Brief Report

Inflammatory Bowel Disease-Mimicking Colitis Associated With Nintedanib-Based Therapy in a Lung Cancer Patient

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nintedanib, inflammatory bowel disease mimic, nintedanib-associated colitis, lung cancer therapy, inflammatory bowel disease

Nintedanib is a competitive nonreceptor and receptor tyrosine kinase inhibitor used for the treatment of interstitial lung diseases and non-small-cell lung carcinomas. The therapeutic mechanism of action is likely achieved by its effect on the platelet-derived growth factor receptor, fibroblast growth factor receptor, and vascular endothelial growth factor receptor signaling pathways. Several side effects have been described, including diarrhea and hepatic enzyme (predominantly transaminases) elevation.[1]

A 62-year-old male patient with a history of hypertension, type 2 diabetes, and ischemic heart disease was diagnosed with *KRAS*-mutant lung adenocarcinoma in 2016. The patient underwent lobectomy and was given a postoperative combination of cisplatin and vinorelbine. In 2019, multiple brain metastases were discovered and treated with irradiation that resulted in regression. In 2020, following the diagnosis of multiple pulmonary, mediastinal, and retroperitoneal lymph node metastases, he received 6 cycles of docetaxel-carboplatin-bevacizumab followed 6 months later by 4 cycles of atezolizumab. In 2021, 6 months after the cessation of atezolizumab, 6 cycles of palliative third-line chemotherapy, docetaxel-nintedanib combination was given due to progressing disseminated disease.

Two weeks after the patient received the docetaxel-nintedanib treatment, the patient developed severe, hemorrhagic diarrhea. Subsequent colonoscopic examination revealed diffuse colitis from the rectum to the coecum with panmucosal congestion, erythema, scattered erosions, and shallow ulcers covered by fibrinous exudate and minimal focal bleeding (Figure 1A). The patient did not have any gastrointestinal symptoms before the cancer diagnosis or during the prior chemotherapeutic regimens; therefore, endoscopy was not performed earlier. An infectious etiology was suspected, and multiple (ascending, transverse, and descending colon as well as rectum) biopsy samples were taken. Microbiological studies proved to be negative for *Salmonella, Shigella, Yersinia, Campylobacter* species, and *Clostridioides difficile*.

Microscopically, a uniform picture was noted in all biopsy fragments, with diffuse and dense lamina propria lymphoplasmacytic infiltration, continuous basal plasmacytosis, and shortened, architecturally distorted crypts (Figure 1B). Signs of active inflammation, including the presence of lamina propria neutrophils and eosinophils with cryptitis and crypt abscesses were also present (Figure 1C). Scattered withering and drop-out crypts with attenuated, hypereosinophilic cytoplasm and numerous apoptotic bodies, a suggestive feature of iatrogenic/drug-induced colitis, were present among the distorted ones (Figure 1C and D). Typical signs of taxane-related injury (eg, ring mitosis) were scrutinized but not identified. Evidence of lamina propria hyalinization, viral cytopathic effects (ie, inclusion bodies), volcano lesion or pseudomembrane formation, skip lesions, granulomata, intraepithelial lymphocytosis, and subepithelial collagen deposition were likewise absent. Although viral serological tests were not performed, cytomegalovirus and adenovirus immunohistochemistry reactions were negative.

Regarding differential diagnosis, after an extensive chart review, no history of inflammatory bowel disease, diarrheal illness related to the previous chemotherapeutic regimes (including the previous atezolizumab and taxane-based protocol) or other significant gastrointestinal disease

