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CLINICAL REVIEW

Current clinical issue of skin lesions in patients with inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is associated with a number of extraintestinal complications, including skin lesions. Most reports have shown that skin lesions are found in 10–15% of IBD cases, although this depends on the definition of skin lesions. The representative skin lesions in patients with IBD are erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, and so on. These lesions are often associated with IBD progression, and intestinal lesions in particular require appropriate treatment. Recently, another clinical issue regarding skin lesions in patients with IBD, a so-called paradoxical reaction, during the treatment with anti-tumor necrosis factor (TNF)-α agents has emerged. These reactions are termed paradoxical reactions because the skin lesions sometimes resemble psoriasis, although the anti-TNF-α agents have been historically used to treat psoriasis. Paradoxical reactions are reportedly found in approximately 5–10% of patients using anti-TNF-α agents and are no longer rare. Now that the use of biologics is at its culmination, reports regarding paradoxical reactions are predicted to increase in number; thus, we must recognize skin lesions with IBD patients including this type of adverse events and manage them appropriately while consulting with dermatologists.

Keywords Inflammatory bowel disease · Extraintestinal · Skin lesion · Paradoxical reaction · Anti-tumor necrosis factor

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disease involving idiopathic inflammation, mainly in the gastrointestinal tract; defined more specifically, it comprises ulcerative colitis (UC) and Crohn's disease (CD). Both are characterized by onset at a young age, and the number of affected patients has risen sharply in recent years in Europe and the United States, as well as in Japan [1]. IBD is associated with a number of complications in the extraintestinal organs such as the eyes [2–5], joint [6–8], skin, and so on. Some of these manifestations appear to be related to the activity of the underlying gut inflammation [9, 10]. Recently, it was also reported that presence of extraintestinal manifestations was significantly associated with the increased disability [11], and the occurrence of IBD drug-related adverse events that necessitated treatment cessation [12]. Therefore, the management of extraintestinal manifestations is important for patients with IBD.

Recently, another clinical issue regarding skin lesions in patients with IBD, a so-called paradoxical reaction, during the treatment with anti-tumor necrosis factor (TNF)-α agents has emerged [13]. Despite recognition of anti-TNF-α agents as safe, potential side effects include allergic reactions [14, 15] and opportunistic infections such as reactivation of tuberculosis [16, 17]. In addition, anti-TNF-α agents can cause psoriasiform skin lesions in a subgroup of anti-TNF-α-treated patients with IBD [13]. This review deals with the skin lesions related to patients with IBD including paradoxical reaction as adverse events associated with anti-TNF-α therapies.

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The skin lesions in patients with IBD

Extraintestinal lesions are reportedly found in 6–47% of IBD cases [8–10, 18–24], while skin lesions are found in 10–15% of IBD, depending on the definition of skin lesions [8, 18]. Other reports stated that lesions occur at a higher rate [25, 26]. It was reported that the skin lesions in patients with IBD were more common in CD than UC [22, 23]. In addition, HLA-B*27 is associated with skin lesions in patients with IBD [22]. The representative skin lesions in patients with IBD are erythema nodosum (EN), pyoderma gangrenosum (PG), Sweet's syndrome (SS), paradoxical reaction, and so on. The skin lesions found in patients with IBD are described below in order.

Erythema nodosum (EN)

Erythema nodosum is the most common skin manifestation of IBD. Its prevalence varies depending on the study population and the type of study. It is reported in 3–10% of patients with UC and 6–15% of patients with CD [8, 9, 18]. Many studies indicated a marked female preponderance with a female to male ratio of about 5:1, but reasons for this gender-specific difference remain unclear [27, 28]. In the cases of 85% or more, EN appears after the diagnosis of IBD [9]. Furthermore, EN is frequently associated with eye and joint involvement, isolated colonic involvement, and PG [28]. In some cases, EN may be symptoms of underlying diseases such as sarcoidosis [29] or Behçet's disease [30]. EN also develops secondary to upper respiratory infections and gastrointestinal infections [31]. The causes of EN are often unknown, but it is sometimes comorbid with IBD and is correlated with its activity. However, EN severity does not always correspond to disease activity of IBD [32].

