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A Multidisciplinary Approach to a Rare Cause of Pulmonary Cavitating Nodules - Pyoderma Gangrenosum

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Abstract **Case Report**

Pyoderma Gangrenosum (PG) is an inflammatory skin disorder associated with chronic inflammation and neoplastic conditions. It is relatively rare, with an estimated annual incidence of 3 to 10 cases per million people, with the highest occurrence between 20 and 50 years of age. Proper differential diagnosis is essential to guide appropriate treatment and management strategies for affected individuals. This case study presents a compelling instance of PG with a unique twist-the extracutaneous involvement of the pulmonary system, an uncommon and diagnostically challenging manifestation requiring multidisciplinary management.

Keywords: Pyoderma Gangrenosum, Multidisciplinary Approach, Skin Ulcer, Cavitatory, Nodule.

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INTRODUCTION

Pyoderma Gangrenosum (PG) is an inflammatory skin disorder associated with chronic inflammation and neoplastic conditions. It's estimated worldwide annual incidence ranges from 3 to 10 cases per million population, affecting individuals of all genders and age groups [1]. The peak incidence is observed between the ages of 20 and 50 years [1, 2]. Proper differential diagnosis is essential to guide appropriate treatment and management strategies for affected individuals. Pulmonary PG can manifest with various presentations, such as cavitating or non-cavitating lesions, often accompanied by necrosis and superimposed infections [3]. Notably, these pulmonary lesions may emerge independently of or in conjunction with skin manifestations, contributing to the complexity of diagnosis. Cytological evaluation of affected tissues typically reveals non-specific neutrophilic and lymphocytic infiltrates, providing valuable diagnostic insights. Fortunately, pulmonary PG lesions show positive responses to corticosteroid treatment, indirectly supporting the diagnostic process.

CASE PRESENTATION

A 67-year-old female homemaker from Barara, presented to the Pulmonology Outpatient Department (OPD) with a non-productive cough persisting for three weeks. She denied experiencing breathlessness, orthopnea, paroxysmal nocturnal dyspnea, fever, loss of appetite, weight loss, or hemoptysis. The patient had uncontrolled diabetes managed with oral hypoglycemic agents, with no other significant past medical history. At the time of her first presentation, her general and systemic examination did not reveal any abnormalities.

The patient was referred to the pulmonology department for further evaluation, including a CT scan of chest. Initial investigations showed a Total Leukocyte Count (TLC) of 10,600/microliters, haemoglobin level of 9.9 gm/dL, an elevated Erythrocyte Sedimentation Rate (ESR) of 110 mm/h, and a high C-Reactive Protein (CRP) level of 174.8 mg/L (Table 1). Liver and renal function tests were within normal limits, while sputum tests for Acid-Fast Bacilli (AFB) and Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) were negative. Screening for HIV, HBsAg, and HCV was non-reactive (Table 2).

Table 1: Laboratory Investigations with results and normal ranges

Investigation	Result/Value	Normal Range/Value
Total Leukocyte Count (TLC)	10,600/microliters	4,000 - 11,000/microliters
Haemoglobin Level	9.9 gm/dL	12.0 - 15.5 gm/dL
Erythrocyte Sedimentation Rate (ESR)	110 mm/h	0 - 20 mm/h
C-Reactive Protein (CRP)	174.8 mg/L	0 - 10 mg/L

Table 2: Normal results for diagnostic tests include Liver and Renal Function Tests, negative findings for Tuberculosis, Viral Markers.

Diagnostic Test	Result
Liver Function Tests	Within normal limits
Renal Function Tests	Within normal limits
Sputum Tests for Acid-Fast Bacilli (AFB)	Negative
Cartridge-Based Nucleic Acid Amplification Test (CBNAAT)	Negative
HIV Screening	Non-reactive
HBsAg Screening	Non-reactive
HCV Screening	Non-reactive

Chest X-ray (PA view) revealed shadows in both right and left upper zones, with a peripheral non-homogeneous opacity, central lucency, and thick walls in the right middle zone, suggestive of a cavitating lesion (Figure 1).

