focal ischemia of the mucosa, thus leading to local inflammation, mucus stack, and bacterial overgrowth. Hemorrhage is a common complication of diverticular disease accounting for more than 40% of lower gastrointestinal bleeding episodes in some series [51]. Mucosal ulceration could lead to gradual and mild bleeding, whereas erosion of the vasa recta, which traverses the circular muscle, may cause a rapid hemorrhage. Inflammation of the diverticulum may lead to a peri-diverticular abscess within the colonic subserosa, and this can cause serositis, adhesions, and formation of an inflammatory mass that may ultimately heal by fibrosis, causing a stricture and an obstruction or adhesion to the nearby organ(s)

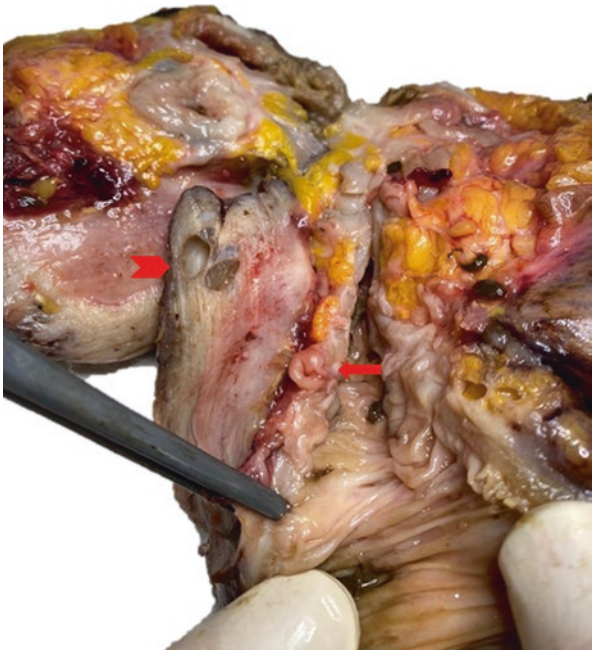

Fig. 5.6 Adhesion between the colon and uterus. Arrow: diverticulum; arrowhead: uterus with Naboth's cysts

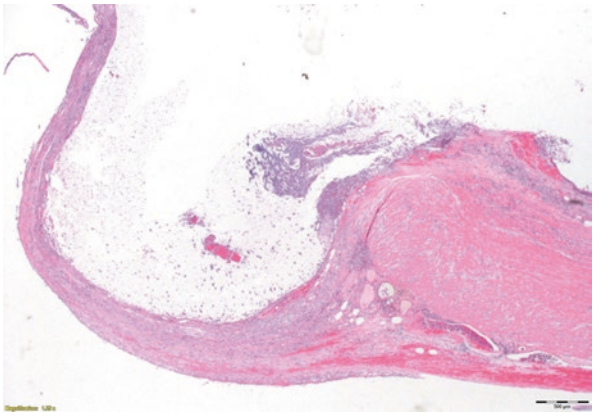

Fig. 5.7 Thinning of the diverticulum wall preceding perforation

(Fig. 5.6) till fistula formation. Inflamed diverticula can perforate, causing purulent peritonitis (Figs. 5.7 and 5.8), or can undergo rupture in the free peritoneal cavity, causing fecal peritonitis. The infection can also spread systemically, causing bacteremia or sepsis. Chronic low-grade inflammation has also been reported within and around diverticula in participants who underwent sigmoid resection for symptomatic uncomplicated diverticular disease (SUDD) but not diverticulitis [52]. These findings correlate with the overexpression of TNF-α in participants with a history of diverticulitis and diverticular disease [53]. When diverticulosis becomes

Fig. 5.8 Perforation of a diverticulum with an induced fibrin-purulent reaction covering the colonic serosa

symptomatic, it is called DD. The most common conventional complication of DD is diverticulitis, which is essentially a pericolic inflammatory process that originates within the diverticula and extends into the surrounding tissues but spares the non-diverticular colonic mucosa. DD may show a low-grade microscopic inflammation related to the severity of the disease [54]. Tumor necrosis factor-alpha (TNF-α) is overexpressed concerning the severity of the histological inflammation [55]. It is also overexpressed in segmental colitis-associated diverticulosis (SCAD), which is considered a 'bridge' between a classical IBD and a complication of a long-lasting DD [56]. The presence of an inflammatory infiltrate was assessed by a semiquantitative lymphocytic and neutrophil count on ten colonic fields with a high-power field (HPF) technique at 40× magnification, assessed at the bottom and on the whole crypts [57]. Hematoxylin–eosin staining was performed to assess the histology of the sigmoid tract. Count lymphocyte assay (CLA) for T cells was performed using anti-CD3 (pan-T) monoclonal antibodies. Lymphocyte infiltration was graded as: Score 0 (normal) = 3–5 cells; Score 1 (mild) = 6–8 cells; Score 2 (moderate) = 9–10 cells; and Score 3 (severe) = >10 cells. The neutrophilic infiltrate was also evaluated to assess active or nonactive inflammation using a semiquantitative grading: Score 0 (absence of neutrophilic infiltrate) = nonactive; Score 1 (focal presence of neutrophil) = mild; Score 2 (presence of neutrophil intermediate between 1 and 3) = moderate; and Score 3 (diffuse neutrophilic infiltrate) = severe. Neutrophils were localized using anti-CD15 monoclonal antibodies. As the severity of histological inflammation is based on the severity of the neutrophil infiltrate, the choice to assess

