Pulmonary manifestations of pyoderma gangrenosum: 2 cases and a review of the literature

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Summary
Pyoderma gangrenosum (PG) is a rare ulcerative neutrophilic dermatologic disease that occasionally is accompanied by extracutaneous manifestations, amongst these is pulmonary involvement. The etiology is unknown. More than 50% of PG cases are associated with an underlying systemic disease such as inflammatory bowel disease, rheumatoid arthritis, hematological disorder or malignancy. Extracutaneous manifestations are rare and only 29 cases of pulmonary involvement have been reported previously in the literature. Pyoderma gangrenosum is usually diagnosed in the third to sixth decade, but early debut in childhood is also described. Skin manifestations are usually evident before pulmonary involvement, although primary lung affection is seen. Pulmonary involvement is diagnosed simultaneously or from a few weeks up to several years after the diagnosis of cutaneous PG. The most important differential diagnoses are lung cancer, lung abscess and Wegener’s granulomatosis. Histological specimens will exclude these diagnoses. The treatment of PG is immune modulation, but due to the rarity of the disease, only one randomized treatment trials exists [1] and the long term course of PG with pulmonary involvement is unknown. We present two cases of pulmonary manifestations of pyoderma gangrenosum and a review of the literature.

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Introduction

Pyoderma gangrenosum (PG) is an ulcerative, destructive, non-infectious, neutrophilic dermatologic disease. The etiology is unknown. More than 50% of PG cases are associated with an underlying systemic disease such as inflammatory bowel disease, rheumatoid arthritis, hematological disorder or malignancy. However, visceral involvement by PG is rare and only 29 cases with pulmonary manifestations have been described previously in the literature (Table 1).

PG is diagnosed from the clinical picture in conjunction with PG compatible histology. There are no pathognomonic laboratory tests or specific pathologic changes. The skin lesions are usually painful and rapidly progressing while the pulmonary manifestations can be asymptomatic or present with continuous fever, dyspnea, cough and hemoptysis. Thoracic radiographs and computer tomography (CT) of thorax can show cavitation as well as non cavitating lesions and other aetiologies such as lung infection, malignancy and necrotizing vasculitis obviously needs to be excluded. The treatment of PG is immune modulation generally by the use of prednisolone, azathioprine, or ciclosporine but due to the rarity of the disease, only one randomized treatment trial exists to our knowledge [1].

We here present two case reports of patients with pyoderma gangrenosum with pulmonary involvement and a review of the literature.

Case one

A 61 year old male was referred from the Department of Dermatology to the Department of Respiratory Diseases due to cavitating pulmonary lesions. Three months earlier he had a rapidly progressing ulceration localized in both groins and on the back. Based on skin biopsy specimens showing histopathological changes compatible with PG, the clinical appearance of the lesions and the exclusion of other diseases (see below) he was diagnosed with PG. The patient started treatment with oral and topical steroids and ciclosporine and the cutaneous lesions improved. He had no complaints from other organ systems.

Blood samples, including sedimentation rate, C-reactive protein (CRP) and anti-neutrophilic-cytoplasmic antibodies (ANCA), anti-nuclear antibodies (ANA) and IgM rheumatoid factor (IgM-RF) were normal. During the investigational set-up for underlying diseases a CT of thorax and upper abdomen was performed due to unexplained weight loss, showing cavitating infiltrates in the right lung (Fig. 1).

A transthoracic needle biopsy of the infiltrate showed chronic and granulomatous inflammation but no malignant cells or signs of vasculitis. T-spot (Oxford Immunotec) for tuberculosis was negative. A bronchoscopy was performed and bronchoalveolar lavage fluid (BALF) showed macrophages (89%), neutrophilic granulocytes (6%) and lymphocytes (5%). Culture of the BALF showed >100,000 *Haemophilus influenza* and the patient was treated with amoxicillin without any clinical or radiological improvement. Thus, an infection was not considered the cause of the lesions. Aspergillus galactomannan binding antigen was negative and culture of BALF grew no fungi. No malignant cells were identified.

Since the suspicion of cancer, abscess, tuberculosis or fungal infections could not be sustained, it was concluded that the pulmonary infiltrates represented extracutaneous manifestations of PG. The dose of ciclosporine and prednisolone were increased and prednisolone later slowly tapered.

