Brief report

Ustekinumab for pyoderma gangrenosum–like skin ulcerations in late-onset leukocyte adhesion deficiency

Florian Schmid, MD,[a] Kerstin Kerl-French, MD,[b] Barbara Meier-Schiesser, MD, PhD,[b] Kai Lehmberg, MD,[c] and Peter H. Hoeger, MD[a,d] *Hamburg, Germany, and Zurich, Switzerland*

Background: Leukocyte adhesion deficiency type 1 (LAD-1) is a congenital immunodeficiency leading to impaired trafficking of neutrophils to inflammation sites. Solitary or multiple pyoderma gangrenosum (PG)-like skin ulcers (PGLUs) have been reported previously in 13 children (aged 0.5-19 years) with LAD-1.
Objective: Our aim was to report the case of a 10-year-old boy presenting with PGLUs as the first manifestation of LAD-1 treated with ustekinumab.
Methods: We obtained *in situ* cytokine profiles.
Results: PGLUs were triggered by cutaneous ringworm infection (*Trichophyton tonsurans*). Skin biopsy samples showed increased intralesional expression of IL-17A, Il-23, and IL-1β as compared with their expression in healthy controls. After an unsuccessful attempt at treatment with oral methylprednisolone, ustekinumab induced regression of the ulcerations, associated with complete normalization of the cytokine profile.
Conclusions: PGLUs, triggered by ringworm infection, can be a late harbinger of LAD-1. Ustekinumab is a safe and effective therapeutic option for patients with LAD-1 and PGLUs while bridging the time until stem cell transplantation. (J Allergy Clin Immunol Global 2024;3:100233.)

Key words: *Leukocyte adhesion deficiency, pyoderma gangrenosum–like ulcers,* in situ *cytokine profiles, ustekinumab therapy*

Abbreviations used
HSCT: Human stem cell transplantation
LAD: Leukocyte adhesion deficiency
LAD-1: Leukocyte adhesion deficiency type 1
PG: Pyoderma gangrenosum
PGLU: Pyoderma gangrenosum–like skin ulcer

INTRODUCTION

Leukocyte adhesion deficiency type 1 (LAD-1 [Mendelian Inheritance of Man database accession no. 116920]) is a rare inborn error of immunity (incidence <1 in 10^7 births) caused by mutations of the *ITGB2* (CD18) gene.[1] Among the 4 leukocyte adhesion deficiency (LAD) subtypes reported, LAD-1 is the most common.[1,2] More than 300 cases with 200 different *ITGB2* mutations have been identified so far.[2] On the basis of percentage of CD18-expressing neutrophils, LAD-1 can be classified as severe (incidence <2%), moderate (incidence 2%-30%) or mild (incidence >30%).[3] Deficiency of the β2-integrin subunit of the leukocyte cell adhesion molecule on the surface of leukocytes leads to impaired neutrophil adhesion and trafficking. LAD-1 is characterized by recurrent infections, impaired pus formation, and delayed wound healing.[1,4] Severely affected neonates present with delayed umbilical cord separation and subsequent abdominal wall infections.[1] In recent years, several cases with late onset have been published,[5] and a therapeutic effect of ustekinumab has been observed.[6] We report a patient who presented at age 10 years with pyoderma gangrenosum (PG)-like skin ulcers (PGLUs) following widespread ringworm infection. We studied his *in situ* cytokine profiles before and after treatment with ustekinumab and have reviewed published cases of late-onset LAD-1.

