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Case Report

Pyoderma gangrenosum, as the first clinical presentation of systemic lupus erythematous, a case report and comprehensive literature review

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Background: Pyoderma gangrenosum (PG) can be related to a range of systemic and hematologic diseases. The relationship between systemic lupus erythematosus (SLE) and PG has rarely been discussed.

Case Presentation: In this case study, we report on an SLE patient who presented with PG. The patient is a 53-year-old woman with the chief complaint of developing painful erythematous pustules on her right flank 3 days after hysterectomy surgery. In the span of 3 months, the patient was treated with antibiotics and intra-lesional corticosteroids with no improvement. Meanwhile, she developed symptoms such as polyarthralgia, pleural effusion, hemolytic anemia, and thrombocytopenia, while anti-dsDNA came out positive.

Result: Based on pathology results in combination with clinical and para-clinical findings according to the SLICC criteria for SLE 2012, our patient was diagnosed as an active case of SLE presenting with PG. We also searched for and gathered the latest articles on this issue (from 2017 until 2022) to present the most updated review study on the topic in this article.

Conclusion: Considering the abundance of PG and SLE concomitance reported cases (more than 30), it might be time to pay more attention to SLE as the underlying cause of PG and keep in mind that any unhealing ulcer in patients with connective tissue disorders should be evaluated for PG. Considering the various treatment options for PG, it is essential that the treatment of choice should cover symptoms of both PG and the underlying disease.

Keywords: Pyoderma gangrenosum, Lupus erythematous, Lupus panniculitis, Dermatology, Rheumatology.

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Neutrophilic disorders (NDs) are a diverse range of cellular dysfunction disorders, specified as the accumulation of neutrophils in the skin which can involve other organs (1, 2). The pathophysiology of NDs is debated scarcely, but these disorders share several pathological and clinical characteristics with autoinflammatory syndromes (3). A suggested clinicopathological categorization divides these disorders into deep or hypodermal forms (as PG), dermal type or plaque forms (namely Sweet syndrome), and epidermal or superficial forms (4, 5). PG is a rare, cutaneous condition that presents with rapidly developing painful ulcers (6, 7). PG's exact pathogenesis has remained unknown, but it seems to be immune-mediated (8, 9). PG is diagnosed by ruling out other causes of ulcerative skin lesions (10, 11), while its underlying causes are only discovered in 50-70% of cases (12). The most common PG associations are inflammatory bowel diseases (IBD), rheumatoid arthritis, seronegative arthritis, and hematologic malignancies (4, 7, 13, 14).

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Although leg ulcers can occur in SLE patients (15, 16), PG has rarely been reported in association with SLE. In the present study, we report a 53-year-old woman who was diagnosed with SLE after presenting PG.

Case Presentation

A 53-year-old postmenopausal lady was referred to the rheumatology clinic with a complaint of developing painful erythematous pustules on her right flank after a hysterectomy surgery 3 months earlier. Pustules rapidly grew in size and number, gradually culminating in a single indurated plaque with undermined borders, warm in palpation with tenderness and central necrosis (figure 1). In a span of three months, the patient had several referrals to dermatology and infectious diseases clinics. She received various outpatient treatments including antibiotics and intradermal corticosteroids which did not result in healing; so, she was admitted to the rheumatology ward for a thorough diagnostic workup. When the patient was referred to the rheumatology department, she complained of a diffuse macular non-tender rash on both forearms, which later disappeared spontaneously. The patient did not report any significant past medical history. Regarding the primary diagnosis of soft tissue infection, wound and blood culture results came back negative for bacterial growth. Soft tissue sonography of the right flank showed no sign of collection or deep abscess.

Collagen vascular-related serologic biomarkers and a wound biopsy was requested. The test results came back with a high erythrocyte sedimentation rate (ESR) of 125 mm/hour and positive antinuclear antibody (ANA), while other laboratory tests for complete blood count (CBC), platelets, P-ANCA, C-ANCA, anti-Ro, anti-La, anti-ds-DNA, anticardiolipin antibodies, and lupus anticoagulant were normal/negative (table 1). The patient was discharged awaiting the pathology results. About a week later, while the pathology result came back in favor of pyoderma gangrenosum (figure 2), the patient referred to the emergency department with deteriorated general condition. She complained of fever, malaise, polyarthralgia with severe pain in her right knee, dyspnea, nausea, and vomiting. There was a slight enlargement of the right flank ulcer alongside necrosis and discharge.