only the acute infiltrate may be considered adequate in such a context [55]. According to Pucilowska et al. [58], acute injury on the colonic mucosa causes normal mesenchymal cells to be activated to a fibrogenic phenotype with consequent normal healing of fibrosis. During normal healing, excess extracellular matrix deposition is prevented by post-transcriptional or post-translation regulation of collagen, reversal of the fibrogenic phenotype, or selective death of fibrogenic cells. If these events do not occur or are not sufficiently active or if the fibrogenic cell population expands, fibrosis may occur. However, in a recent study, Järbrink-Sehgal et al. [59] have assessed all colonic segment biopsies, from left to right, using standard endoscopic forceps. The corresponding hematoxylin and eosin-stained slides were investigated for either the presence or the absence of markers of histological inflammation, such as surface epithelium, mucin depletion, Paneth cells, cryptitis or crypt abscesses, apoptosis of the epithelium, normal architecture/crypt branching, chronic inflammatory gradient from the base to the surface, basal plasmacytosis, and granulomas. The number of lymphoid aggregates, follicles, and neutrophils was counted in the lamina propria, and intraepithelial lymphocytes were counted/100 colonocytes [60]. The surface epithelium and chronic inflammatory gradient were intact in all participants, and basal plasmacytosis and granulomas were absent in all samples. There was a trend of increased numbers of cecal lymphoid aggregates in cases vs. controls ($P = 0.07$), but no other associations between diverticulosis and inflammatory markers were found. Kealy et al. [61] reported that the density of microscopic lymph follicles and aggregates increased in the necropsied colons of patients with diverticular disease than in those without, suggesting that lymphoid follicles may be weak points in the mucosa and that diverticula could develop at these points. The Järbrink-Sehgal population-based study, assessing the whole colon for inflammation, regardless of diverticula localization, complements the findings by Peery et al. [59, 62], demonstrating the absence of colonic mucosal inflammation in diverticulosis or symptomatic diverticulosis, therefore questioning the role of chronic low-grade inflammation in diverticula's genesis. Similarly, in the symptomatic diverticulosis subanalysis, Järbrink-Sehgal et al. [59] found no association between symptomatic diverticulosis with abdominal pain or diarrhea and serological or mucosal inflammation throughout the colon. These findings uphold other findings of an absence of colonic mucosal inflammation in the sigmoid, using serological immune markers and histological cytokine levels in patients with symptomatic diverticulosis and SUDD compared with controls without diverticulosis [63]. The same conclusion was drawn by Peery et al. [62] in a large colonoscopy-based study of individuals without a history of diverticulitis or overt peri-diverticular inflammation. It was found that colonic diverticulosis was not associated with mucosal inflammation and no association was found between colonic diverticulosis and chronic gastrointestinal symptoms. There was no evidence for mucosal inflammation in individuals with diverticulosis and chronic gastrointestinal symptoms, the so-called symptomatic uncomplicated diverticular disease.

