Recent advances in pathobiology and histopathological diagnosis of inflammatory bowel disease

Takuji Tanaka¹,²,³ and Shigeyuki Sugie⁴

¹Department of Tumor Pathology, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu City, Gifu 501-1194, Japan.
²The Tohkai Cytopathology Institute: Cancer Research and Prevention (TCI-CaRP), 5-1-2 Minami-uzura, Gifu 500-8285, Japan.
³Department of Pathology, Murakami Memorial Hospital, Asahi University, 3-23 Hashimoto-cho, Gifu 500-8523, Japan.
⁴Department of Pathology, Murakami Memorial Hospital, Asahi University, 3-23 Hashimoto-cho, Gifu 500-8523, Japan.

Abstract
In order to make a diagnosis of ulcerative colitis (UC) or Crohn’s disease (CD) which belongs to inflammatory bowel disease (IBD), it is important to evaluate pathologic material in conjunction with clinical, laboratory and endoscopic findings. There are several exceptions to the classical principles of IBD that may lead to diagnostic confusion. UC and CD have a variety of characteristic but also non-specific pathologic features. There are several exceptions to the classical principles of IBD that may lead to diagnostic confusion. This short review summarizes current diagnostic problems and advances with regard to histopathological findings of inflammation and dysplasia in biopsy specimens from UC and CD patients.

Keywords: IBD, ulcerative colitis, crohn’s disease, pathobiology, histopathology, differential diagnosis

Introduction
Worldwide, the frequency of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn’s disease (CD) increased rapidly through the last century [1,2]. However, tends to be at the uppermost limit in developed countries [3]. On the other hand, the increase in the patients with IBD in the area where the frequency was low until now [2,4], and the increase in the child cases of IBD are postulated [5-8]. Although the etiology of IBD is still unknown, it is supposed that immunological, hereditary, and environmental factors are involved by connecting with each other [6,9,10]. Several studies have suggested that a gene NOD2 contributes to development of CD [11-13]. However, all the CD patients do not have alterations of NOD2 [14], especially Japanese CD patients [15-17]. There is a differential genetic background of CD susceptibility between Japanese and European populations [18]. Recently, interesting findings showing an unexpected role of NOD2 in shaping a protective assembly of gut bacterial communities have been reported [19]. The findings also suggest that licensing of dysbiotic microbiota is a critical component of risk of CD.

Histopathology of UC and CD
UC and CD possess respectively their characteristic pathological findings. The pathological characteristics of UC include continued lesions from rectum that limit to the large bowel, and inflammation located in the mucosa. Histopathologically, chronic inflammation is uniform and accompanied with cryptitis (Figure 1) and crypt abscess (Figure 2), resulting in distinct cryptal distortion. In contrast, pathological lesions of CD are found in small intestine, large bowel or both. CD could affect the whole alimentary tract. Thus, affected regions of CD are variable, when compared with UC. We should note the pathological findings of CD that are different from UC. Distribution of the lesions of CD is spots-like and continuous histopathologically and macroscopically. Inflammation of CD is found all in the intestinal tract layers. In addition, distortion of crypts in the mucosa is not prominent when compared with UC. Additionally, there are characteristic longitudinal ulcers in the intestinal tract of the patients with CD and histopathologically epithelioid cell granulomas (Figure 3). Gastric mucosal lesions are found with a high rate in CD patients. The lesions are focal inflammation containing granuloma(s) sometime and histologically called “focal enhanced gastritis”. In early stages of CD, we often notice the aphthous lesions in the alimentary tract. We should differentiate the lesions that occur in CD from infectious enteritis. Since histopathology of amebic colitis (Figure 4) resembles that of colonic CD and UC, and IBD can also be carriers of amebae [20-22], we must be careful of the presence of an amebae in the colonic mucosa of biopsies when diagnose IBD or not [23]. When diagnose such lesions in biopsy specimens, it is quite important to know the chronicity of inflammation. We should check the presence of infiltration of lymphocytes and plasma cells in the depth of mucosa (focal/ diffuse basal lymphoplasmacytosis), level branch and distortion of crypts, and mucosal atrophy.

Cytomegalovirus (CMV) and amebae infection in IBD patients
UC can present non-typical findings that are different from classic characteristics. They include mucosal inflammation nest (cecal...
patch) in the right colon, cecum in particular, appendices aperture circumference mucosa that is a discontinuous lesion of that of left colon and lack or slight of spot inflammation in the rectal mucosa (rectal sparing). It should be keep in mind that discontinuous distribution of spots-like lesions, and endoscopic or histological rectal sparing are detected in the cases of UC patients receiving long-term treatment. Moreover, it is possible to find CMV infection when inflammation recurred in UC patients that obtain remission for a long-term. Therefore, it is necessary not to overlook CMV-infected large cells and inclusion bodies on the occasion of biopsy tissue diagnosis.

Recently, de novo IBD that develops after solid organ transplantation and is a more common UC than CD is recognized. The incidence of de novo IBD in the transplanted patients is ten-times higher than the expected incidence of IBD in the general population. The major risk factor of de novo IBD is considered to be CMV infection. Significance of CMV infection is also reported in a murine colitis model.