EN consists of painful tender raised erythematous nodules (Fig. 1). They are found predominantly on the extensor surfaces, nearly always in the pretibial region. Diagnosis is based on typical clinical presentation. In most cases, EN can be easily recognized as symmetrical, raised, tender, red, or violet subcutaneous nodules of 1–5 cm in diameter [9]. Although the inflammation of subcutaneous adipose tissue causes EN, the pathogenic mechanisms involved in EN remain unclear. Histopathologically, infiltration of neutrophils, lymphocytes, and histiocytes can be found in the septum of subcutaneous adipose tissue.

Symptomatic relief is the therapeutic goal. The prognosis of EN is good, and the disease is largely self limiting and heals without scars [20]. The most important thing in the therapy of EN is to treat gastrointestinal lesions. The representative supportive care is leg elevation, analgesics, potassium iodide, and compression stockings [9, 33]. For severe cases of EN, non-steroidal anti-inflammatory drugs (NSAIDs) and/or steroids are required [34]. Ideally, NSAIDs should be avoided because of the risk of worsening the bowel disease. However, some patients may require NSAIDs, which usually provide effective relief of pain. Occasionally, anti-TNF-α agents are used in cases in which the aforementioned treatment was poorly effective [35, 36], and a report based on a cohort study previously showed that the treatment was effective in 80% (8/10) of cases [37]. Repeated recurrence is believed to occur in approximately 30% of patients, but the lesions heal without leaving scars.

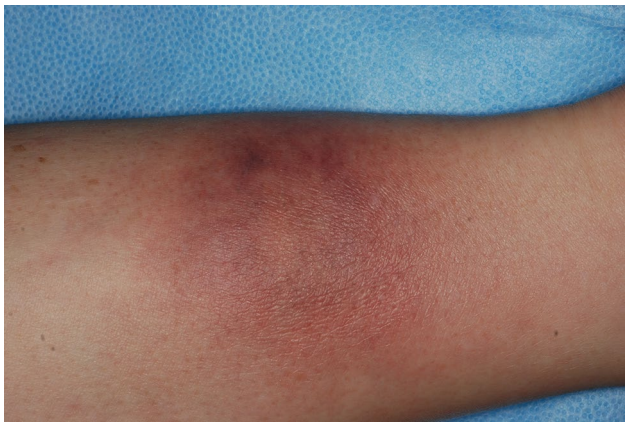

Fig. 1 The skin lesion of erythema nodosum. Tender erythematous plaques developed in the lower extremities of a middle-aged woman with ulcerative colitis. The eruptions healed in 4 weeks without specific treatments

Pyoderma gangrenosum (PG)

Pyoderma gangrenosum is a less common but more troublesome skin manifestation associated with IBD [38]. It is present in between 0.5 and 2% of both UC and CD patients and it may be more common in UC and in female [27, 39, 40]. IBD precedes the appearance of PG and less than 15% of PG cases appear before the diagnosis of IBD [9]. PG is associated with pancolitis as initial IBD location, permanent stoma, eye involvement, and EN [28]. In addition, PG is known to develop mostly in patients with some kind of underlying diseases; as a matter of fact, it is comorbid with IBD in 36–50% of affected patients [41] and with rheumatoid arthritis [42] or Takayasu disease [43] in others. The presence of abnormal neutrophils and T cells leads to immune dysregulation, leading to lesions of PG. Increased levels of inflammatory mediators including IL-1β, IL-8, IL-17, and TNF-α contribute to the development of the disease but there are still several unknown factors [44]. PG is often related to the disease activity, and in some cases PG is

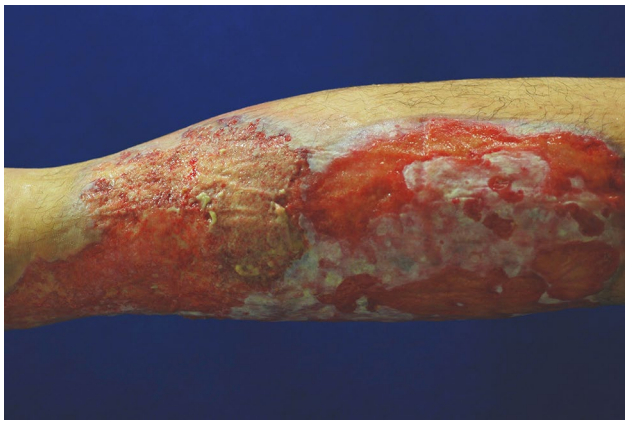

Fig. 2 The skin lesion of pyoderma gangrenosum. A middle-aged man had a 3-month history of refractory skin ulcers on his lower legs after a minor trauma. The ulcers gradually enlarged, forming purpuric borders, vegetative granulation tissues, aseptic skin abscess and necrosis. After clinical workup, comorbid ulcerative colitis was diagnosed

associated with severe relapse of IBD. However, some cases of PG are not correlated with IBD disease severity.