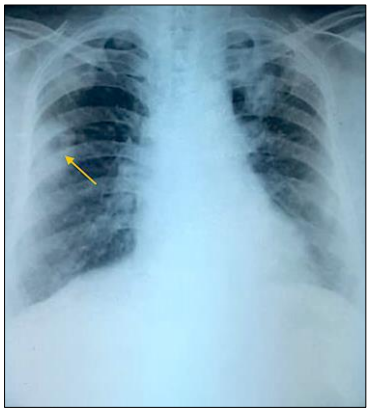

Figure 1: Showing non-homogeneous opacity with central lucency, and thick walls in the right middle zone, suggestive of a cavitating lesion

Additionally, left lower zone haziness was noted. Subsequent CT scans showed multiple well-defined nodular lesions, some with cavitation, in both lungs. The largest lesion measured 4.7 x 2.4 cm in the anteromedial basal segment of the lower lobe. No pleural effusion or pleural thickening was observed, and there was no significant mediastinal lymphadenopathy (Figure 2).

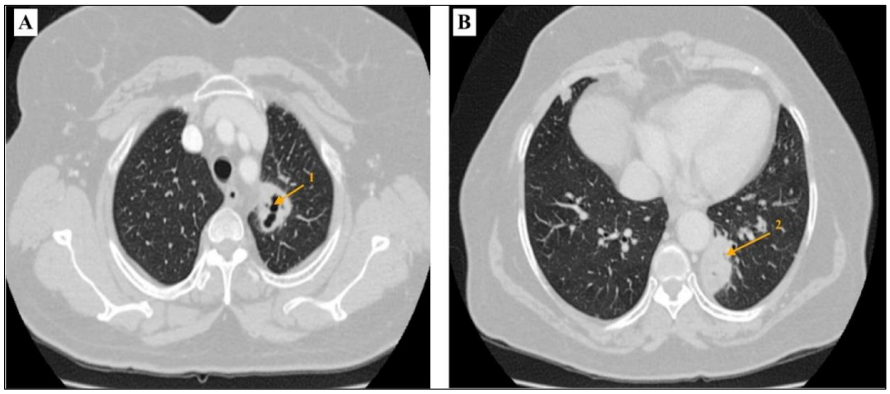

Figure 2: (A) Showing well-defined nodular lesion with cavitation in posterior segment of left upper lobe. (B) Showing largest lesion measured 4.7 x 2.4 cm in the anteromedial basal segment of the lower lobe.

Based on the imaging features, the initial report suggested various differential diagnoses, including infective etiologies (pulmonary tuberculosis and fungal infections), granulomatosis with polyangiitis (wegener's granulomatosis), cavitating metastasis, and rheumatoid lung.

Given the diagnostic uncertainty, the patient was referred for further evaluation, including a CT-guided Fine-Needle Aspiration Cytology (FNAC). Bronchoscopy was performed, and tests for AFB and CBNAAT were negative. Bronchial wash culture and sensitivity, as well as fungal culture and sensitivity, also yielded negative results, ruling out an infective etiology.

Bronchial wash cytology and bronchial biopsy did not show any evidence of malignancy. The CT-guided FNAC, taken from the wall of the largest cavitating nodule in the left lower lobe in the prone position, revealed only neutrophilic infiltrates and came back negative for malignancy. Due to the patient's reluctance to undergo further evaluations, empirical Anti-Tuberculous Therapy (ATT) was initiated with 5 tablets of a Fixed Drug Combination (4FDC), and she was advised for follow-up.

Three months later, the patient sought consultation at the dermatology OPD due to skin lesions. Dermatological examination revealed multiple discrete and coalesced shallow ulcers with sloping edges. The ulcer floors exhibited yellowish necrotic slough with areas of red granulation tissue and surrounding erythema. In addition, multiple scaly excoriated papules and plaques, some oozing, were observed, along with dryness and scaling of the bilateral lower limbs (Figure 3). Notably, her symptoms had not improved despite the anti-tuberculous therapy.

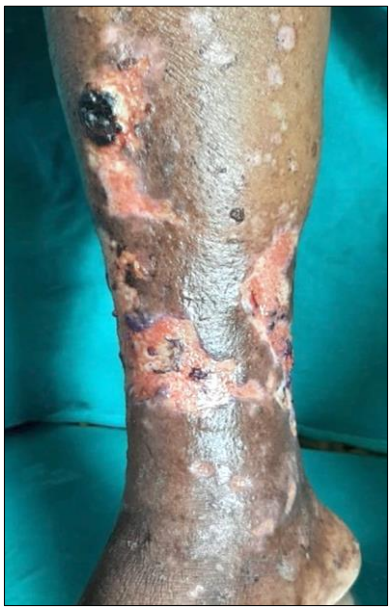

Figure 3: Dermatological Examination showing multiple ulcers, necrotic slough, granulation tissue, and scaly lesions on Bilateral Lower Limbs

A repeat chest X-ray, performed after three months of ATT, indicated a mild increase in the size of the shadows, along with progressive cavitation in the left upper lobe nodule. Subsequent CT scans showed varying-sized, well-defined nodular lesions with cavitation in both lungs, including a larger lesion measuring approximately 3.7 x 3.2 x 3.2 cm in the apico-posterior segment of the left upper lobe (Figure 4).