RESULTS AND DISCUSSION

A 10-year-old boy, the fourth child of healthy consanguineous parents, presented with painful ulcers on the scalp, neck, and gluteal region that had started as pustular plaques over the prior 2 weeks. No previous cutaneous or extracutaneous infections were reported. Mild lymph node enlargement in the nuchal, axillary, and inguinal areas were noted. The patient's spleen and liver were not palpable, and he was afebrile. His total leukocyte count was 45/nL (reference range 4-10.5/nL) with 76% neutrophils. His C-reactive protein level was 94.4 mg/L (reference range <5 mg/L). He was initially treated with oral antibiotics (cefuroxime and clindamycin), which were discontinued following a positive culture result for *Trichophyton tonsurans* after 5 days of therapy. The ulcers exhibited overlapping wound margins reminiscent of PG (Fig 1, *A*). Throughout the course of therapy, the number of circulating neutrophils remained high (28-60/nL). In the absence of clinical improvement after 7 days of itraconazole therapy, a

From [a]the Department of Pediatrics and [d]the Department of Pediatric Dermatology, Catholic Children's Hospital Wilhelmstift, Hamburg; [b]the Department of Dermatology, University of Zurich; and [c]the Department of Pediatric Haematology and Oncology, University of Hamburg.

Written informed consent was obtained by both parents and the patient.
Received for publication June 5, 2023; revised December 19, 2023; accepted for publication December 20, 2023.
Available online February 29, 2024.

Corresponding author: Peter H. Hoeger, MD, Catholic Children's Hospital Wilhelmstift, Liliencronstr 130, D-22143 Hamburg, Germany. E-mail: hoeger@kkh-wilhelmstift.de.

2772-8293

https://doi.org/10.1016/j.jacig.2024.100233

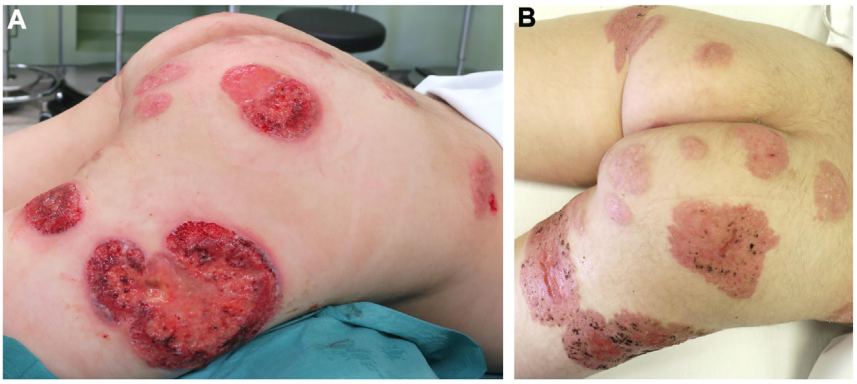

FIG 1. PGLUs. **A,** Before ustekinumab, overlapping wound margins on growing ulcers were visible. **B,** Two weeks after the second dose of ustekinumab (45 mg administered subcutaneously), reepithelialization was nearly complete.