The rash presents in various aspects and can be roughly classified into four different types: ulcerative, pustular, bullous, and vegetative [45]. Among these types, the clinical symptoms of ulcerative PG are pathognomonic; the lesions have dike-shaped bulging margins and are often penetrating [46] (Fig. 2). Regarding pathological findings, abnormal neutrophil function and impaired cellular immunity may play an important role in PG [47]. A skin biopsy is not essential for diagnosis but can be useful for ruling out other diseases. Further, CD patients with PG are reportedly more often anti-neutrophil cytoplasmic antibody positive and anti-*Saccharomyces cerevisiae* antibody negative than CD patients without PG; these serological characteristics can sometimes help with the diagnosis [48].

The most important target in the therapy of PG is gastrointestinal lesion as with the therapy for EN. However, what is different from treatment for EN is that medical treatments including steroids, calcineurin inhibitors, and anti-TNF-α agents are often required for PG. Local treatment consisting of topical steroids and tacrolimus can be effective in patients with moderately severe disease [9, 44, 45, 49, 50]; however, when the disease is more severe, treatments for refractory IBD should be considered, namely the systemic administration of steroids, combined use of azathioprine and methotrexate [9, 33, 44, 45], oral administration of tacrolimus [51], intravenous injections of cyclosporine [52, 53], or use of anti-TNF-α agents [54–58]. In addition, there have been some cases treated with granulocyte and monocyte adsorption apheresis in patients with PG accompanied with IBD [59, 60]. The lesions may last for many months, and more than 25% of patients will have recurrent episodes [27]. Finally, new ulcers reportedly form atop healed ulcers; as a result, the disease leaves scars.

Sweet's syndrome (SS)

Sweet's syndrome was first reported by Sweet in 1964 [61], and because it was histopathologically characterized by a dense neutrophilic infiltration in the dermis, it is often classified as a neutrophilic dermatosis [62]. Depending on its etiopathology, SS can be classified into three categories: classical or idiopathic, malignancy-associated, and drug-induced SS. The association between IBD and SS was first described in 1989 [63]. SS is a rare extraintestinal manifestation of IBD and precise incidence is lacking. However, it has been considered as third skin lesion related to IBD [38]. SS is more common in CD (70%) and in female (87%). SS is associated with active IBD in 67–80%, but precedes the onset of intestinal symptoms in 21%. It is noted that all SS cases with IBD presented with colonic involvement [64–67]. The pathophysiological basis of the relationship between SS and IBD remains mostly unclear, but since they are more commonly found in women, the roles of genetic factors and hormonal involvement have been suggested. Interestingly, there have been reports of SS that developed as a result of the administration of granulocyte colony-stimulating factor [68, 69]. In addition, a patient with SS experienced improvement of her skin lesion after receiving granulocyte and monocyte adsorption apheresis [70]; these reports indicated a strong association between neutrophils and the pathophysiology of SS.

Regarding clinical symptoms, the condition develops suddenly with a fever of 38–40 °C. The rash consists of painful