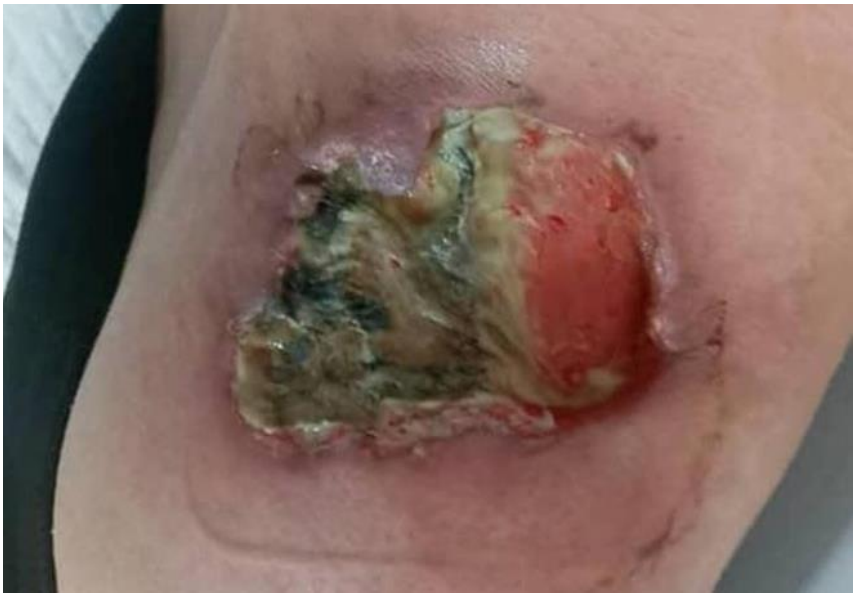

Figure1. Ulcerative lesion on the right flank

During the second admission, laboratory results revealed bicytopenia (hemoglobin: 6.8 g/dL, Platelet: 47’000/µL) and elevated levels of inflammatory biomarkers (ESR: 70 mm/hr, LDH: 1502 U/L). Serologic biomarkers were positive for ANA, anti-RO, and anti-ds-DNA (table 1). Chest x-ray showed a mild unilateral pleural effusion and chest CT scan report mentioned atelectasis in the lower lobes of both lungs with moderate bilateral pleural effusion, consistent with transudate pleural effusion in pleural fluid analysis. The cardiac evaluation was normal. As advised by the rheumatologist, a second biopsy with extended margins was taken from the wound. In the second biopsy, pathological findings revealed lymphocytic vasculopathic reaction and extensive hyalinizing fat necrosis, consistent with lupus erythematous profundus (figure 3). According to the SLICC criteria for SLE 2012, wound biopsy results in combination with clinical and para-clinical findings confirmed active SLE with PG presentation. Starting

Prednisolone 1mg/kg/day showed immediate improvement of systemic symptoms, serositis, and bicytopenia came upon in the following days, and the wound began to regress after two weeks. In 8 weeks, the prednisolone dosage was tapered to 5-7.5 mg daily. Considering the extensive necrosis of the right flank ulcer, the patient received a daily dose of 500 mg of mycophenolate mofetil, which facilitated wound healing to a significant extent after 4 weeks (figure 4).