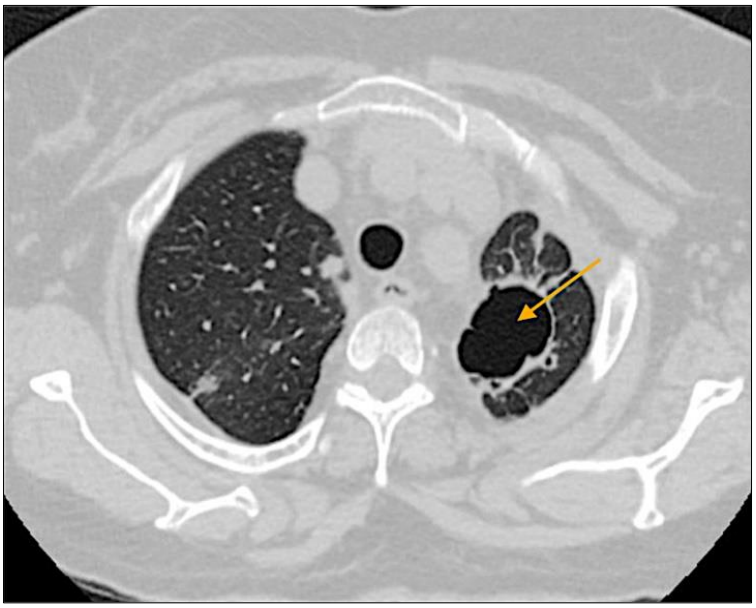

Figure 4: Showing cavitatory lesion measuring approximately 3.7 x 3.2 x 3.2 cm in the apico-posterior segment of the left upper lobe

Several discrete, small-sized non-calcific necrotic lymph nodes were noted in various regions, with the largest measuring approximately 5 mm in short axis diameter in the pre-carinal region (Figure 5).

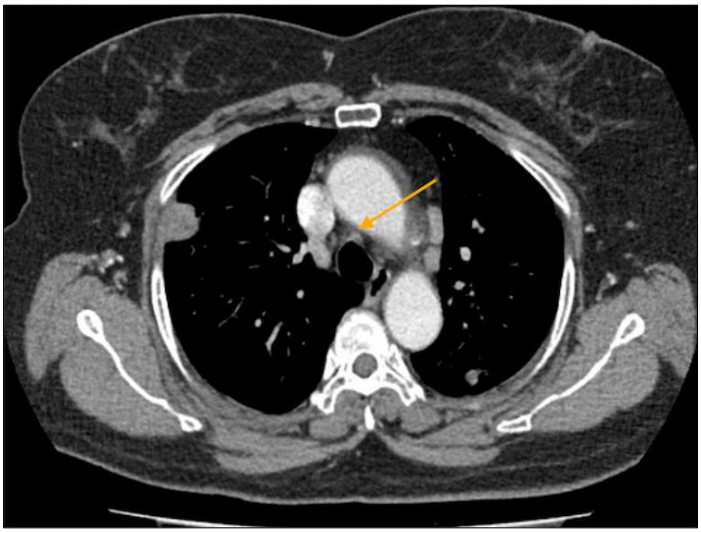

Figure 5: Showing necrotic 5mm lymph node in para-tracheal area

The largest lesion identified in the previous CT scan had increased in size to 3.7 x 2 cm and continued to exhibit cavitation, with smaller new nodular lesions observed in its vicinity (Figure 6).