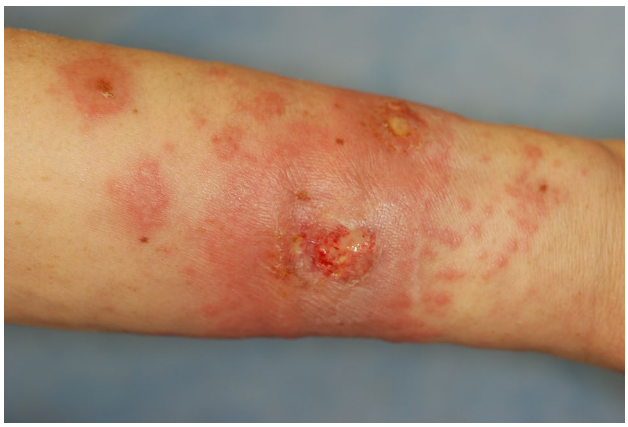

Fig. 3 The skin lesion of Sweet's syndrome. Multiple edematous plaques suddenly developed on the upper extremities of a middle-aged woman who had a 14-year history of ulcerative colitis. The lesions were composed of round or annular erythematous edematous plaques and papules, some of which had small ulcers in the center of the plaques. The eruptions were accompanied by pyrexia

elevated erythematous lesions that develop more commonly on the face and extremities (Fig. 3). In some cases, a large number of pustules are found on the erythema. The condition is also commonly accompanied by joint pain and stomatitis. Histopathologically, the upper and middle layers of the dermis show edema and an extensive infiltration of a large number of inflammatory cells, primarily neutrophils. Blood test results lack specificity and show only elevated C-reactive protein levels and leukocytosis with a neutrophil predominance [9].

Similarly to EN and PG, treating gastrointestinal lesions is most important part of SS treatment. First-line treatment of SS is systemic steroids. High-potency topical steroids or intralesional glucocorticoids may be used for localized disease [23]. For refractory cases, cyclosporines are indicated [71]; the use of vedolizumab was also recently reported [72]. The lesions do not leave scars upon healing.

Stomatitis aphthosa (SA)

Stomatitis aphthosa is believed to be found in 4% of UC cases and approximately 10% of CD cases [8, 73]. SA tends to develop mostly when intestinal lesions are severe and tends to be associated with the activity of the underlying disease, but it can also be found during the remission phase [9, 23]. In 25% of patients, SA develops before IBD is diagnosed [9]. In addition, a study showed that a majority of patients with multiple SA had underlying IBD [74].

Compared to common aphthosa, SA that develops as a complication tends to be larger, more numerous, and persist longer; SA is painful and develops throughout the oral cavity from the buccal mucous membrane to the peritonsillar area. Reddening can be found at the lesion margins, while a yellow pseudomembrane-like deposit is seen at the bottom of the lesions [33].

Controlling intestinal inflammation is important in the treatment; the application of topical steroids and local anesthetics is recommended. Systemic steroids are used for severe or refractory cases [33, 75]. It was also reported that the response rate of anti-TNF agents in IBD patients with SA was 78.1% (25/32) [37].

Metastatic Crohn's disease (MCD)

Metastatic Crohn's disease is a rare skin lesions of patients with CD and is defined as granulomatous lesions that are non-contiguous with the gastrointestinal tract [25, 76]. The exact incidence of MCD has not been reported thus far. In adults, the diagnosis of MCD is most commonly established after the patient is diagnosed with CD; however, in children, MCD is believed to be diagnosed before CD in 50–86% of cases [76]. MCD is reportedly associated with colon lesions but not disease progression [77, 78].

Representative skin lesions are erythema, induration and ulcerations, abscess-like lesions, skin tags, isolated lymphedema, and so on. These are found mainly in the lower extremities and intertriginous areas. Also, genital lesions have been reported especially in children [79]. Pathologically, many of its features overlap with those of the gastrointestinal lesions related to CD. However, a diffuse infiltrative pattern, paucity of acute inflammatory cells, and presence of multinucleated giant cells are typical in lesions of MCD while absent in GI lesions of CD [80].

While compiled therapeutic methods are extremely few, treatment can be broadly classified as local versus systemic. A prospective evaluation of the therapeutic effect of topical tacrolimus in four cases of MCD showed that the treatment was effective in three cases [50]; however, all other reports are case reports of topical steroids [81]. Virtually all studies on systemic treatment are case reports of steroids [78], azathioprine [82], cyclosporines [83], and anti-TNF-α agents [84, 85]. Another report showed that surgical resection and debridement was effective in four of five cases, but the efficacy of surgical treatment is limited [86].