5.6 Segmental Colitis-Associated Diverticulosis (SCAD)

As the name suggests, SCAD is a colonic inflammatory disorder that occurs in patients with superimposable characteristics mimicking the clinical and endoscopic features of inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis. By definition, SCAD is a pathological entity characterized by a chronic inflammatory response involving the interdiverticular mucosa of the colonic segment involved. The rectum, by definition, is free of inflammation [64]. A nonspecific, nongranulomatous, and localized inflammatory process involving the sigmoid colon (i.e., 'sigmoiditis') and sparing the rectum and a more proximal colon defines this pathology. The true prevalence of the disease is probably underestimated, with an incidence varying between 0.3 and 4% [61, 65, 66]; however, a Dutch retrospective study reported an incidence as high as 8% [67]. SCAD is now viewed as a specific inflammatory pathology paired with diverticulosis whose etiology is still not entirely known [66, 68]. Most cases occur in males, with rectal bleeding being the most frequent initial presentation (hematochezia: more than 70%). Usually, the entity is almost exclusively a disorder of the elderly, often after the age of 50 years [69]. SCAD represents a distinct clinical and pathological entity sharing some features with other forms of inflammatory bowel diseases (IBDs). The pathogenesis of SCAD is multifactorial and includes genetic susceptibility, alteration in the colonic microbiome, local ischemia, and mucosal prolapse [61, 70, 71]. SCAD is pathologically defined by a nonspecific segmental or localized nongranulomatous inflammatory process, usually confined to the sigmoid colon. The right colon and rectal inflammatory sparing are confirmed by histologically normal mucosa in the endoscopically documented left diverticular ostia. When it is present, the perianal disease, a marker more suggestive of Crohn's disease, is also missing. In more than 60% of patients with recurrent SCAD, the second episode of the disease had clinical evidence more than a decade after the initial clinical episode, indicating that the disease often seems to be a self-limited inflammatory process that resolves with no future disease episodes or requirement for ongoing treatment. Increased TNF-α concentrations have been reported in Crohn's disease and ulcerative colitis, and SCAD [69]. The hematoxylin and eosin-stained specimens of the inflamed colonic tract were used to evaluate either the whole mucosal damage or the activity of the inflammation. Mucosal damage was reflected by a score representing the mean value of the single scores of the following histological characteristics: polymorphonuclear infiltration of the epithelium and lamina propria, crypt abscesses, loss of glandular parallelism, crypt shortening and ramification, mucus epithelial depletion, and involvement of the muscularis mucosae and submucosa. Each histology score ranged from 0 (normal) to 3 (severe). The inflammation activity was expressed by the total number of neutrophils in the lamina propria, counted with software in five high-power fields, selected based on high cellular density. The inflammation activity was considered mild ($\geq$5 and <10 cells/mm^2), moderate ($\geq$10 and <15 cells/mm^2), or severe ($\geq$15 cells/mm^2) [69]. In SCAD, biopsies were collected from the interdiverticular mucosa, which, by definition, is affected by the disease [65, 70].

The endoscopic classification of SCAD was based on a score formulated by Tursi et al. The disease was classified into four different endoscopic patterns (types A, B, C, and D), mirroring the symptoms reported by patients. Patients with milder lesions (types A and C) report mild abdominal pain or diarrhea. In contrast, more severe lesions (types B and D) are always accompanied by abdominal pain, rectal bleeding, or sometimes subocclusive attacks (type D) [70]. Moreover, Tursi et al. [72] showed a lower rate of recurrence in patients with mild endoscopic and clinical patterns (types A and C) compared with patients with severe endoscopic and clinical patterns at entry (types B and D). Four different endoscopic patterns (Table 5.1) are recognized, associated with peculiar histological characteristics [61, 70, 73–75]. Type A is characterized endoscopically by red patches involving colonic folds and diverticular sparing. Types B and D are characterized endoscopically by ulcerative colitis (UC)-like changes with erosions and hyperemic areas involving the colonic folds and severe inflammation involving the overall diverticula containing the mucosa, respectively. Type C is characterized by Crohn's disease-like changes, with isolated aphthous ulcers and transmural inflammatory changes [74].

On light microscopy, histological features include cryptitis, crypt abscesses, and expansion of the lamina propria by mononuclear cells, sometimes arranged in prominent basal lymphoid aggregates. Features of chronicity, including basal lymphoplasmacytosis, crypt distortion, and Paneth cell metaplasia, are usually seen. A granulomatous cryptolytic reaction (Figs. 5.9 and 5.10) confined to the damaged crypts might also be seen. In general, the inflammatory infiltrate is limited to the mucosa. Histological features in SCAD appear in variable combinations [65]. A correlation with the clinical and endoscopic characteristics, not histology alone, is essential for establishing the correct diagnosis in cases of suspected SCAD [46, 72]. Occasionally, histological features of ischemic colitis could lead to the speculation that a small percentage of SCAD might represent a type of ischemic colitis because diverticula in such areas could favor, by compression of the vasa recta, ischemic lesions. Biopsies of the rectum should be histologically normal and, in this regard, are mandatory. In patients who must undergo segmental resection for control of symptoms, the resected sigmoid colons show the features described above, along with the bowel's luminal surface and contiguous diverticular pouches. However, the

Table 5.1 Relationship between macroscopic (endoscopic) and microscopic (histological) morphological features

	Endoscopic pattern (%)	Pairing histological features
A	Crescentic fold disease (52%)	Mild lymphoid and neutrophil infiltrate; sparing of the glandular structure
B	Mild-to-moderate UC-like (30–40%)	Active inflammatory infiltrate, glandular distortion, reduction of goblet cells, intraepithelial abscesses, rectal sparing
C	Crohn's–colitis-like (11%)	Active and chronic inflammation with prominent lymphoid follicles, sometimes micro-fistulas in the mucosa and/or cryptolytic granulomas but no epithelioid granulomas.
D	Severe ulcerative colitis-like (7%).	Heavy acute and chronic inflammatory infiltrate, glandular distortion with massive depletion of goblet cells, cryptitis with cryptic abscesses, rectal sparing