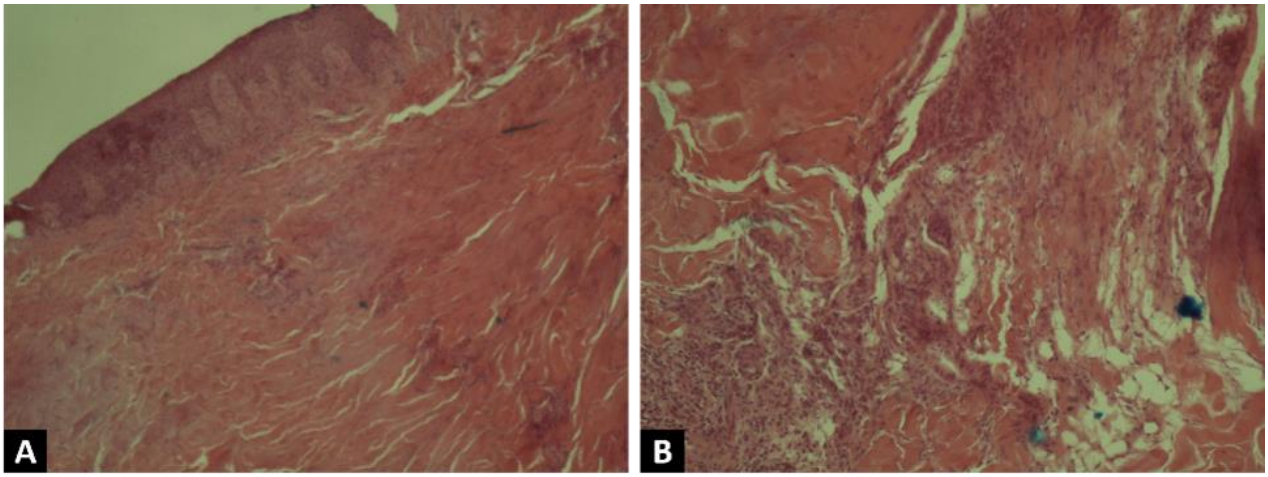

Figure 2. A) Superficial and mid-dermis do not show any specific pathologic changes except for mild fibrosis. B) Infiltration of neutrophils, forming abscess foci in the deep dermis. Severe fibrosis is present at the edges of the slide.