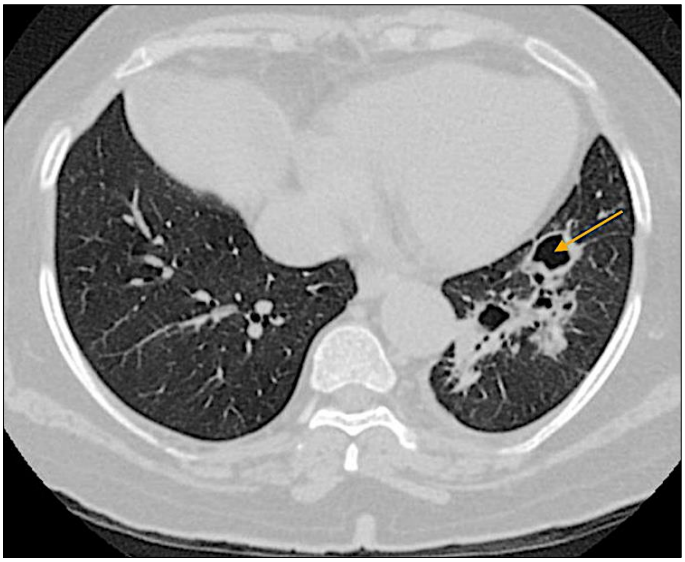

Figure 6: Showing largest lesion of 3.7 X 2cm with cavitation

In light of these findings, a multidisciplinary discussion was convened, involving radiology, dermatology, and pulmonary medicine specialists. Dermatology department proposed several differential diagnoses based on the skin lesions, including granulomatosis with polyangiitis, rheumatoid disease, monoclonal gammopathy of undetermined significance, and pyoderma gangrenosum. Meanwhile, pulmonary medicine considered granulomatosis with polyangiitis and rheumatoid lung as potential diagnoses.

Following the multidisciplinary discussion, it was collectively decided to proceed with further testing to explore potential autoimmune and vasculitic etiologies in the patient's complex presentation. Laboratory investigations were performed, including tests for Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), Antineutrophil Cytoplasmic Autoantibody, Cytoplasmic (c-ANCA), Rheumatoid factor (RA factor), and Antinuclear Antibody (ANA) profile, all of which returned negative results, effectively ruling out Granulomatosis with Polyangiitis and Rheumatoid Disease as likely causes.

With these results, the following differential diagnoses were considered: Monoclonal Gammopathy of Undetermined Significance and PG. Additionally, a Urine Bence Jones protein test returned positive,

prompting further evaluation. Serum protein electrophoresis yielded normal results with no M-band detected.

A skin biopsy was conducted, revealing that the sections from the skin showed an ulcerated epidermis extending into the deeper dermis with multiple micro-abscesses and skin debris. The periphery exhibited fibrinoid necrosis of small to medium-sized vessels with foci of leukocytoclasis, and occasional giant cells were observed. Importantly, no granulomas were detected. The impression from the skin biopsy was consistent with PG (Figure 7).

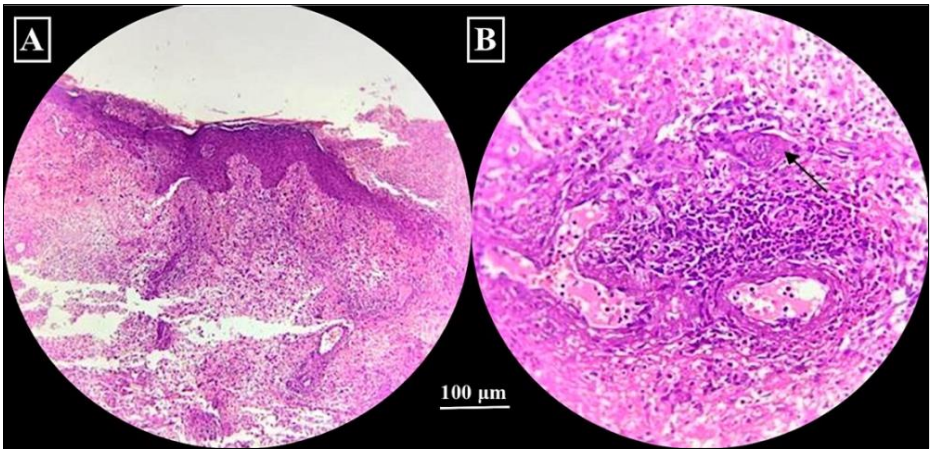

Figure 7: Histological analysis of a skin biopsy specimen with hematoxylin and eosin stain reveals: 7A) Erosion of the epidermis reaching into the deeper dermal layers, accompanied by micro-abscess formation and cellular debris. 7B) The surrounding area exhibits fibrinoid necrosis in small to medium-sized vessels, along with regions of leucocytoclasis. Noteworthy are occasional giant cells, as indicated by the arrow in 7B

Subsequently, the patient was initiated on a treatment regimen comprising prednisolone and minocycline. A follow-up evaluation after one month indicated a positive response to treatment, with improvements observed in both lung and skin lesions. Chest X-ray results also showed improvement (Figure 8, 9).