**Indeterminate colitis**

By a part of IBD, there are cases called “indeterminate colitis” when diagnosis of UC or CD is difficult. Most cases of “indeterminate colitis” are related to fulminant colitis, a condition in which the classical features of UC or CD may be obscured by severe ulceration with early superficial fissuring ulceration, transmural lymphoid aggregates, and relative rectal sparing. Approximately 20% of patients with “indeterminate colitis” develop severe pouch complications that occur in 8-10% of UC and 30-40% CD. Although the name “indeterminate colitis” was used for the findings in the
punched-out type ulcerations like simple ulcers are the most characteristic pathological feature, while non-specific diffuse ulcerations and granulomatous lesions are similar to CD and UC. Thus, it is sometimes difficult to differentiate IBD from intestinal Behçet’s disease based on extraintestinal symptoms as well as intestinal lesions [37]. One interesting case, in which a patient who was diagnosed with Behçet’s disease after the diagnosis of UC have been established for more than 15 years [39] was reported. It is likely that a similar pathogenesis mediates the development of Behçet’s disease and IBD, especially UC.

**Colorectal cancer (CRC) in IBD patients**

It is known that the risk of CRC development significantly increases in the patients of IBD [1,40]. Patients with UC and CD bear an about 10- and 4-fold increased risk, respectively, for developing CRC [1,41]. The risk increases more in the cases with long disease years [1], those with affected area, those with pan-colitis that developed during childhood. The risk for neoplasm also depends on therapeutic responsiveness of chronic inflammation and seems pathogenetically to be similar in UC and CD. In many cases in which altered crypts relevant to IBD, dysplastic crypts (Figure 6a) other than CRC (Figure 6b) are frequently found and thus it is considered that CRC in IBD arises from this cryptal dysplasia. Dysplasia does not form clear pathological lesions (called flat dysplasia) and therefore it is difficult to detect it by endoscopic examination. Many random biopsies is required for the surveillance and several guidelines are proposed.

There is protruded lesion other than flat dysplasia in dysplasia developed in the large bowel of IBD. These lesions are called “dysplasia-associated lesion or mass (DALM)” [35,42-44] and often coexist with CRC. It has been considered that in such cases intestinal tract should be excised. However, some protruded dysplastic lesions resemble conventional adenoma and can be excised by endoscope. The lesions are called polypoid IBD-associated dysplasia (polypoid dysplasia) [45-49]. Polypoid dysplasia should be distinguished from the conventional adenomas. Many cases of polypoid dysplasia develop in younger patients rather than the patients with the conventional adenomas and have active inflammation and a long disease period. Histopathologically, polypoid dysplasia shows severe inflammatory cell infiltration and dysplastic crypts and non-dysplastic crypts are intermingled in the colorectum.

Recently, programmed cell death 4 (PDCD4) has been demonstrated to be a new tumor suppressor gene in several tissues [50-52], including colorectum [53]. Although normal colonocytes and hyperplastic polyposis show strong PDCD4 nuclear immunostaining, a significantly lower PDCD4 nuclear expression is observed in tubular/serrated adenomas and invasive CRC [54]. PDCD4 immunostaining and mRNA levels decreased significantly as the phenotypic changes occurring during colon carcinogenesis progressively increased. In

![Figure 5. Cytomegalovirus (CMV, arrow heads) detected by immunohistochemistry using a monoclonal antibody against CMV in a colonic biopsy specimen from a UC patient.](image)

![Figure 6. Dysplastic crypt (a) found surrounding adenocarcinoma glands (b, arrow heads) in a colon from a UC patient.](image)
addition, expression of a major PDCD4 regulator, miR-21, is significantly upregulated in preneoplastic and neoplastic lesions, consistent with PDCD4 downregulation [54]. As found in sporadic colorectal oncogenesis, non-lesional colonocytes and inactive IBD show strong PDCD4-nuclear immunostain, but lower PDCD4 nuclear expression is found in both active IBD (Figure 7) and IBD-associated dysplastic lesions (Figure 7) [55]. We recently confirmed these immunohistochemical findings of PDCD4 in Japanese UC patients with CRC (Figure 7). PDCD4 down-regulation in both active IBD and dysplasia is significantly associated with miR-21 up-regulation [55]. The findings indicate that PDCD4 nuclear down-regulation, which parallels miR-21 up-regulation is involved in the molecular pathway of IBD-associated colorectal carcinogenesis. Thus, PDCD4 nuclear expression could be a novel maker in the histological assessment of IBD-associated dysplastic lesions. Additionally, PDCD4 has a potential value as a molecular target in cancer therapy [51,52,56], although recent data suggest that PDCD4 function may depend on cell type and/or genetic background [52].

Conclusion
As mentioned above, pathologists play the important role in the diagnosis of IBD, especially in differential diagnosis of UC and CD, determination of the grade of inflammation, presence or absence of complications, including dysplasia and CRC.

List of abbreviations
IBD: Inflammatory bowel disease
UC: Ulcerative colitis
CD: Crohn’s disease
CMV: Cytomegalovirus
CRC: Colorectal Cancer
DALM: Dysplasia-associated lesion or mass
PDCD4: Programmed cell death 4

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
All authors participated in the conception and design of the study. TT and SS summarized the extracted data. TT wrote the manuscript with contributions from SS. All authors read and approved the final manuscript.

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