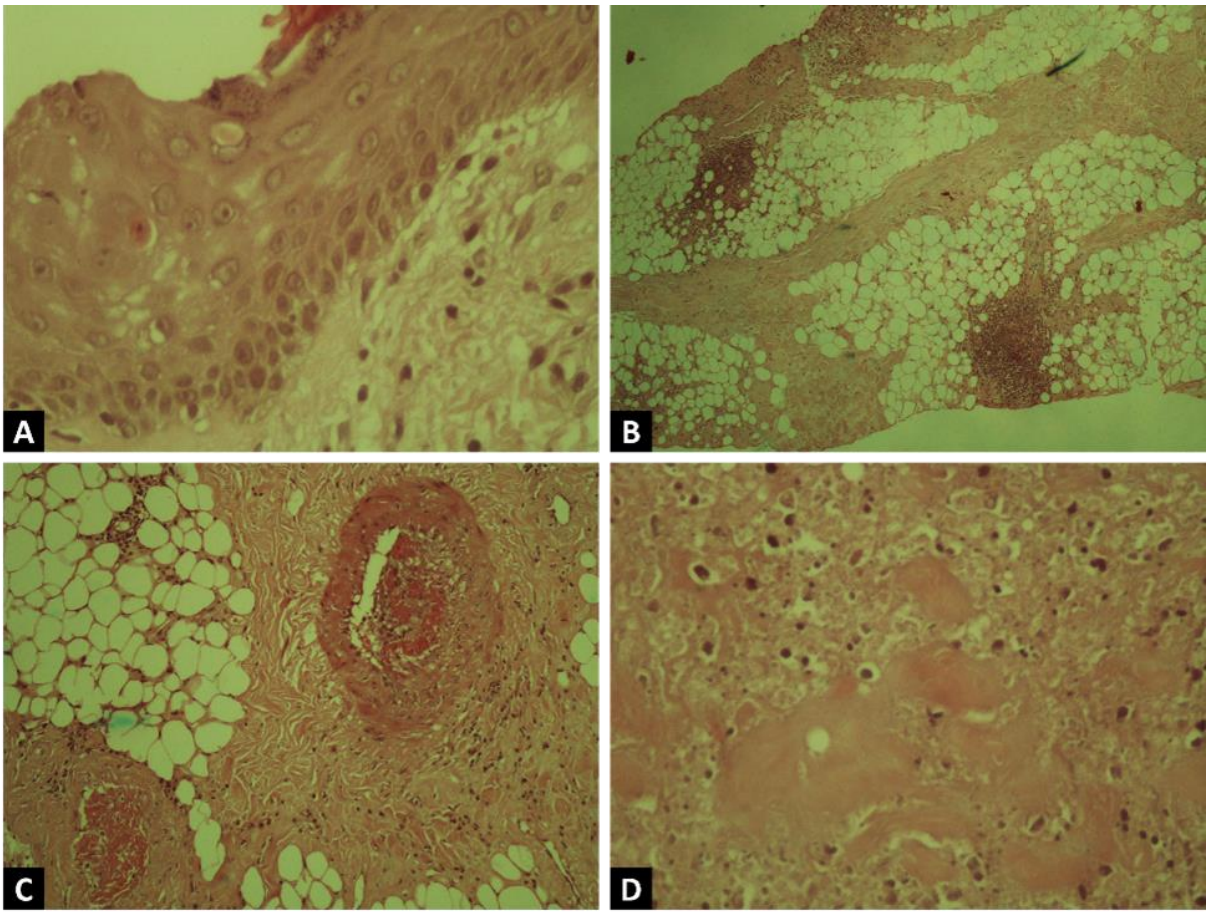

Figure 3. A) Mild interface changes in the basal layer and dyskeratotic cells in the epidermis, in favor of collagen-vascular disease. B) Panniculitis in the depth of the lesion. Lymphocyte aggregation in subcutaneous fat, in favor of lupus panniculitis. C) Fibrinoid necrosis and vasculopathy in subcutaneous fat septate. D) Necrosis, nuclear debris, and fibrinoid material in subcutaneous fat, consistent with lupus panniculitis.

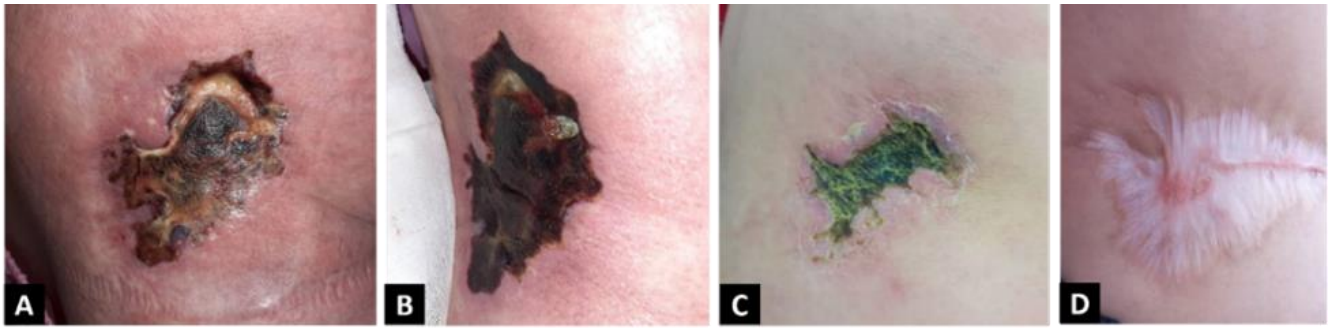

Figure 4. Right flank wound during treatment course (A, B, C, and D)

Table 1. Key features of complete blood count (CBC) and serologic biomarkers

Variables	First admission	Second admission	Normal range
WBC (/mm3)	4,000	8,700	4,000-10,000
Neutrophils (%)	65	72	45-75
Lymphocytes (%)	25	21	15-45
HGB (gr/dl)	10	6.8	12-16
Platelet (/mm3)	225,000	47,000	140,000-440,000
ANA	Positive (titer: 5.4)	Positive (titer: 3.3)	<0.8
Anti-dsDNA	Negative (titer: 90)	Positive (titer: 154)	<100
Anti-Ro	Negative (titer: 7.9)	Positive (titer: 253)	<12
Anti-La	Negative (titer: 0.7)	Negative (titer:1.1)	<12
Lupus anticoagulant	Negative	Negative	-
P-ANCA	Negative	Negative	-
C-ANCA	Negative	Negative	-
Anti-MPO	Negative (titer: 0.5)	Negative (titer: 1.1)	<10
Anti-PR3	Negative (titer: 0.2)	Negative (titer: 2.7)	<10
ESR	Raised (titer: 125)	Raised (titer: 70)	<30

NET: Neutrophil extracellular traps, NDs: Neutrophilic diseases, PG: Pyoderma gangrenosum, SLE: Systemic lupus erythematosus.

Discussion

The association between PG and SLE has been reported in several studies and thanks to the exponential growth of knowledge, new cases are being reported every day. From 1971 to 2018, 25 cases have been reported on this subject. In our review study, was discuss 11 more cases brought about since 2018. Yet it seems that the real incidence of PG and SLE is much more than it seems. Previous studies have discovered the association of PG with several autoimmune diseases. The incidence of PG in lupus patients has been reported in multiple studies. In the majority of cases, PG symptoms were revealed a while after diagnosing lupus (24 cases). In a few cases, the symptoms of both diseases appeared simultaneously (7 cases), while the occurrence of PG before any signs of lupus is pretty rare (only 5 cases in total). Adachi et al. suggested that PG is a product of

abnormal neutrophil migration systems (17). Additionally, the response of toll-like receptors is enhanced in PG ulcerative lesions (18). While an imbalance between neutrophil clearance and production is observed in SLE, decreased degradation of neutrophil extracellular traps is associated with clinical manifestations of SLE (19). This could hint towards the similarity of mechanisms and pathophysiologic features of both diseases.