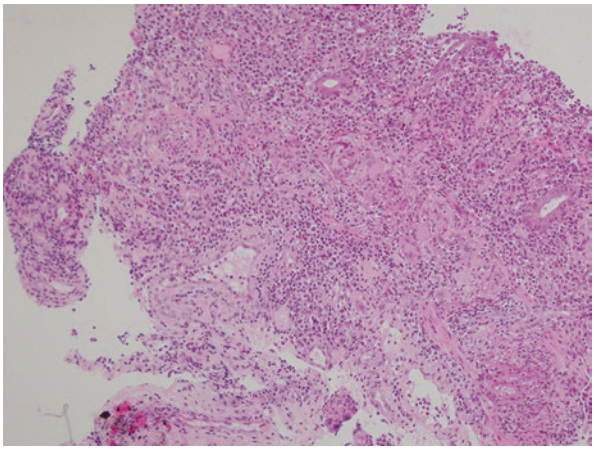

Fig. 5.9 Segmental colitis-associated diverticolosis type C: active and chronic inflammation with cryptolytic granulomas but no epithelioid granulomas

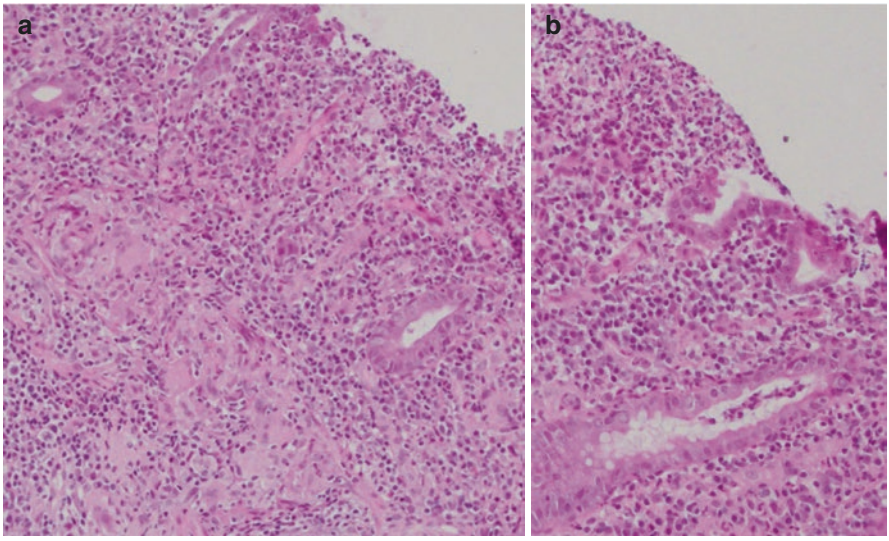

Fig. 5.10 (**a**) Details of a cryptolitic granulomatous reaction. Foreign-body giant cells are scattered around the colonic glands. (**b**) Cryptic abscess and erosion of the mucosal surface

extension of acute inflammation into the bowel wall near the diverticula, with abscess formation, fibrosis, and often perforation, is absent. Some patients with true diverticulitis develop an inflammatory reaction that mimics Crohn's disease [49] in patients without previous or present evidence of Crohn's disease elsewhere in the gastrointestinal tract. The resection specimens demonstrate a Crohn's-like reaction to the inflamed diverticula. It can be challenging to differentiate diverticular disease-associated segmental colitis from ulcerative colitis or occasionally from Crohn's colitis. Clinically, the rectum is infrequently spared in ulcerative colitis, and the inflammatory process extends beyond the segment of the bowel involved by the

diverticula [64]. Even in ulcerative colitis cases with rectal sparing, the rectal mucosa shows some quiescent colitis features on biopsy with fibrosis of the lamina propria, basal plasmacytosis, and distortion of the glandular architecture. Crohn's patients usually have involvement of different bowel segments as well. In addition, since cryptolytic granulomas represent sigmoid diverticulitis, caution should be exercised to avoid an inappropriate diagnosis of Crohn's disease [49]. Histological observation of a significant increase in immunohistochemical TNF-α expression in patients with SCAD [72] allows for correct differential diagnosis of SCAD concerning other forms of chronic colitis, particularly UC and CD. Other entities in the differential diagnosis, emphasizing segmental left-sided colitis that might mimic ulcerative colitis, include infectious entities such as Shigella and Salmonella species, NSAID-associated colitis, and diversion colitis. Endoscopists must provide pathologists with the information that the patient has a diverticular disease, communicate sparing of the rectum and the remainder of the bowel, and obtain biopsies from both the involved segment of the bowel and the spared rectum so that the distribution of disease can be histologically documented [64].

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