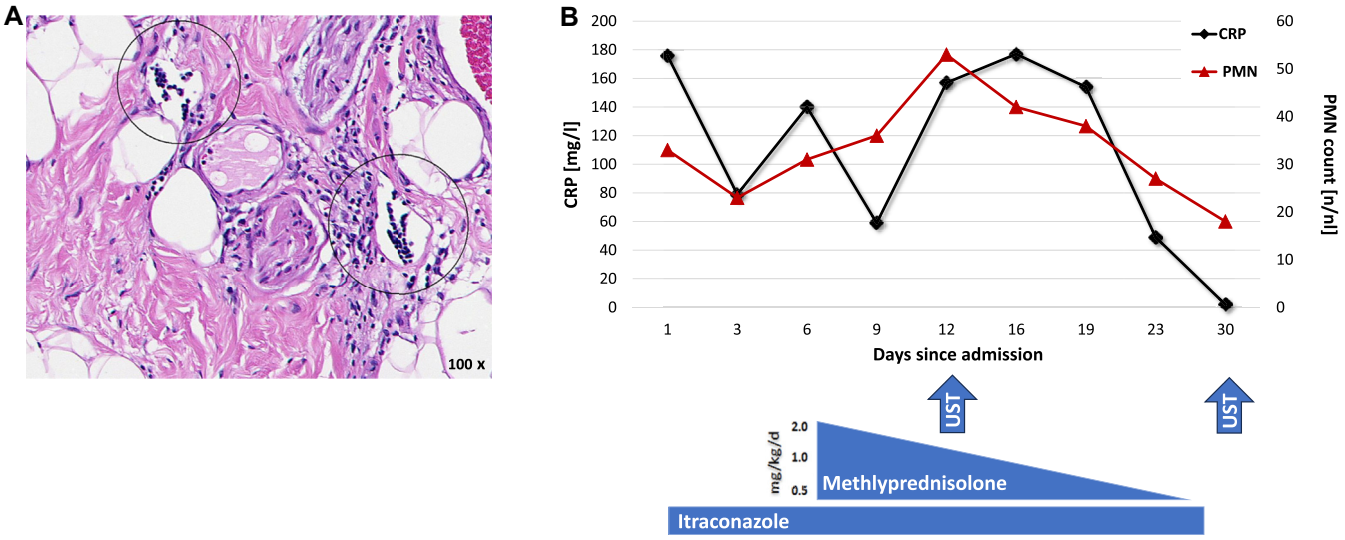

FIG 2. A, Histopathology revealing mainly intravascular neutrophils. Hematoxylin-eosin staining; original magnification, ×100. Courtesy of Dr Heinz Kutzner (Institute for Dermatopathology, Friedrichshafen, Germany). **B,** C-reactive protein (CRP) levels and neutrophil counts before and after ustekinumab (UST) therapy.

course of oral methylprednisolone was initiated (initial dose, 2 mg/kg body weight per day over 3 days, followed by tapering over 13 days), but without significant improvement. Histology revealed a high number of intravascular PMNs, but unlike in classical PG, there were only a few extravascular PMNs (Fig 2, *A*). Because of these findings, a defect in leukocyte migration was suspected. Flow cytometry revealed diminished expression of CD11b (2%) and CD18 (5%) in the peripheral PMNs. Next-generation sequencing established the diagnosis of LAD-1 with a mutation of *ITGB2* (IVS13c.1877+1G<A). An *in situ* cytokine profile showed increased expression of IL-1β, IL-17A, IL-23, and IL-12 in the affected skin (Fig 3). Therefore, therapy with the IL-12/IL-23-inhibitor ustekinumab was initiated as described previously.[6] Ustekinumab led to continuous improvement of the skin ulcers (Fig 1, *B*), paralleled by (near) normalization of C-reactive protein levels and PMN counts (Fig 2, *B*). The patient's cytokine profiles after the first and third doses of ustekinumab revealed a steady and significant decrease (Fig 3).

Five months later, the patient developed severe abdominal pain. Angiography revealed celiac trunk stenosis. Attempts at interventional recanalization via balloon dilatation and venous bypass failed, leading to acute intestinal ischemia and subsequent resection of large parts of the small intestine and cecum. The cause of the initial stenosis was likely an intravascular leukocyte clot. An adverse effect of ustekinumab was considered unlikely because the time interval after the last dose was too long and no thrombotic events have been reported in children undergoing long-term ustekinumab treatment.[7] After the patient had completely recovered, he underwent human stem cell transplantation (HSCT) (at age 14 years). Following HSCT, no new cutaneous ulcers occurred. Sadly, however, the patient died of adenoviral septicemia 1 year after HSCT.