In this study, we made an effort to gather all previous case reports, considering SLE and PG association to make a new summarized source for future studies (table 2). In previous studies, the occurrence of PG in association with different types of lupus, such as bullous SLE and juvenile lupus are mentioned (20-22). It is worth mentioning that the development of PG after multiple surgeries, especially after cosmetic breast reduction, abdominoplasty, and C-Section has been reported in several articles (23, 24). Also, the occurrence of PG associated with antiphospholipid syndrome (APS) has been reported (25). Our case had a distinctive feature: Despite previous reports of an association between these diseases, the presentation of PG long before any SLE symptoms and positive antibodies is very rare. Additionally, in this case, the first pathology results were completely compatible with PG; however, after the systemic symptoms surfaced, the second biopsy showed hyaline necrosis in favor of lupus panniculitis. The shifting of pathological and serological features of our patient's disease in the span of a few weeks is a unique characteristic of this case.

Considering the case at hand, the reported cases of PG and SLE concomitance have summed up to 36. Therefore, it might be time to pay more attention to SLE as the underlying cause of PG and keep in mind that any unhealing ulcer in association with lupus or other connective tissue diseases, should be evaluated for PG criteria. The treatment management of PG in the setting of SLE should cover all systemic complications of both diseases. In the setting of SLE, starting with prednisolone as the mainstay of treatment and then adding other immunomodulatory medications such as cyclosporine, methotrexate, and thalidomide based on individual differences should be considered (26-28, 33). The limitation of our study was the fact that we did not take the first skin biopsy sample deeply. Even though the strength of this study is its long-term follow-up of the patient and observing day-by-day improvement of her condition by medication.

Table 2. A review of prior studies (since 2017) regarding the association between PG and SLE

Reference	Gender/Age	Location of the lesion (Number)	Time of PG onset compared to SLE diagnosis	Lupus activity at the time of PG onset	Treatment
Mora SE (2017) (26)	F/22	Leg (2)	2 years before diagnosing SLE by positive Ab	No activity	Thalidomide and Prednisolone
Khibri H (2018) (27)	M/67	Both legs, scrotum, tongue	Simultaneous, presenting sign of lupus	ANA + Anti-sm +	Corticosteroids and hydroxychloroquine
Choi YJ (2018) (28)	F/61	Leg (1)	7 years after	No activity	Prednisolone and Cyclosporine
Shrestha S (2018) (29)	F/61	Hand & feet (4)	Simultaneous, presenting sign of lupus	Only ANA +	Prednisolone
Sander M (2019) (30)	F/59	Calf (1)	After, NM exactly	NM	Cyclosporine
Magdoud O (2019) (31)	F/43	Thigh, shoulder, hand (6)	4 years after	NM	Corticosteroids
Manov A (2020) (32) *	F/55	Inguinal, forearm, and lower extremities	After, NM exactly	ANA + Anti-ss & Anti-ds DNA +	Corticosteroids

Reference	Gender/Age	Location of the lesion (Number)	Time of PG onset compared to SLE diagnosis	Lupus activity at the time of PG onset	Treatment
Teoh SC (2021) (33) **	M/35	Lower limb, scrotum	Simultaneous, presenting sign of lupus	ANA+ Anti-sm+	Prednisolone, Hydroxychloroquine, methotrexate, cobalamin
Rkiouak A (2021) (34)	F/19	Leg (1)	8 years after	No activity	Prednisolone
Gupta H (2022) (35)	F/46	Right breast (1)	1 year after	NM	Corticosteroids
Our Case (2022)	F/52	Right Flank (1)	3 months before diagnosing lupus by positive anti-ds Ab	No activity	Prednisolone Mycophenolate

NM: Not Mentioned. *The patient also had a history of using cocaine with levamisole. **The patient also had severe B12 deficiency.

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Ethics approval: Written informed consent was obtained from the patient for participation in the study and the rights of the subject were protected. To observe ethical principles, the name and distinct facial/physical characteristics of the patient were not included in the paper.

Conflicting interests: All the authors declare that there is no conflict of interest.

Author's contribution: All authors contributed to the preparation of data and finalization of this article.

Data availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Informed consent: Written informed consent was obtained from the patient for participation in the study and the rights of the subject were protected.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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