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Uncommon assotiation of pyoderma gangrenosum and pemphigus vulgaris: a case report and diagnostic challenge

Pyoderma gangrenosum (PG) is a rare, non-infectious neutrophilic dermatosis that typically presents as painful skin ulcers, most commonly affecting middle-aged women. While its exact pathogenesis remains unclear, it is often associated with systemic diseases. We see reports about idiopathic cases and drug-induced variants, too. However, PG associated with autoimmune blistering disorders such as pemphigus vulgaris is a highly uncommon phenomenon and has not been pre-viously recorded.

A unique case is present of PG in a patient with pemphigus vulgaris to increase clinicians' awareness of this occasional combination and its diagnostic and therapeutic complexities, given limited therapeutic options.

A 50-year-old woman with relapsed pemphigus vulgaris was included in a clinical study of the efficacy of a neonatal Fc receptor (FcRn) inhibitor in this dermatosis on the background of basic therapy with prednisolone 0.5 mg/kg/day. During treatment, new skin lesions appeared under the mammary glands and rapidly transformed into large, painful ulcers with purulent discharge. Despite systemic immunosuppressive therapy, the lesions did not heal, which raised the suspicion of pyoderma gangrenosum. Differential diagnosis excluded infectious lesions and systemic comorbidities, including oncopathology. Due to the lack of timely histological results of biopsy specimens from the affected area, the diagnosis of PG was established clinically. Since standard systemic immunosuppressive therapy could not be changed according to the study protocol, we have limited our treatment to topical antiseptics and silver cream. After 4 weeks, we observed significant clinical improvement, and ulcers healed within four months. Three-year follow-up of the patient after this case and the completion of the study confirmed a stable remission of both PG and pemphigus vulgaris.

Conclusions. PG can develop on the background of pemphigus vulgaris due to pathergy — a phenomenon when a minor trauma, including that provoked by acantholysis, triggers exaggerated immune responses in fragile skin, chiefly in areas prone to friction and moisture. Diagnosis in such cases is significantly complicated, especially in atypical localization. Clinical judgment, visual assessment, and medical history remain key for the timely detection. The illustrated case is the first documented example of the association of PG and pemphigus vulgaris in Ukrainian practice.

Keywords

Pyoderma gangrenosum, pemphigus vulgaris, case report, diagnostic challenges, management.

Pyoderma gangrenosum (PG) is an uncommon, non-infectious autoinflammatory disease from the group of neutrophilic dermatoses that affects up to 10 cases per 1 million people annually, with a female prevalence, especially at the age of 40+ [10]. It negatively impacts quality of life and carries [11].

The etiology and pathogenesis of this dermatological nosology remain incompletely elucidated [8]. Nevertheless, the PG may be an indicator of various underlying conditions. We are aware of the well-known concurrent systemic diseases. They are inflammatory bowel disease, hematologic malignancy, hidradenitis suppurativa, rheumatological disorders, PAPA syndrome, or IgA monoclonal gammopathy.

Nowadays, drug-induced cases are increasingly being recorded. Such triggers could even be sys-

temic retinoids, insulin, BRAF/MEK inhibitors, tyrosine kinase inhibitors, immune checkpoint inhibitors, VEGF inhibitors, Anti-CD-20 antibodies, TNF-α inhibitors, Interleukin inhibitors [4], which we use for the management of many skin and other autoimmune conditions. The paradox is that these same medications can be successfully applied for PG treatment [3, 6, 7, 9].

However, most cases are idiopathic as associated risk factors cannot be detected, and the association with blistering disorders was not discussed widely.

Classically, PG manifests as an erythematous papule or pustule that rapidly develops into a painful skin ulcer or multiple ulcerations [4, 10] that destroy all skin layers, not rarely muscles and tendons. It does not have a typical localization and commonly starts at the site of trauma, injury, stoma, or along the scar on the thin skin area. Severe pain, which causes significant discomfort, nervousness, and mobility loss, is another characteristic of this dermatosis. The ulcer has a long, persistent course and a poor healing tendency. A purulent necrotic mass is usually at the base of the ulcer. Borders are well-defined, undermined, violaceous, raised due to swelling, and the surrounding zone is erythematous. Typical cribriform appearance is a clinical clue for the diagnosis [12].

Any epidermis integrity damage caused even by minor trauma such as scratching or irritation, sometimes due to high humidity or increased local temperature, can be a trigger factor, too. Such reasons may also be an increased immune response and inflammation in autoimmune dermatoses, particularly in pemphigus vulgaris. All these demonstrate the notorious pathergy phenomenon. Moreover, drugs and even those that are successfully used to treat pemphigus (systemic steroids, immunobiology therapy, cytostatics) could act as provoking factors [7].