Hidradenitis suppurativa (HS)

Hidradenitis suppurativa is a chronic inflammatory recurrent and debilitating follicular skin disease with an average age at onset of 23 years and 3:1 predilection in women versus men [87, 88]. The incidence of HS in patients with IBD and without IBD was 3.3–23% and 0.1–1.0%, respectively [89–91]. HS is reportedly more likely to be comorbid with CD than with UC [91, 92]. In addition, the development of HS in patients with IBD was recently reported to be associated with smoking, obesity, small intestinal lesions, and anal lesions [93].

The pathophysiology of HS consists of: (1) a fragility of the hair follicle infundibulum and the formation of an epidermal cyst; and (2) an excessive innate immune response to non-infectious stimuli. Abnormalities of the Notch signal are reportedly involved in the etiopathology of IBD [94], and the same abnormalities are reportedly involved in the etiopathology of HS [95]. Notch signal abnormalities cause a differentiation abnormality of the outer root sheath cells and lead to the formation of keratin-rich epidermal cysts. When the epidermal cyst is destroyed, keratin is released into the dermis, which induces macrophage activation via Toll-like receptors; as a result, inflammatory cytokines such as IL-1β and TNF-α are released and stimulate dendritic cells. In turn, the IL-23 released from dendritic cells causes inflammation by inducing Th-17 cells. Furthermore, mutations of γ-secretase, which is involved in the cleavage of Notch receptors, have also attracted attention as a cause of HS [96]. The incidence of squamous cell carcinoma is reportedly as high as 3.2% in HS patients [97].

Deteriorated quality of life (QOL) is often found in IBD patients [98, 99]; however, patients with HS also have a low QOL [87]. The goal of treatment is to improve and maintain patient QOL; to achieve this goal, surgical resection, topical clindamycin, and oral tetracycline antibiotics can be considered. Multiple randomized controlled trials have shown that adalimumab, which has also been used to treat IBD, was also beneficial for the treatment of refractory cases [100–102].

Paradoxical reaction

The indications of anti-TNF-α agents have been extended to various refractory diseases such as UC, CD, psoriasis, and Behçet's disease; they are now widely used. To date, various adverse events affecting the skin, such as skin infections, lupus-like rashes, erythema multiforme, and vasculitis, have reportedly developed as side effects related to anti-TNF-α agent treatment [103]. Previous reports from other countries have shown that the overall incidence of skin adverse events resulting from the use of anti-TNF-α agents in IBD patients was approximately 20.5–29%, which was considered extremely high [104, 105]. Adverse events consisting of a psoriasis-like eruption developing during treatment with anti-TNF-α agents have recently been focused. The reaction was first reported in 2004 [106], and it was called a paradoxical reaction [107] because TNF inhibitors had originally been used to treat psoriasis [108, 109]. Paradoxical reactions have been observed with an underlying disease, including rheumatoid arthritis, ankylosing spondylitis, IBD and Behçet's disease, and can appear anytime during the administration of anti-TNF-α agents. A report of 573 patients with IBD previously revealed that psoriasis-like eruptions had an occurrence rate of 10.1% [104]; a similar study of 917 patients showed an occurrence rate of 8.9% [105]. In addition, an extremely recent study conducted on 732 IBD patients reported an occurrence rate of psoriasis-like eruptions of 5.3% [110], while a nationwide population-based cohort study showed that in IBD patients who had received anti-TNF-α agents for 6 months or longer, the incidence of psoriasis had a hazard ratio of 2.357 and a 95% confidence interval of 1.668–3.331 compared with anti-TNF-α agent-naïve patients [111]. From these results, this paradoxical reaction can no longer be considered rare. Further, previous reports have shown that psoriasis-like eruptions increased with treatment duration of anti-TNF-α agents and that their cumulative occurrence rate was 1.1% at 1 year, 6.75% at 5 years, and 28.9% at 10 years; this suggested that the differences between the reports may have been due to differences in treatment course and follow-up duration [104]. Regarding the difference of frequency of paradoxical reaction in anti-TNF-α agents, Afzali et al. reported that it was 1.3%, 4.1%, and 6.4% in 1004 IBD patients treated with infliximab (IFX), adalimumab (ADA), and certolizumab, respectively [112]. In addition, the risk factors associated with the development of this psoriasis-like rash include age (40s), female sex, tobacco smoking, elevated body mass index, history of introduction of treatment using antibody preparations at a young age, and a family history of psoriasis or atopic dermatitis. The inhibitory factors include the combination use of thiopurines [104, 113–117].