In Table I,[2,5-14] we summarize 13 previously published cases of patients with LAD presenting with PGLUs. In 5 of these patients and as in our patient, the lesions were the initial manifestation of LAD. The median patient age at PGLU development was 3 years

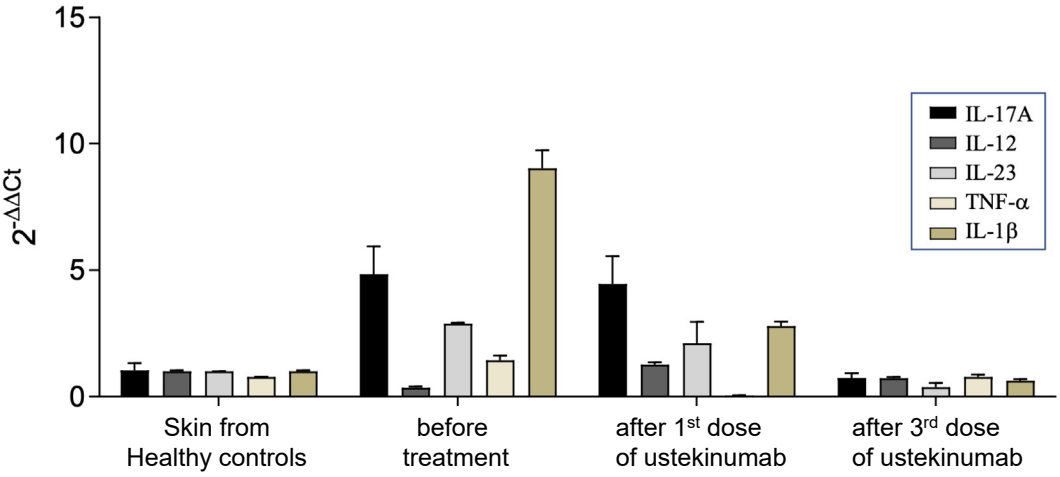

FIG 3. *In situ* cytokine profiles. Quantitative RT-PCR reveals gene expression of IL-17A, IL-12, IL-23, TNF-α, and IL-1β before ustekinumab therapy, as well as after the first and the third doses of ustekinumab. Gene expression is reported as 2-ΔΔCt, which represents the target gene expression relative to the reference gene (*RPL27*). Total RNA was isolated from human skin samples obtained from healthy donors (n = 2) or from the affected patient by using the RNeasy Fibrous Tissue Kit (Qiagen, Basel, Switzerland) according to the manufacturer's instructions. RNA was converted into cDNA by standard reverse transcription with the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific, Life Technologies, Carlsbad, Calif). Quantitative RT-PCR was performed using Power SYBR Green PCR Master Mix (Applied Biosystems, Life Technologies).

(range 0.5-19 years). Of the 13 patients presenting with PG, 12 were classified as having moderate (CD 18 expression 2%-30%) or mild (CD 18 expression >30%) LAD-1. Most of the ulcers reported were located on the lower extremities. One-fifth of the case patients had positive skin cultures for bacterial or mycotic infections.

We report PGLUs induced by ringworm infection as the first manifestation of LAD-1 in a 10-year-old boy. The IL-12/ IL-23-inhibitor ustekinumab led to clinical remission.

Patients experiencing mild or moderate forms of LAD-1 typically survive into adulthood, whereas many children with severe forms die in early childhood.[8] Late manifestations are likely attributable to different genotypes, allowing for residual expression of ß2-integrin (CD18) in a small percentage of PMNs.[15,16] The mutation in intron 13 of *ITGB2* (IVS13 c.1877+1G<A) that was found in our patient has not been described previously. As evidenced by a previously reported series of 4 patients with moderate LAD-1 and mutations in the splicing region of an intron (IVS10+4A>G), mutations in noncoding regions might be associated with late onset and PGLUs.[10] An alternative explanation for late and attenuated manifestation could be somatic revertant mosaicism: in adult patients with compound heterozygote *ITGB2* mutations with decreased expression of CD18 in neutrophils, postzygotic reversion of these mutations was identified in $CD18^+$ T-cell populations.[4,16]