Despite the widespread belief that the typical localization of ulcers is the shin, the under-breast area affection in women is possible. First, this area is rich in fat tissue and sweat glands. It is more sensitive and prone to friction or trauma from mammary gland movement due to the exceedingly thin epidermis. Thus, ulceration spreads in depth mightily fast. Besides, warm and wet skin in this area is common for females. Second, the problem may be complicated by the mammary glands generous size, excessive sensitivity caused by rash, and, as a result, the refusal of bra use. In addition, a large breast makes it difficult for air to reach the injured skin, contributing to the development of infections, and due to that, the healing process could be slowed down. Chronic friction, a perfect environment for chafing, and the blisters or erosions caused by pemphigus presence — all contribute to PG development. A bullous variant of such dermatosis is less common, and it is challenging to recognize this disease in time. Therefore, we can accurately diagnose PG only if active comorbid conditions are available.

Regarding the diagnostic methods, unfortunately, no laboratory test would unequivocally confirm the diagnosis of PG. The skin biopsy result is not specific either. Despite that, they are essential for differentiating and ruling out other diagnoses, especially malignancy [9].

Treatment for this specific ulcerative process is always individual and depends on the type and severity of PG. It takes a long time (mostly a few months) and still does not often produce the desired efficacy, as the affected area is mostly not responsive to topical or systemic treatment. The treatments include systemic glucocorticosteroids, immune biology therapy, and topical medicines [4, 5]. However, they might cause serious side effects. Ultimately, the correct management of the healing process, which can last more than 3—4 months and always leaves scars, close monitoring, and patient follow-up is mandatory [2, 5].

This article aims to draw attention to rare autoimmune diseases such as PG and emphasize an unusual association with pemphigus vulgaris, which could be challenging and lead to late recognition of this puzzle in most cases.

Case presentation

A 50-year-old female patient of our clinic was under supervision due to relapsed pemphigus vulgaris, a potentially life-threatening condition. She had suffered from dermatosis for 1 year, and previous first-line treatment with systemic corticosteroids showed a poor response. Therefore, she was offered participation in a clinical trial to study the efficacy and safety of a new targeted immunobiological drug for treating pemphigus. Since the patient met all the inclusion criteria for the study and provided written informed consent, she was enrolled in this project.

Baseline characteristics of the patient's dermatological status: multiple blisters and extensive erosions in the skin and oral mucosa (genitals and scalp were intact), up to 7 cm, caused a burning sensation and severe discomfort. The PDAI (Pemphigus Disease Area Index — scale for pemphigus activity evaluation) was 35 and characterized moderate disease severity.

According to the study protocol, the baseline therapy of pemphigus was oral prednisone at a dose of 0.5 mg per kg daily. Investigational medicinal product — a 5 ml placebo solution with recombinant human hyaluronidase or 1000 mg of an investigated neonatal Fc receptor (FcRn) inhibitor that reduces

circulating IgG levels — was administered subcutaneously weekly (the first phase of the trial was double-blinded).

During this therapy, we observed a significant clinical improvement and achieved PDAI 5, indicating the presence of more than 3 lesions and/or at least one > 6 cm in diameter. Lesions on the trunk, extremities, hard palate, and buccal mucosa resolved completely, leaving only hyperpigmentation. However, erosions beneath the breast did not show a tendency to heal. Furthermore, new blisters up to 2 cm in diameter appeared on the unchanged skin under both mammary glands. In contrast, over the next 2 weeks, the lesions rapidly spread and merged, extending to the abdominal skin, exposing the hypodermis. Ulcerated areas reached 15 cm in diameter on the right side and 17 cm on the left (Fig. 1).

Purulent masses covered the ulcers. The axillary regional lymph nodes were slightly enlarged and sensitive upon palpation. The patient reported unbearable pain, atypical for pemphigus. Subfebrile fever of 37.3—37.7 °C was noted for the last 5 days, along with weakness. Concurrently, the patient was enrolled in phase 2, an open-label extension trial.

Other findings. The patient became tearful, irritable, and depressed. She began to be haunted by negative thoughts. Her sleep worsened. Laboratory investigations revealed lymphocytosis, slight elevation of monocytes, and C-reactive protein (CRP). Additional laboratory analysis revealed normal liver enzymes, creatinine, blood glucose levels, negative HIV and syphilis antibodies, and urine and stool analysis without abnormalities. An EKG and chest X-ray indicated no cardiac, pulmonary, or other organ involvement. We did not discover any underlying systemic disease.

