Journal of Dermatology, letter to the editor

Title: Successful treatment of multicentric Castleman's disease associated with dystrophic epidermolysis bullosa using anti-interleukin-6 receptor antibody.

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Article type: letter to the editor
Total word count: 494 words
One figure
Funding: none
Conflict of interest: None of the authors have any conflicts of interest associated with the work presented in this manuscript.
Hideyuki Ujiie is an Editorial Board member of Journal of Dermatology and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.
Authorship: All authors had full access to the data and played a role in writing this manuscript.

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To the editor,

Recessive dystrophic epidermolysis bullosa (RDEB) is a hereditary skin disorder caused by variants in *COL7A1*, which encodes type VII collagen (COL7) (1).

Multicentric Castleman's disease (MCD) is a rare disorder characterized by fever, polyclonal hypergammaglobulinemia, and widespread lymph node enlargement (2). Its etiology predominantly involves excessive interleukin 6 (IL-6), contributing to the disease's clinical features.

Here, we report a case wherein MCD appears to have developed as a secondary condition to RDEB. This case was notably managed with tocilizumab, an anti-IL-6 receptor monoclonal antibody, demonstrating its therapeutic efficacy.

Case report

A 22-year-old Japanese female suffering from widespread ulcers was diagnosed with RDEB during infancy. This diagnosis was confirmed by identifying the compound heterozygous variants c.6573+1G>C and c.8109+2T>A in the *COL7A1* gene (3). At age 16, flat elevated nodules developed on her back, and they gradually increased in size and number (Fig. 1a, b). Skin specimens from the nodules revealed prominent plasma cell infiltration (Fig. 1c, d), and blood tests indicated elevated IL-6 (76.6 pg/ml). At age 20, she suddenly developed renal dysfunction. She also had recurrent anemia, fever, and malaise. Computed tomography (CT) showed multiple lymphadenopathies (Fig. 1e), and a biopsy from an inguinal lymph node indicated a high proportion of plasma cells. Immunohistochemistry showed numerous CD38-positive plasma cells, but the ratio of IgG4-positive cells was not elevated. HHV8 was also negative in both skin and lymph node specimens. From these clinical and histopathological findings, we diagnosed

idiopathic multicentric Castleman's disease (MCD), and oral prednisolone was started. Due to the prominent skin erosion, we started treatment with tocilizumab for early prednisolone dose-tapering. With treatment, there was an improvement in fever, fatigue, renal dysfunction, and weight loss, as well as mild improvements in skin itching, nodules on the back, and swelling of the lymph nodes. However, the formation of blisters remained unchanged.

Discussion

This case highlights a rare association between MCD and RDEB. MCD's characteristic symptoms and the pivotal role of IL-6 in its pathogenesis are well-documented (2). Several studies have reported that serum IL-6 levels are higher in DEB patients than in healthy controls (4). IL-6 induces systemic inflammation and acute-phase protein production (5). While it is difficult to definitively state the correlation between RDEB and MCD here, considering the slightly young age of onset and the nodules are mainly distributed on the erosions, there might be a possibility that the severity of EB is implicated in the onset of MCD.

MCD can be challenging to treat, as it often shows resistance to conventional therapies like corticosteroids. Notably, monoclonal antibodies that mitigate the activity of IL-6 by targeting IL-6 receptors have shown efficacy in alleviating MCD symptoms.

This case, possibly the first of its kind to be treated with tocilizumab, emphasizes IL-6's role in inflammatory responses in severe forms of EB (5) and its association with recurrent fever in EB patients. Our findings suggest that targeting IL-6 with monoclonal antibodies may be a novel therapeutic approach for managing inflammatory conditions including itchy of EB.

Figure legends

Clinical photos show flat elevated nodules on the back (a, b). Skin specimens from the nodules reveal prominent plasma cell infiltration (H&E staining x40 (c) and x200 (d)). Computerized tomography (CT) reveals multiple lymphadenopathies (white arrows) (e).

