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RESEARCH

Prolonged Postoperative Wound Healing Due to Anti-IL-6 Autoantibody as a Phenocopy of Inborn Errors of Immunity

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Abbreviations

ACAA	Anti-cytokine autoantibodies
CRP	C-reactive protein
CRT	Chemoradiotherapy
FBS	Fetal bovine serum
HC	Healthy control
IEI	Inborn errors of immunity
IL-6	Interleukin-6
LPS	Lipopolysaccharide
PBMCs	Peripheral blood mononuclear cells
TNF	Tumor necrosis factor

To the Editor

Anti-cytokine autoantibodies (ACAAs) are a critical cause of secondary immunodeficiency, mimicking inborn errors of immunity (IEI; https://iuis.org/committees/iei/). ACAAs neutralize cytokine activity, leading to immune dysregulation and increased susceptibility to infections and autoimmune diseases [1]. Interleukin-6 (IL-6), primarily produced by activated monocytes and macrophages in response to infection or tissue injury, plays a pivotal role in immune responses of the wound healing. During the early inflammatory phase, IL-6 modulates immune cell activation and local inflammation. In the later stages, it facilitates tissue repair through angiogenesis and fibroblast activation, contributing to the proliferative phase [2]. Intractable infections are commonly observed in patients with antimicrobial-resistant pathogens but have rarely been reported in those with anti-IL-6 autoantibody [E5-7].

We report herein the case of a middle-aged woman with secondary immunodeficiency due to anti-IL-6 autoantibody. A lack of C-reactive protein (CRP) elevation served as a diagnostic clue during prolonged wound healing of a postoperative lesion complicated by methicillin-resistant *Staphylococcus aureus* infection.

Case Presentation

The patient was a 59-year-old Japanese woman with no apparent history of severe or recurrent infections. She had remained afebrile for over 30 years following a postpartum febrile episode associated with a common cold. Her family history revealed that her thirty-year-old eldest son was undergoing treatment for rheumatoid arthritis; however, no cases of IEI or early mortality suggestive of hereditary disorders were identified.

Gingival swelling and mandibular pain developed one year prior to presentation. Magnetic resonance imaging and positron emission tomography-computed tomography (Supplementary Fig. 1A), in conjunction with a biopsy from the affected site, led to the diagnosis of oral cancer (salivary duct carcinoma) with lung metastases. Surgical resection followed by adjuvant chemoradiotherapy (CRT) was scheduled. The patient underwent bilateral neck lymph node dissection, segmental mandibulectomy, plate insertion, and soft tissue reconstruction (Supplementary Fig. 1B). Postoperatively, an abscess developed in the mandibular region. Despite incision, drainage, and prolonged antibiotic therapy, a persistent purulent discharge from the surgical wound was observed (Supplementary Fig. 1C, D). Twelve months

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after the initial surgery, the infected plate was removed, and postoperative antimicrobial therapies were intensified, ultimately resulting in successful wound closure without a recurrent infection (Supplementary Fig. 1E). Although fluctuations in white blood cell count were observed in response to surgical intervention and CRT, inflammatory markers, including CRP, procalcitonin, and serum amyloid A, remained within normal limits throughout the clinical course (Supplementary Fig. 1F).

Conventional immunological study revealed no abnormalities in lymphocyte subsets or serum immunoglobulin levels. Screening for autoantibodies associated with rheumatic diseases and paraneoplastic syndromes yielded negative results. With the patient's consent, a comprehensive genetic panel analysis for IEI-related genes, including STAT3 abnormalities, was performed; however, no pathogenic variants in 394 known genes were identified [E2]. Based on these findings, known monogenic inborn errors of immunity were ruled out through targeted panel testing, and secondary immunodeficiency due to the presence of anti-IL-6 autoantibody and phenotypic mimicry was suspected, prompting further investigation.

Given prior findings suggesting the presence of circulating anti-IL-6 autoantibody, an enzyme-linked immunosorbent assay was performed using serum samples from the patient and healthy controls (HCs). Five out of six stored HCs' sera exhibited undetectable levels of anti-IL-6 autoantibody; however, highly elevated concentrations of the autoantibody were observed in patient serum samples obtained at two different points (Supplementary Fig. 2A). Intracellular IL-6 expression in $CD14^{+}$ monocytes after lipopolysaccharide (LPS) stimulation was comparable to that of one of the HCs (Supplementary Fig. 2B, *upper panels*). LPS-stimulated tumor necrosis factor (TNF) production was similar to that observed in the HC, confirming the absence of any intrinsic defect in cytokine synthesis.

To evaluate extracellular IL-6 production capacity, peripheral blood mononuclear cells (PBMCs) from the patient and the HC were cultured overnight in fetal bovine serum (FBS)-containing medium with LPS stimulation. The patient's PBMCs produced inflammatory cytokines, including IL-6, TNF, IL-1β, and IL-8, at levels comparable to those of the HC (Supplementary Fig. 2C, *FBS*). However, when the assay was conducted in culture medium supplemented with either the patient's or the HC's serum, IL-6 was undetectable in both in the presence of the patient's serum. This finding suggests that the patient's serum contains IL-6-neutralizing components that inhibit the detection of IL-6 (Supplementary Fig. 2C, *Pt and HC*). In light of these findings, the case was considered a phenocopy of IEI associated with autoantibodies, as classified in the IUIS category.