Bacterial and candidal infections were ruled out. Therefore, a long-persisting ulcer that rapidly increased in size and caused severe pain syndrome without a tendency to heal, even in the background of systemic glucocorticosteroids and, probably, immune biology therapy, led to the suspicion of neoplasia. We have performed a biopsy; however, due to logistic problems caused by the war in Ukraine, we have not received the conclusion in time.

Considering the medical history, clinical presentations, and laboratory data, we started to manage a patient with a preliminary diagnosis of PG without a confirmed diagnosis. The patient continued participating in the study as clinical manifestations of pemphigus remained, and the current dermatological status did not require the study interruption.

Per study protocol, we were limited in therapy tactics: we could not increase the dose of prednisolone and prescribe other systemic therapies such as dapsone, cytostatics, or immunosuppressants, or

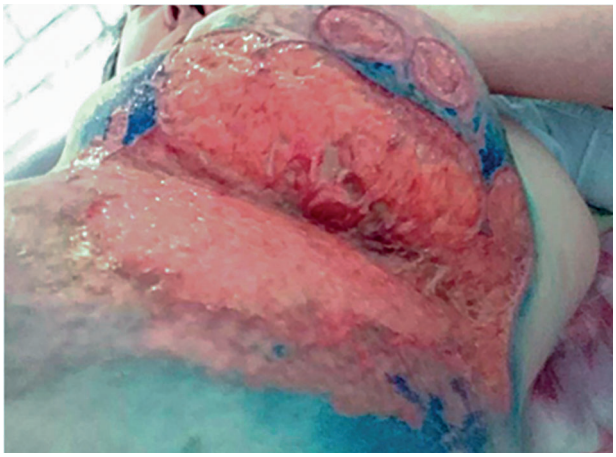

Fig. 1. **Large cribriform ulcer with purulent masses under the left mammary gland exposed hypodermis**

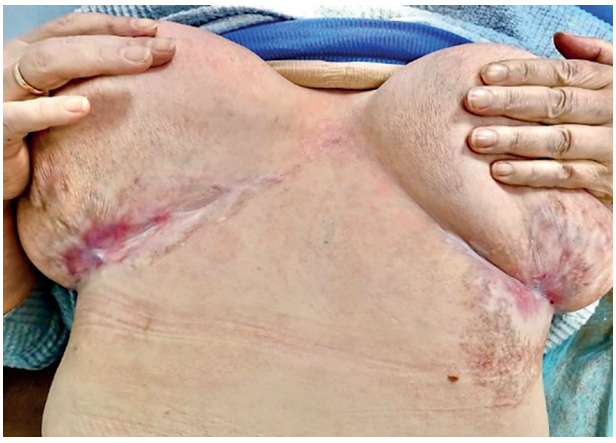

Fig. 2. **Post-inflammatory dyschromia and adhesion scars remained at the site of the healed ulcers under the mammary glands**

topical/intralesional glucocorticosteroids, calcineurin antagonists, or other biologic therapies. Therefore, we recommended an antiseptic solution with 0.05 % chlorhexidine and cream with silver to clean the ulcers. For relieving pain, we prescribed nonsteroidal anti-inflammatory drugs and painkillers.

Three weeks after starting targeted immunotherapy with the neonatal Fc receptor (FcRn) inhibitor and topical treatment, the process stabilized, the ulcerated surfaces were cleared entirely of purulent overplacement, and the pain syndrome had resolved. A month later, we noted signs of granulation and re-epithelialization. We continued topical treatment with methylene blue solution and an ointment that promotes wound healing. Four months after initiating this therapy, we achieved complete closure of ulcerative defects under the mammary glands, albeit occasionally with scarring (Fig. 2).

After 3 years of follow-up, the patient did not experience a recurrence of PG and pemphigus vulgaris.