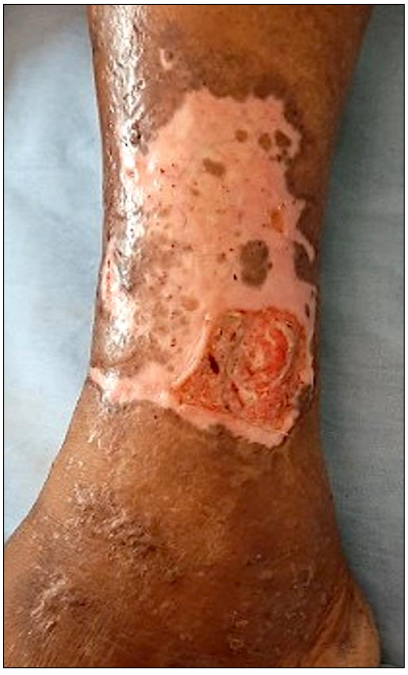

Figure 8: Skin lesions resolving post-treatment

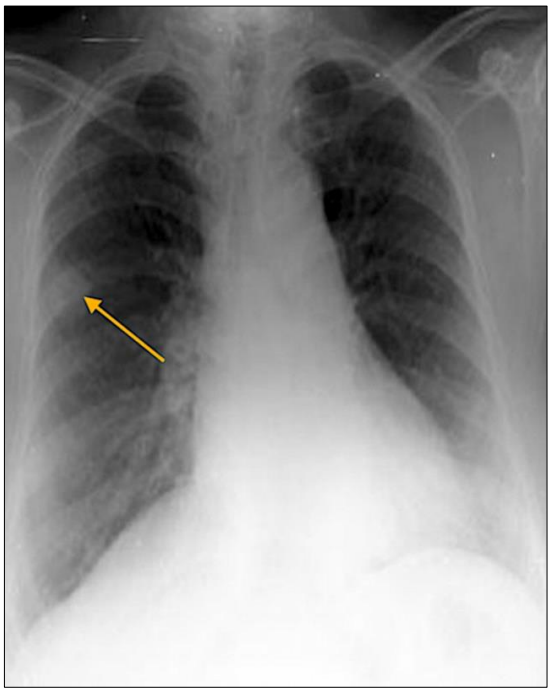

Figure 9: Showing decrease in the size of the cavity following treatment

DISCUSSION

Pyoderma Gangrenosum (PG) is classified as an inflammatory neutrophilic dermatosis and is often linked to underlying chronic inflammation and neoplastic diseases. It's estimated worldwide annual incidence ranges from 3 to 10 cases per million population,

affecting individuals of all genders and age groups [1]. The peak incidence is observed between the ages of 20 and 50 years [1, 2].

This case is noteworthy due to its extracutaneous involvement of PG. It has been well-documented that pulmonary involvement in PG may lead to life-threatening consequences and necessitates prompt recognition and treatment [3]. Therefore, understanding the clinical characteristics and management of pulmonary PG is of paramount importance. Pulmonary PG often presents with cavitating or non-cavitating lesions, which may be accompanied by necrosis and superimposed infections [3]. These pulmonary lesions may emerge before, during, or after the onset of skin manifestations, adding to the diagnostic complexity. Cytological evaluation typically reveals non-specific neutrophilic and lymphocytic infiltrates. Fortunately, these lesions tend to respond well to corticosteroid treatment, indirectly supporting the diagnosis of PG. Histopathological examination of skin biopsies also plays a crucial role in confirming the diagnosis.

The most important differential diagnosis of PG lung involvement is granulomatosis with polyangiitis, rheumatic nodules, and monoclonal gammopathy of undermined significance.

Granulomatosis with polyangiitis often presents with lung nodules and masses. These may appear as single or multiple heterogeneous masses, varying in size from a few millimetres to over 10 cm. The distribution can be random or peri-broncho vascular, subpleural, angiocentric, and rarely centrilobular, often with relative apical sparing [4]. Central cavitation occurs in up to 50% of cases, more commonly in larger nodules, and the cavity wall may exhibit varying degrees of thickness and irregularity. CT imaging may reveal distinctive signs such as the halo sign (surrounding areas of ground glassing), reverse halo/atoll sign, radiating scars, pleural tags, and more. Other pulmonary features include consolidation, airway wall thickening/stenosis, pleural effusion, and mediastinal adenopathy. Notably, nasopharyngeal and kidney involvement along with positive c-ANCA can also be indicative of this condition [5].