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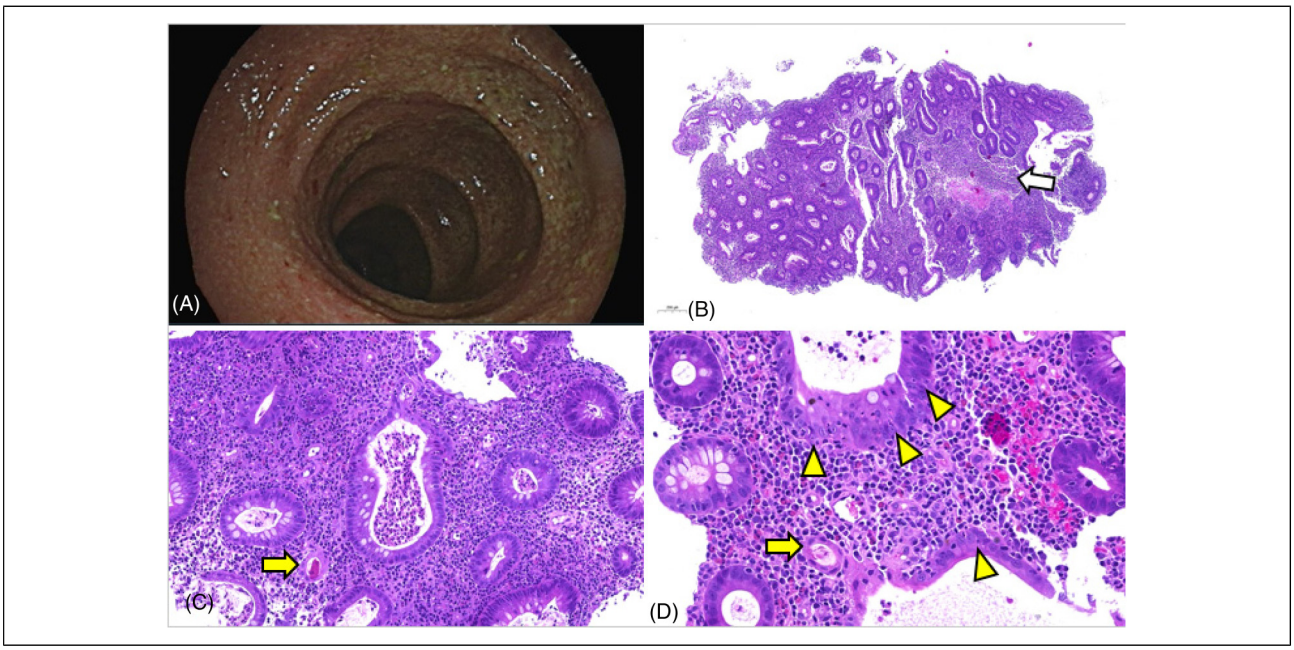

Figure 1. Endoscopic and histologic appearance of nintedanib-associated colitis. (A) The endoscopy reveals an oedematous mucosa with loss of normal vascular markings, diffuse mucosal friability, and hyperaemia. Scattered petechiae with erosions and aphthous ulcers covered by fibrinous exudate were extensively noted. (B) Microscopically, low-power examination shows marked crypt architectural distortion with a dense lymphoplasmacytic infiltration of the lamina propria and basal plasmacytosis (white arrow). (C and D) Cryptitis and numerous crypt abscesses were seen. The presence of randomly scattered attenuated, withering crypts with eosinophil cytoplasm (yellow arrows) and several apoptotic figures (arrowheads) suggested an iatrogenic etiology.

was noted. The apoptotic injury and chronic active colitis pattern noted in the current case could also be caused by various other chemotherapeutical and biological anticancer agents, including angiogenesis inhibitors (eg, bevacizumab[2]), Src tyrosine kinase inhibitors (eg, dasatinib), and immune checkpoint inhibitors (eg, atezolizumab).[3] Based on morphology alone, many drug-induced colitides are impossible to distinguish from each other. Although docetaxel-related injury seemed less likely based on the lack of relatively specific features such as mitotic arrest (ie, ring mitosis), certainty regarding the culprit agent can only be stated when profound clinicopathological correlation is available.[3] Therefore, in our case, it must be emphasized that the patient's symptoms developed 6 months after the cessation of atezolizumab therapy and coinciding exactly with the initiation of nintedanib. Ultimately, based on an integrative review of all clinical and histologic features, a working diagnosis of nintedanib-associated inflammatory bowel disease-mimicking chronic active colitis was favored over inflammatory bowel disease or other drug-induced injury.[4] Subsequently, the docetaxel-nintedanib therapy was stopped, and the diarrheal symptoms regressed in the following weeks.

Only a handful of nintedanib-associated colitis cases, mostly with superficially active and focally active morphologies, have been reported.[5-7] Probable nintedanib-associated colitis was first described by Oda et al. in 2017. Although the authors described the colitis as chronic active, no histologic signs of chronicity (eg, crypt distortion or basal plasmacytosis) were described in the text or demonstrated on the figures.[5] Further 2 case studies of a 68-year-old and a 61-year-old male patient reported histological findings of acute superficial inflammation and increased lymphoplasmacytic infiltration of the lamina propria, but again, no signs of crypt architectural distortion or basal plasmacytosis were documented.[6,7] According to Chandler's research, a causal relationship between nintedanib therapy and ischemic colitis was hypothesized based on the analysis of spontaneous reports of suspected adverse drug reactions and observational data from large health care databases.[8] Furthermore, a single abstract also described a case of histologically proven nintedanib-associated colitis with an ischemic pattern of injury.[9]

Even though diarrhea is a known adverse effect of nintedanib therapy, so far the histologic features of this condition were not thoroughly documented, and no case with a true chronic colitis pattern was reported. Herewith, we offer the first histologically well-illustrated report of chronic active, inflammatory bowel disease -like colitis clinically associated with nintedanib therapy.

Declaration of Conflicting Interests

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

Trial Registration

Not applicable, because this article does not contain any clinical trials.

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