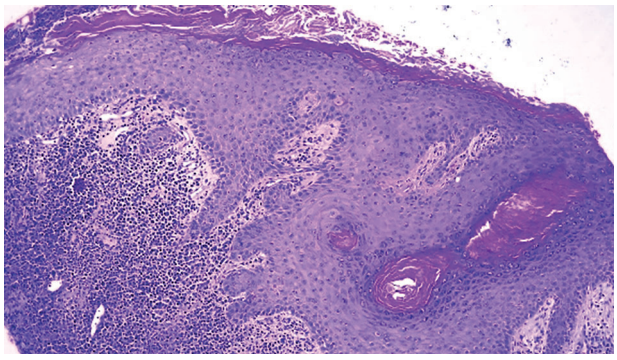

Fig. 3. **Histopathology, H&E, 20x. Neutrophilic infiltrated epidermis, hypogranulosis, dystrophy, and acanthosis. Dermis is infiltrated by lymphocytes and plasmocytes**

Unfortunately, we received the biopsy result when the ulcers had wholly healed. The conclusion — pathohistological changes correspond to a chronic ulcerative process — was uninformative; however, features of malignancy were not detected. The pathomorphological picture showed that a homogenous eosinophilic mass, infiltrated by neutrophils, covered the ulcerative defect of the epidermis; at the extant epidermis, hypogranulosis, dystrophy, and irregular acanthosis. Diffuse lymphocytic and plasmocytic infiltration of the dermis, mainly with perivascular distribution. Underlying fat tissue is infiltrated by lymphocytes, too (Fig. 3).

Conclusions

The development of PG, a rare autoimmune dermatosis, is usually associated with systemic comorbid conditions; however, idiopathic forms can occur against the background of immunosuppression resulting from prolonged systemic glucocorticoid therapy, which probably happened with our patient. Diagnosing this condition in such cases can be tricky, especially if the localization is also atypical. The area under the mammary glands in women is an ideal circumference for developing irritation and inflammation due to increased sweating, humidity, and constantly elevated local temperature. In the presence of a bullous process in the form of pemphigus vulgaris, the PG onset is generally missed. Only after 2—3 weeks, when fresh, seemingly elements of pemphigus rapidly increase and deepen, forming ulcers, there is a suspicion that it is not a pemphigus lesion.

Laboratory examination methods are not specific, and the war in Ukraine delayed the process of histopathological examination in our case. Therefore, we had to treat the patient with an unconfirmed diagnosis. It once again emphasizes that diagnostics in dermatology should be based on the skills of visual assessment of dermatological status and comprehensive analysis of the patient's medical history and general condition. Additional examination methods can only help establish the diagnosis to a small extent.

Regarding such patient management, we had to work in limited conditions. Since the patient was a participant in a clinical trial of the efficacy and safety of a targeted immunobiological drug, we could not provide complete treatment according to medical guidelines. Nevertheless, neonatal Fc receptor inhibitor, 0.5 mg/kg/day of systemic prednisolone, topical therapy, and gentle care of the affected area helped to achieve the entire ulcer healing within 3 months. Clinical remission of pemphigus vulgaris and PG has been observed for 3 years.

This case is the first report of pyoderma gangrenosum associated with pemphigus vulgaris: two severe skin diseases with unknown etiology and overlapping pathogenetic mechanisms. To date, no such cases have been reported in the literature. Due to excessive skin fragility caused by acantholysis in pemphigus, a pathergy phenomenon may occur, which is a triggering factor in PG. Thus, clinicians should be aware of the potential risk of PG developing in the background of pemphigus vulgaris.

Data availability statement.
The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.
Ethics statement.
Informed consent was obtained from the patient to publish any potentially identifiable images or data in this article.
No conflict of interest.
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References