PG is an autoinflammatory dermatosis that is characterized by neutrophilic skin ulcerations and frequently associated with other chronic inflammatory conditions (eg, Crohn disease, ulcerative colitis, rheumatic arthritis). Proinflammatory cytokines such as IL-1α/β, IL-8, IL-12, IL-15, IL-17, IL-23, IL-36, and TNF-α are overexpressed in lesional skin.[17,18] The autoinflammatory cascade, and the upregulation of T_H17 cells via IL-1ß and IL-23 in particular, ultimately result in increased neutrophil recruitment and activation.[19-21]

On the other hand, ulcers in patients with LAD-1, despite their clinical similarity with PG, are characterized by a relative lack of extravascular neutrophils (Fig 2, *A*) owing to impaired PMN recruitment.[1,7] The focal absence of neutrophils not only weakens the antimicrobial response but also leads to overexpression of IL-1ß, IL-17, and IL-23, as demonstrated *in situ* in our patient (Fig 3). Whereas in immunocompetent persons, phagocytosis of apoptotic PMNs by tissue macrophages leads to downregulation of IL-23 expression,[22] the absence of this downregulation in LAD releases an uninhibited inflammatory cascade, which eventually leads to PGLUs.

Therapeutic options for PG-like wounds in patients with LAD-1 are still under discussion.[8] TNF-α blockade has been reported in 3 patients, with variable response.[5,8,11] Other options include systemic steroids, intravenous immunoglobulins, immunmodulating drugs (ie, methotrexate, azathioprine, and mycophenolatmofetil) or IL1β-antagonists (eg, anakinra) (Table I).

Ustekinumab, a mAb against IL-12 and IL-23, was successfully used in a patient with LAD-1.[6] As depicted in Fig 3, not only did ustekinumab lead to reduced levels of IL-12 and IL-23, but IL-1ß level was equally reduced. Ustekinumab thus curbs hyperinflammation and facilitates healing of the ulcers.[6]

The only causative treatment, however, is allogeneic hematopoietic stem cell transplantation (allo-HSCT), which in a retrospective analysis of 84 patients with LAD resulted in a 3-year overall survival of 84%.[23]

We conclude that ustekinumab is a safe and effective therapeutic option for patients with LAD-1 with PGLUs, and it can be useful in bridging the time until HSCT.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

TABLE I. PGLUs in previously reported patients with LAD-1

Age* (y)	Sex	PG-like lesions			Maximal neutrophil count (n/μL), no (%)	CRP level (mg/dL)	CD18 (%)	Swab results	Therapy	Outcome	Reference
		Location	No.	Diameter							
0.5	F	Legs	Multiple	NS	43,600 (88)	Normal	NS	Negative	Antibiotics, prednisolone	Healing of the PG with scars	12
2	M	NS	NS	NS	43,500	NS	68	Negative	Topical and systemic antibiotics	NS	10
2	F	NS	NS	NS	11,900	NS	45	Negative	Topical and systemic antibiotics	NS	
2	M	NS	NS	NS	19,300	NS	50	Negative	Antibiotics, systemic steroids	NS	
2	M	NS	NS	NS	23,400	NS	19	Negative	Antibiotics, systemic steroids	NS	
3	M	Back, face	Multiple	NS	33,000	11.6	9	NS	Antibiotics, prednisolone, sulfasalazine, cyclosporine, methotrexate, azathioprine, etanercept, adalimumab, infliximab, anakinra, zinc sulfate	Recurrent PG with symptom-free intervals of up to 7 years	11
3	M	Legs	Multiple	NS	NS	NS	1-30	*Klebsiella pneumoniae, Pseudomonas aeruginosa, Candida parapsilosis, Aspergillus spp*	Antibiotics, antimycotics, systemic steroids, cyclosporine, methotrexate, infliximab, adalimumab, mycophenolate mofetil, cyclophosphamide, dapsone, donor granulocyte infusion, systemic recombinant G-CSF	Delayed wound healing and thin scars. Septic shock with subsequent death due to fungal sepsis	13
4	F	Thighs	Multiple	NS	41,800 (95)	>10	1-30	*Staphylococcus aureus, P aeruginosa*	Antibiotics, systemic steroids, clchicine	Recurrent PG with final improvement after initiation of steroids	9
9	F	Arm	1	NS	NS	NS	5-15	*Fusarium spp*	Antibiotics, antimycotics, systemic steroids, cyclosporine, topical tacrolimus, infliximab	Recurrent PG with ultimate improvement after initiation of infliximab	8
11	M	Legs	Multiple	5 × 5–21 × 15 cm	35,000 (87)	5.5	NS	*Proteus mirabilis, Enterococcus faecium, Staphylococcus epidermidis, Clostridium difficile*	Antibiotics, systemic steroids, mycophenolate mofetil, colchicine, intravenous immunoglobulins	Recurrent PG with ulimate improvement after initiation of intravenous immunoglobulins	5
13	F	Legs, face	Multiple	3 cm	12,960 (81)	Normal	1	Negative	Antibiotics, antimycotics, steroids, bone marrow transplantation	Healing after bone marrow transplantation	14
13	F	Thigh	1	32 × 28 cm	49,842 (89)	4.8	12.4	Negative	Antibiotics, steroids, cyclosporine	Improvement after initiation of steroids and cyclosporine	2
19	M	Sacral region	1	NS	NS	NS	34	Negative	Systemic steroids, ustekinumab	Healing with residual scarring	6