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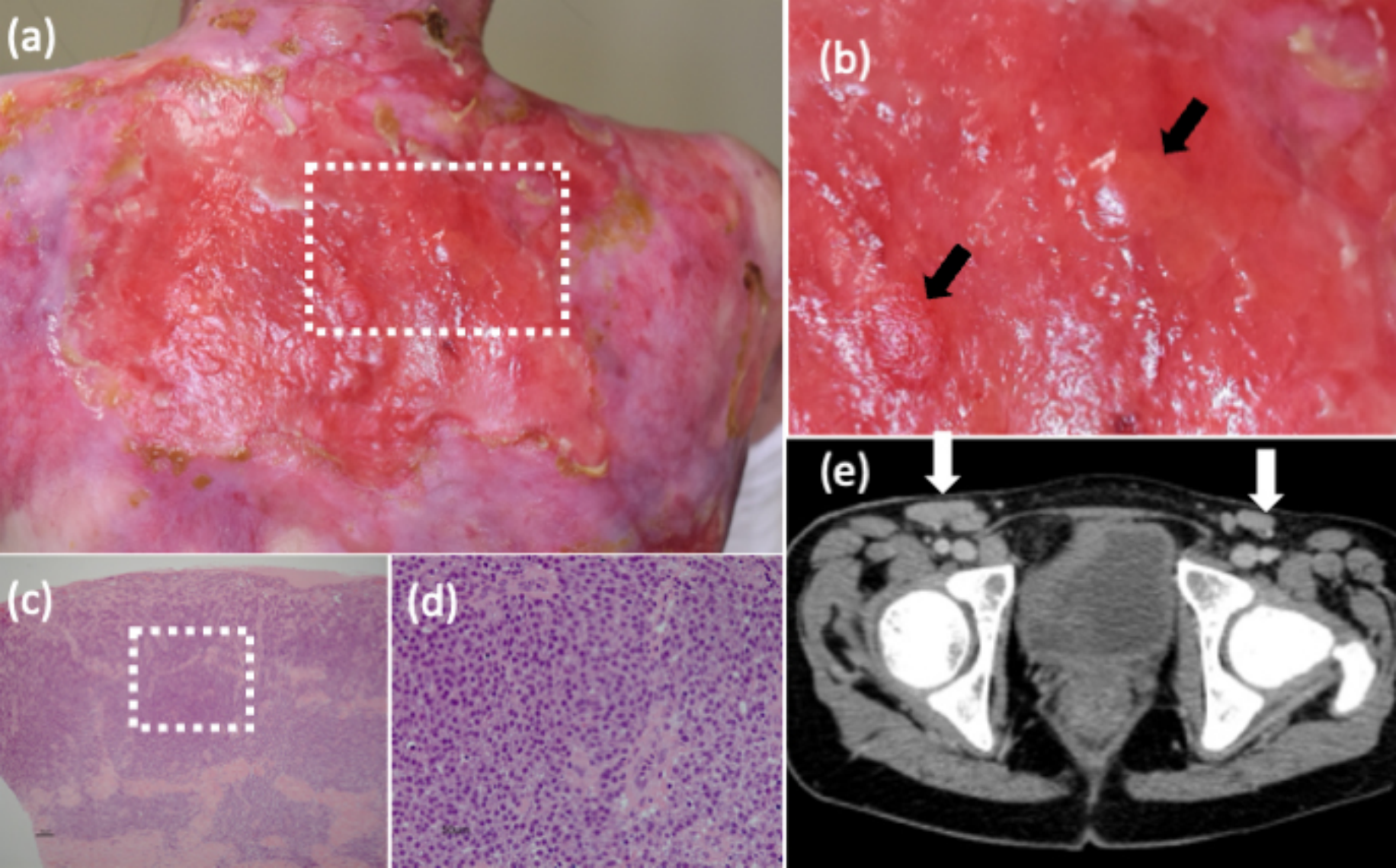
(a)
(b)
(c)
(d)
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