Rheumatoid nodules are a rare occurrence, affecting less than 1% of patients with rheumatoid arthritis [6]. These nodules tend to favour the upper and middle lung zones and can appear as single or multiple, peripheral or pleural nodules of varying sizes. Interestingly, they may not necessarily correlate with the course of arthritis and can manifest before the arthritis becomes clinically evident. Cytological studies typically reveal non-specific necrotic material. Other pulmonary manifestations of rheumatoid arthritis include airspace consolidation, reticulation, honeycombing, ground glass densities, and bronchiectasis [7].

Pulmonary manifestations in Monoclonal Gammopathy of Undetermined Significance are often observed as nodules, which can present as ground glass or solid nodules on CT scans. Biopsies may reveal Thioflavin T amyloid deposits, and associated findings might include sarcoidosis and pleural effusions [8].

In a review article by Borda LJ *et al*., [3], the joints emerge as the most common site of extracutaneous involvement in PG, affecting approximately 20% of cases manifesting as arthritis, synovitis, and bursitis. Ocular involvement, seen in about 5% of PG cases, leads to inflammation of the uvea, retina, or optic nerve, potentially resulting in vision loss if not promptly addressed. Pulmonary and gastrointestinal involvement are the rare manifestations (less than 5% of cases), presents with various symptoms, including cough, shortness of breath, chest pain, abdominal pain, diarrhoea, and bleeding. Central nervous system involvement, an exceedingly rare occurrence (less than 1% of cases), is characterized by symptoms such as headaches, seizures, and focal neurological deficits.

PG is primarily a skin disorder often associated with underlying inflammatory bowel disease, connective tissue disorders, or malignancies. Pulmonary involvement is the most common extra-cutaneous manifestation and may occur before, during, or after the appearance of skin lesions [3-9]. These pulmonary manifestations present as cavitating or non-cavitating nodules, often with areas of necrosis. The nodules are typically peripheral, multiple, and bilateral. Additional thoracic findings may include reticular opacities, honeycombing, consolidation, and mediastinal lymph nodes. Cytological evaluation commonly demonstrates non-specific inflammatory changes characterized by neutrophilic and lymphocytic infiltrates.

PG is a complex condition with diverse clinical presentations and potential extracutaneous involvement, particularly in the pulmonary system. Proper differential diagnosis is essential to guide appropriate treatment and management strategies for affected individuals. Understanding the distinct radiological features and clinical associations with other conditions can aid in accurately identifying and managing PG-related pulmonary manifestations.

In our case, the patient demonstrated a remarkable recovery in response to systemic corticosteroid treatment. Subsequent follow-up chest X-rays and CT scans revealed substantial improvement. Therefore, while empirical, corticosteroid therapy proved to be highly effective in this instance. Our patient has remained free from any recurrence for the past eight months.

Numerous studies have reported favourable outcomes with systemic corticosteroid therapy [9]. In a review article authored by Alavi A. *et al*., [1], it is

emphasized that high-dose corticosteroids should be the primary choice of treatment for progressive, severe, and disfiguring pyoderma gangrenosum cases. For patients with early presentations and prompt diagnoses, topical and intralesional therapies, coupled with meticulous wound care, can effectively manage acute cases. As inadequate treatment can result in intense pain, stress, anxiety and depression. Therefore the treatment of such cases is of paramount importance.

Recent studies have explored the use of biological agents like infliximab, adalimumab, etanercept, IL-1 antagonists, and IL-12/23 antagonists, offering potential therapeutic options for pyoderma gangrenosum cases. Nevertheless, it's important to note that as of now, there is no universally recognized gold standard treatment for PG.

CONCLUSION

This case stresses upon the importance of inter-departmental discussions, follow up of case and discussions with referring consultants, without which diagnosis based upon imaging alone would not have been possible. Due to the lack of conclusive laboratory or histological diagnostic criteria, PG is regarded as a "diagnosis of exclusion" and is commonly misdiagnosed. Pulmonary involvement in pyoderma gangrenosum is rare. Diagnosis becomes especially difficult when the pulmonary involvement precedes skin lesions. Therefore, the rapid response to steroid treatment indirectly supported the diagnosis of pyoderma gangrenosum.

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