The rash develops throughout the body, including on the arms and legs, hair-covered areas, flexor surfaces of the limbs, axillary regions, and genital region [113, 118]. When the rash develops at infrequent locations such as the flexor surfaces of the limbs, the axilla, inguinal region, and gluteal clefts, the condition is called inverse psoriasis [113]. These eruptions are of the pustular (56%), plaque (50%), and guttate (12%) types; combinations of multiple disease types have also been reported in 15% of cases; most cases of pustular-type rash presented clinically as palmoplantar pustulosis [114]. We experienced this type of paradoxical reaction during ADA treatment in a patient with CD (Fig. 4a, b).

Further, in recent years, several other paradoxical reactions due to the use of anti-TNF-α agents have been reported; typical cases include sarcoidosis [119–121], synovitis–acne–pustulosis–hyperostosis–osteitis (SAPHO) syndrome [122], and amicrobial pustulosis of the folds [123].

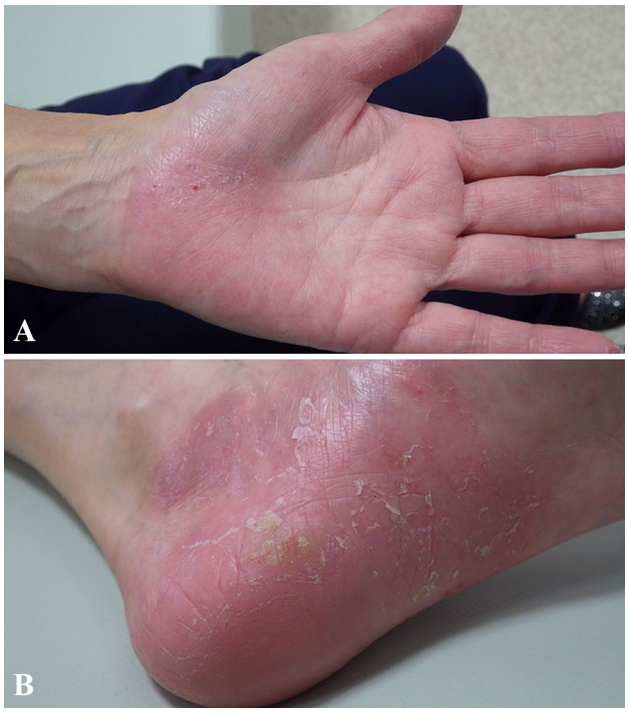

Fig. 4 **a, b** The skin lesion of paradoxical reaction. Ill-defined erythemas with desquamation and small erosions suddenly developed in the palmoplantar areas of a middle-aged woman who had a 27-year history of Crohn's disease. These skin lesions appeared 18 months after she was first administered adalimumab

Others

Other skin lesions that are believed to be associated with IBD are less frequent but have been reported in multiple instances. Such skin lesions include lichen planus [124, 125], vasculitis [126, 127], acquired epidermolysis bullosa [128, 129], and linear IgA bullous dermatosis [130, 131].

What is the exact mechanism of paradoxical reaction?

Genetics

Some have suggested that paradoxical reaction may represent a genetic pre-disposition towards psoriasis given the known overlap in risk loci between various immune-mediated diseases. In the study by Rahier et al., 12.9% of the IBD patients with psoriasiform skin lesions had a positive family history of psoriasis [113], that supports the hypothesis of common susceptibility genes shared with psoriasis. Genetic analysis data demonstrated that the mean psoriasis genetic burden score using the cumulative sum of odds ratios was higher in those who developed psoriasis compared to those who did not. Additional analysis showed two SNPs [allele (A) rs28998802 (*NOS2*), allele (G) rs3802826 (*ETS1*)] as genetic polymorphisms pre-disposing towards psoriasis [132]. ETS1 is a transcription factor that is important for CD8 T-cell differentiation in the thymus, which may have a potential role in immune regulation by inducing expression of matrix metalloproteases, defensins, chemokines, and cytokines [133]. *NOS2* encodes inducible nitric oxide synthase (iNOS) which is expressed by TNF-α-producing dendritic cells in psoriatic lesions. Generally, NOS2 expression, which Th1 cytokines induce, is absent in normal skin but is upregulated in PS lesions [134].