1. Ahronowitz I, Fox L. Severe drug-induced dermatoses. Semin Cutan Med Surg. 2014 Mar;33(1):49-58. https://europepmc.org/article/med/25037258.
2. Baltazar D, Haag C, Gupta AS, et al. A comprehensive review of local pharmacologic therapy for pyoderma gangrenosum. Wounds. 2019;31(6):151-7. PMID: 31215868.
3. Ben Abdallah H, Fogh K, Vestergaard C, Bech R. Pyoderma gangrenosum and interleukin inhibitors: a semi-systematic review. Dermatology. 2022;238(4):785-92. doi: 10.1159/000519320.
4. Dissemond J, Marzano AV, Hampton PJ, Ortega-Loayza AG. Pyoderma Gangrenosum: Treatment Options. Drugs. 2023;83(14):1255-67. doi: 10.1007/s40265-023-01931-3.
5. Feldman SR, Lacy FA, Huang WW. The safety of treatments used in pyoderma gangrenosum. Expert Opin Drug Saf. 2018;17(1):55-61. doi: 10.1080/14740338.2018.1396316.
6. Herberger K, Dissemond J, Brüggestrat S, et al. Biologics and immunoglobulins in the treatment of pyoderma gangrenosum — analysis of 52 patients. J Dtsch Dermatol Ges. 2019;17(1):32-41. doi: 10.1111/ddg.13741.
7. Honigman A, Kelly RI. Pyoderma gangrenosum: a review of patients' demographics, disease, and treatment in 118 patients. Austr J Dermatol. 2022;63(2):267-9. doi: 10.1111/ajd.13840.
8. Maronese CA, Pimentel MA, Li MM, et al. Pyoderma Gangrenosum: An Updated Literature Review on Established and Emerging Pharmacological Treatments. Am J Clin Dermatol. 2022;23(5):615-634. doi: 10.1007/s40257-022-00699-8.
9. Maverakis E, Ma C, Shinkai R, et al. Diagnostic criteria of ulcerative pyoderma gangrenosum: A Delphi consensus of international experts. JAMA Dermatol. 2018;154(4):461-6. doi: 10.1001/jamadermatol.2017.5980.
10. Maverakis E, Marzano AV, Le ST, et al. Pyoderma gangrenosum. Nat Rev Dis Primers. 2020;6(1):81. doi: 10.1038/s41572-020-0213-x.
11. Nusbaum KB, Ortega-Loayza AG, Kaffenberger BH. Health-related domains of quality of life in pyoderma gangrenosum: a qualitative analysis. J Am Acad Dermatol. 2022;86(6):1382-5. doi: 10.1016/j.jaad.2021.05.040.
12. Yamamoto T, Yamasaki K, Yamanaka K, et al. Clinical guidance of pyoderma gangrenosum 2022. J Dermatol. 2023 Sep;50(9):e253-e275. doi: 10.1111/1346-8138.16845.

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Рідкісне поєднання гангренозної піодермії та справжньої (вульгарної) пузирчатки: клінічний випадок та діагностичні проблеми

Гангренозна піодермія (ГП) — це рідкісний неінфекційний нейтрофільний дерматоз, який зазвичай проявляється болючими виразками на шкірі та найчастіше вражає жінок середнього віку. Хоча точний патогенез залишається незрозумілим, захворювання здебільшого асоціюється із системними патологіями. Також є повідомлення про ідіопатичні випадки та варіанти, індуковані лікарськими засобами. ГП у поєднанні з автоімунними бульозними захворюваннями, такими як справжня пузирчатка, є надзвичайно рідкісним явищем і раніше не фіксувалося.

Представлено унікальний випадок розвитку ГП у пацієнтки зі справжньою пузирчаткою з метою підвищення обізнаності клініцистів про цю рідкісну комбінацію та її діагностичну та лікувальну складність за обмежених терапевтичних можливостей.

До клінічного дослідження ефективності інгібітора неонатального Fc-рецептора (FcRn) за цього дерматозу на тлі базової терапії преднізолоном у добовій дозі 0,5 мг/кг включено 50-річну жінку із рецидивом справжньої пузирчатки. Під час лікування під молочними залозами в неї виникли нові ураження шкіри, які швидко прогресували і трансформувалися у великі болючі виразки з гнійними виділеннями. Попри проведення системної імуносупресивної терапії, ураження не гоїлися. Це викликало підозру щодо наявності ГП. За результатами диференційної діагностики виключено інфекційні ураження та системні супутні захворювання, зокрема онкопатологію. Через відсутність своєчасних гістологічних результатів біоптатів із зони ураження діагноз ГП було встановлено клінічно. Оскільки стандартну системну імуносупресивну терапію неможливо було змінити відповідно до протоколу участі в дослідженні, ми обмежили наше лікування застосуванням топічних антисептиків та кремом зі сріблом. Через

4 тиж спостерігали значне клінічне поліпшення, а загоєння виразок відбувалося протягом 4 міс. Трирічне спостереження за пацієнткою після цього випадку та завершення дослідження підтвердило стійку ремісію як ГП, так і справжньої пузирчатки.

Висновки. ГП може розвинутися на тлі звичайної пузирчатки внаслідок патергії — явища, коли незначна травма, зокрема спровокована акантолізом, спричиняє надмірні імунні реакції в шкірі, особливо в ділянках, схильних до тертя та вологи. Діагностика в таких випадках значно ускладнена, особливо за атипової локалізації уражень. Клінічне мислення, візуальна оцінка та історія хвороби залишаються ключовими для вчасного виявлення патології. Наведений випадок є першим задокументованим в українській практиці прикладом асоціації ГП та справжньої пузирчатки.

Ключові слова: гангренозна піодермія, справжня пузирчатка, клінічний випадок, діагностичні проблеми, лікування.

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