CRP, C reactive protein; *F*, female; *M*, male; *NS*, not specified.
*At time of presentation of cutaneous manifestation.

We thank Dr Heinz Kutzner (for Dermatopathology, Friedrichshafen, Germany), and Professor Ulrich Baumann, MD (Medical School Hannover, Germany) for helpful discussions. Professor Ansgar Schulz, MD, (Medical School Ulm, Germany) kindly performed next-generation sequencing of *ITGB2*.

REFERENCES

1. van de Vijver E, van den Berg TK, Kuijpers TW. Leukocyte adhesion deficiencies. Hematol Oncol Clin North Am 2013;27:101-16.
2. Opalińska A, Burdacki A, Kwaśniak K, Pogoda K, Tabarkiewicz J, Reich A. Pyoderma gangrenosum with an underlying leukocyte adhesion deficiency type 1 (LAD-1) and pregnancy in the shade of COVID-19 epidemic: a patient and physician experience. Dermatol Therapy (Heidelb) 2021;11:643-53.
3. Kambli PM, Bargir UA, Yadav RM, Gupta MR, Dalvi AD, Hule G, et al. Clinical and genetic spectrum of a large cohort of patients with leukocyte adhesion deficiency type 1 and 3: a multicentric study from India. Front Immunol 2020;11:612703.
4. Tone Y, Wada T, Shibata F, Toma T, Hashida Y, Kasahara Y, et al. Somatic revertant mosaicism in a patient with leukocyte adheson deficiency type 1. Blood 2007;109:1182-4.
5. Nord KM, Pappert AS, Grossman ME. Pyoderma gangrenosum-like lesions in leukocyte adhesion deficiency I treated with intravenous immunoglobulin. Pediatr Dermatol 2011;28:156-61.
6. Moutsopoulos NM, Zerbe CS, Wild T, Dutzan N, Brenchley L, DiPasquale G, et al. Interleukin-12 and interleukin-23 blockade in leukocyte adhesion deficiency type 1. N Engl J Med 2017;376:1141-6.
7. Mahé E, Geldhof A, Movshovich E, Schreiber J, Malynn S, Efficace M, et al. Long-term safety of ustekinumab in paediatric patients with moderate-to-severe plaque psoriasis: results from an ongoing observational study. Br J Dermatol 2023;189:e43.
8. Simpson AM, Chen K, Bohnsack JF, Lamont MN, Siddiqi FA, Gociman B. Pyoderma gangrenosum-like wounds in leukocyte adhesion deficiency: case report and review of literature. Plast Reconstr Surg Glob Open 2018;6:1886.
9. Bedlow AJ, Davies EG, Moss AL, Rebuck N, Finn A, Marsden RA. Pyoderma gangrenosum in a child with congenital partial deficiency of leucocyte adherence glycoproteins. Br J Dermatol 1998;139:1064-7.
10. Madkaikar M, Italia K, Gupta M, Desai M, Aggarwal A, Singh S, et al. Leukocyte adhesion deficiency-i with a novel intronic mutation presenting with pyoderma gangrenosum-like Lesions. J Clin Immunol 2015;35:431-4.