It was reported that none of *IL23R* variants was over represented in IBD patients with psoriasiform skin lesions and no significant differences in the minor allele frequencies of *IL12B* and *IL23A* variants was observed. On the contrary, all patients with severe psoriasiform skin lesions and/or anti-TNF-α-induced alopecia, requiring ustekinumab (UST) therapy, were G/G wild-type carriers for the rare coding *IL23R* variant rs1120926 (p.Arg381Gln) [116].

Immune mechanism

The exact mechanism of anti-TNF-α-associated psoriasis is unclear despite the proposal of several hypotheses. Widely accepted hypothesis for the development of anti-TNF-α-associated psoriasis is as reduction in TNF-α in conjunction with an increase in interferon (IFN)-α produced by plasmacytoid dendritic cells [135]. It was demonstrated that the TNF-induced skin lesions are characterized by infiltrating IFN-γ-expressing Th1 lymphocytes and by increased numbers of interleukin (IL)-17A/IL-22-expressing Th17 cells. It is important to note that in addition to binding with their Fab (antigen-binding region) fragment to TNF, IFX and ADA also bind with their Fc (crystallizable fragment) region to the Fc receptors CD64 (Fc-gamma receptor I (FcγRI)) and CD16/32 [Fc-gamma receptor III/II (FcγRIII/II)] expressed by monocytes and macrophages. The activation of the Fc receptors may lead to the paradoxical secretion of proinflammatory cytokines, such as IL-12 and IL-23 [116, 136]. However, this is unlikely to completely explain the development of paradoxical skin lesions.

How to manage the paradoxical reaction

If you encountered IBD patients with anti-TNF-associated psoriasiform skin lesions, how will you treat them? Collamer et al. reported their treatment algorithm for psoriasis-like eruptions as follows: if the rash affects < 5% of the body surface area, local treatment using steroids, vitamin D analogs, or phototherapy should be administered; if the rash affects ≥ 5% of the body surface area, the local treatment should be combined with the systemic administration of methotrexate, retinoid, cyclosporin A, or other agents [137]. Regarding the issue of whether to continue administering anti-TNF-α agents, one report argued that since most skin symptoms can be improved by medication, discontinuing anti-TNF-α agents would not provide much advantage [115]; meanwhile, Rahier et al. also reported that anti-TNF-α agents had to be discontinued in 40% of cases (25/62) and that complete remission was achieved in 96% of those who discontinued anti-TNF-α therapy (24/25) [113]. However, due to IBD symptoms, discontinuation of anti-TNF-α agents can sometimes be difficult; in such cases, shifting the treatment to other anti-TNF-α agents or other types of biologics that have therapeutic effects in both IBD and psoriasiform skin lesions should be considered. The efficacy rate of switching between IFX and ADA was reported 28.6% [104], although it was not high. Recently, the efficacy of UST in IFX-induced psoriasis and arthritis associated with CD was reported [138]. It was reported that ADA-induced paradoxical HS was improved by switching to UST in a patient with CD [139]. Also in CD patients treated with IFX at our facility, shifting the treatment to UST improved the skin symptoms without exacerbating the intestinal lesions. However, we should keep in mind that UST itself might lead to paradoxical reaction [140, 141].

Regarding the re-administration of treatment after discontinuing anti-TNF-α agents, a previous report showed that IFX was reintroduced in 33% (6/18) of IBD patients after the remission of a psoriasis-like eruption but that no

recurrence occurred in any of the patients [142]. It was also reported that concomitant use of thiopurine decreased the risk of skin lesions in analysis of 500 IBD patients receiving anti-TNF-α agents [143]. We consider adding thiopurine in cases with anti-TNF-α therapy alone or keeping thiopurine alone in IBD patients treated with combination therapy if these patients have clinical and endoscopic remission. In addition, we must consider to ask dermatologists for exact diagnosis and treatment.

Summary

Since IBD patients have various complications that are often associated with its progression, treating intestinal inflammation properly is the bottom line. Anti-TNF-α agents have become essential in the treatment of IBD; on the other hand, adverse events including paradoxical reactions mentioned in this review will increase in number in the future. Therefore, we always keep in mind such adverse events and appropriately handle them.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Human rights statement All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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