Discussion

The adult patient presented with a protracted infection postoperatively and prolonged wound healing of the lesion, accounting for anti-IL-6 autoantibody. To the best of our knowledge, this is the first documented case of impaired wound healing associated with the presence of anti-IL-6 autoantibody.

IL-6 is secreted by monocytes and macrophages upon activation in response to infection, playing a critical role in immune cell recruitment, including neutrophils and macrophages, initiation of inflammation, and elimination of pathogens and foreign substances. Additionally, IL-6 induces hepatic production of CRP, serving as a key biomarker of inflammation. In the context of wound healing, IL-6 is essential not only in the inflammatory phase but also in the proliferative phase, where it regulates endothelial cell proliferation and fibroblast activation [2]. Given these functions, the presence of anti-IL-6 autoantibody is expected to mimic IEI phenotypes and contribute to delayed postoperative healing.

Based on the literature review, a comparison of this case with previously reported patients presenting with immune dysregulation due to anti-IL-6 autoantibody revealed a bimodal age distribution, with disease onset occurring predominantly in toddlers and middle-aged adults (Table 1, E5-7). The most frequently identified pathogen was *Staphylococcus aureus*, with recurrent skin abscesses, septic shock, and empyema as common manifestations. These infections were managed with antimicrobial therapy, though one case of empyema resulted in mortality due to respiratory failure. In our patient, the diagnosis was established following persistently negative CRP levels and a postoperative infection. Despite the use of sensitive antibiotics, the infection remained uncontrolled, and impaired wound healing necessitated a reoperation. The detection of neutralizing anti-IL-6 autoantibody in serum samples suggests that ACAAs contributed not only to refractory skin infections but also to delayed wound healing.

Beyond infection and impaired wound healing, the presence of malignant tumors was a notable feature in this case. IL-6 is known to promote tumor cell proliferation, survival, and invasion via the IL-6/JAK/STAT3 signaling pathway while exerting immunosuppressive effects on antitumor immunity [3]. Activation of this pathway is recognized as a poor prognostic factor in multiple malignancies [4]. JAK inhibitors are currently used in clinical oncology, and the therapeutic potential of anti-IL-6 antibody is under investigation. While anti-IL-6 autoantibody may theoretically exert tumor-suppressive effects, our patient developed salivary gland carcinoma with distant metastases. Given the limited information on the patient's past medical evaluations, it

Table 1 Summary of five reported patients with secondary immunodeficiency due to anti-IL-6 autoantibody

case	This case	1 [a)]	2 [b)]	3 [c)]	4 [c)]
Age at diagnosis	59 y	18 m	20 m	56 y	67 y
Sex	Female	Male	Female	Female	Male
Ethnicity or Country of residence	Japanese	Haitian	Czech	Japan	Japan
Comorbidity	Salivary duct carcinoma	None	Preterm infant with neonatal asphyxia and ileal perforations, Maternal drug abuse	Rheumatoid arthritis	None
Clinical presentation at diagnosis					
Intractable infection	Postoperative abscess	Phlegmon	Septic shock	Multiple skin abscesses	Thoracic empyema
Pathogen	*Morganella morganii Staphylococcus aureus**	*Staphylococcus aureus*	*Staphylococcus aureus*	*Staphylococcus aureus*	*Escherichia coli Streptococcus intermedius*
C-reactive protein, mg/L	0.1	<5	2.9	0.5	0.1
Treatment	Antibiotics, Reoperation	Antibiotics	Antibiotics	Antibiotics	Antibiotics
Outcome	Alive	Alive	Alive	Alive	Died of respiratory failure
In vitro *analysis on IL-6 production*					
Intracellular expression in monocytes	Yes	Yes	Yes	n.a.	n.a.
Extracellular production from PBMCs	Yes	Yes	Yes	n.a.	n.a.

* Methicillin-resistant *Staphylococcus aureus*. IL-6: interleukin-6, PBMCs: peripheral blood mononuclear cells, n.a.: not accessible

(a) Puel A, et al. *J Immunol*. 2008;180:647–54. (b) Bloomfield M, et al. *Front. Immunol*. 2019.10.2629. (c) Nanki T, et al. *Ann Rheum Dis*. 2013; 72(6)0.1100-2

remains unclear whether the presence of anti-IL-6 autoantibodies predates the current malignancy by several decades or if their emergence is related to the development of oral cancer. This uncertainty underscores the need for further investigation into the temporal relationship between tumor progression and the production of ACAAs.

A study analyzing ACAAs in approximately 9,000 healthy individuals reported that approximately 65% were positive for anti-IL-6 antibody, with a significant negative correlation observed between anti-IL-6 antibody levels and CRP concentrations [5]. In our study, anti-IL-6 antibody was detected in one healthy control; however, neutralizing activity against IL-6 was absent in this individual. This study has certain limitations. Functional validation of IL-6 signaling, such as STAT3 phosphorylation assays, was not feasible due to limited sample availability and the patient's ongoing chemotherapy, which may interfere with intracellular signaling responses. The notable neutralizing activity supports a pathogenic relevance, although direct confirmation at the signaling level remains lacking. In conclusion, the presence of ACAAs should be considered in cases of postoperative wound healing failure with persistently negative CRP levels. Further research is needed to elucidate the factors influencing the production and neutralizing activity of ACAAs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10875-025-01894-y.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval The patient was studied after the informed consent was obtained. This study was certified by the Institutional Review Board of Kyushu University (no. 531-03).

Competing Interests The authors declare no competing interests.

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