11. Vahlquist A, Håkansson LD, Rönnblom L, Karawajczyk M, Fasth A, van Gijn ME, et al. Recurrent pyoderma gangrenosum and cystic acne associated with leucocyte adhesion deficiency due to novel mutations in ITGB2: successful treatment with infliximab and adalimumab. Acta Derm Venereol 2015;95:349-51.
12. Thakur N, Sodani R, Chandra J, Singh V. Leukocyte adhesion defect type 1 presenting with recurrent pyoderma gangrenosum. Indian J Dermatol 2013;58:158.
13. Hinze CH, Lucky AW, Bove KE, Marsh RA, Bleesing JH, Passo MH. Leukocyte adhesion deficiency type 1 presenting with recurrent pyoderma gangrenosum and flaccid scarring. Pediatr Dermatol 2010;27:500-3.
14. Elenberg Y, Shani-Adir A, Hecht Y, Ephros M, Bibi H. Pyoderma gangrenosum after bone marrow transplantation for leukocyte adhesion deficiency type 1. Isr Med Assoc J 2010;12:119-20.
15. Bouhouche A, Tabache Y, Askander O, Charoute H, Mesnaoui N, Belayachi L, et al. Novel ITGB2 mutation is responsible for a severe form of leucocyte adhesion deficiency type 1. Biomed Res Int 2022;3:1141280.
16. Uzel G, Tng E, Rosenzweig SD, Hsu AP, Shaw JM, Horwitz ME, et al. Reversion mutations in patients with leukocyte adhesion deficiency type-1 (LAD-1). Blood 2008;111:209-18.
17. Ortega-Loayza AG, Friedman MA, Reese AM, Liu Y, Greiling TM, Cassidy PB, et al. Molecular and cellular characterization of pyoderma gangrenosum: implications for the use of gene expression. J Invest Dermatol 2022;142:1217-20.e14.
18. Marzano AV, Damiani G, Ceccherini I, Berti E, Gattorno M, Cugno M. Autoinflammation in pyoderma gangrenosum and ist syndromic form (pyoderma gangrenosum, acne and suppurative hidradenitis). Br J Dermatol 2017;176:1588-98.
19. Wang EA, Steel A, Luxardi G, Mitra A, Patel F, Cheng MY, et al. Classic ulcerative pyoderma gangrenosum is a t cell-mediated disease targeting follicular adnexal structures: a hypothesis based on molecular and clinicopathologic Studies. Front Immunol 2018;8:1980.
20. Takeuchi F, Streilein RD, Hall RP. Increased E-selectin, IL-8 and IL-10 gene expression in human skin after minimal trauma. Exp Dermatol 2003;12:777-83.
21. Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. Nat Rev Immunol 2014;14:585-600.
22. Stark MA, Huo Y, Burcin TL, Morris MA, Olson TS, Ley K. Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17. Immunity 2005;22:285-94.
23. Bakhtiar S, Salzmann-Manrique E, Blok HJ, Eikema DJ, Hazelaar S, Ayas M, et al. Allogeneic hematopoietic stem cell transplantation in leukocyte adhesion deficiency type I and III. Blood Advances 2021;5:262-73.