Follow-up chest radiograph and CT scan of the lungs one year later showed regression, although not complete, of the apical infiltrate. After 2 years of treatment with ciclosporine the patient was switched to methotrexate (12.5 mg/week) in combination with infliximab (5 mg/kg bodyweight every 8th week) due to renal side effect. At follow-up after 1/2 years of treatment with infliximab no relapse of pulmonary infiltrates on chest radiograph had occurred and the cutaneous lesions had healed completely.
<table>
<thead>
<tr>
<th>Name of Authors</th>
<th>Sex</th>
<th>Age at diagnosis (years)</th>
<th>Comorbidity</th>
<th>Symptoms</th>
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<th>Time between skin and pulmonary symptoms</th>
<th>Treatment</th>
<th>Response</th>
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<tr>
<td>McCulloch AJ et al. [8]</td>
<td>F</td>
<td>54</td>
<td>IBD</td>
<td>Chest pain, cough, purulent sputum, fever</td>
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<td>Vignon-Pennamen MD et al. [10]</td>
<td>F</td>
<td>60</td>
<td>Monoclonal IgA gammopathy</td>
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<td>Yes</td>
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<td>Lebbe C et al. [12]</td>
<td>F</td>
<td>58</td>
<td>—</td>
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<td>Urano S et al. [13]</td>
<td>F</td>
<td>37</td>
<td>—</td>
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<td>Merke DP et al. [28]</td>
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<td>0.75</td>
<td>—</td>
<td>Fever and stridor</td>
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<td>F</td>
<td>24</td>
<td>—</td>
<td>Dyspnea, Hemoptysis, fever and cough</td>
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<td>Kasuga I et al. [14]</td>
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<td>50</td>
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<td>Grattan et al. [30]</td>
<td>F</td>
<td>28</td>
<td>Polyarthritis</td>
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<td>Peters FPJ et al. [31]</td>
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<td>48</td>
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<td>Takeuchi K et al. [18]</td>
<td>F</td>
<td>5</td>
<td>—</td>
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<td>Bhat M et al. [19]</td>
<td>F</td>
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<td>Psoriasis Ulcerative Proctitis</td>
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<td>Yes</td>
<td>1 week</td>
<td>Steroid</td>
<td>2 days</td>
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<th>Reference</th>
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<th>Time between skin and pulmonary symptoms</th>
<th>Treatment</th>
<th>Response</th>
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<td>Chahine B et al. [20]</td>
<td>F</td>
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<td>Weeks</td>
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<td>31</td>
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<td>Rajan et al. [27]</td>
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<td>4 months</td>
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<td>Steroid Ciclosporine Dapsone Infliximab 4 weeks after adding infliximab</td>
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<td>Kitagawa KH et al. [5]</td>
<td>F</td>
<td>82</td>
<td>Osteoarthritis Osteoporosis Hyperlipidemia</td>
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<td>Liu ZH et al. [26]</td>
<td>M</td>
<td>65</td>
<td>Hypertension, MI, Hyperlipidemia</td>
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<td>14 years</td>
<td>Steroid Dapsone Steroid Mycopheno late mofetil</td>
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<tr>
<td>Field S et al. [32]</td>
<td>F</td>
<td>52</td>
<td>Proctitis</td>
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<td>Yes</td>
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<td>Kanoh S et al. [6]</td>
<td>M</td>
<td>54</td>
<td>MDS</td>
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<td>2 weeks</td>
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<td>F</td>
<td>57</td>
<td>MDS</td>
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<td>Steroid</td>
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<td>Batalla A et al. [33]</td>
<td>F</td>
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<td>Iron deficiency anemia</td>
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<td>4 months</td>
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<tr>
<td>Bittencourt et al. [22]</td>
<td>M</td>
<td>17</td>
<td>—</td>
<td>Dyspnea, hemoptysis fever cough and chest pain</td>
<td>Yes</td>
<td>6 years</td>
<td>Steroid</td>
<td>2 weeks</td>
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</tbody>
</table>
Case two

A 52 year old woman diagnosed with PG 9 years previously presenting with typical PG lesions of feet and hands and histopathological changes compatible with PG. She was referred to the Department of Respiratory Diseases due to recurrent lung infiltrates. No underlying disease in relation to PG had ever been diagnosed. She was treated with 4,4-diaminodiphenylsulfone, dapsone and corticosteroids for PG. Earlier treatment with ciclosporine was ceased due to severe hypertrichosis and fluid retention. Azathioprine had also been tried but was discontinued due to elevated liver enzymes and nausea.

The patient complained of shortness of breath during exertion and chest pain. She had a productive cough and a low grade fever. Chest radiograph and CT showed several lesions (Fig. 2), one of them cavitating, in the upper right lung and enlarged lymph nodes in the mediastinum. BALF showed lymphocytic inflammation (lymphocytes 95%, macrophages 5%, eosinophil granulocytes 3% and neutrophil granulocytes 0%). BALF culture including analysis for tuberculosis and fungi was negative and cytological examination was without malignant cells. Blood samples showed elevated CRP 1400 nmol/l (<75 nmol/l), negative ANCA, ANA and IgM-RF. Repeated blood and sputum cultures were negative. Lung function test and echocardiography were normal. A transthoracic needle biopsy was performed showing chronic inflammation and no evidence of malignant cells, necrotic material or signs of vasculitis.

Initially, dapsone was suspected as the cause of the patients lung infiltrates but cessation of dapsone treatment lead to worsening of the cutaneous manifestations of PG without improvement of pulmonary symptoms and thus dapsone was reinstituted.

In spite of the negative cultures, a lung abscess was suspected and the patient was treated with high dose antibiotics. However, no improvement was noted neither clinically nor biochemically. Prednisolone 75 mg daily was finally started with immediate normalization of the temperature and CRP, and regression of the lung lesions. When prednisolone was tapered, the symptoms recurred, CRP increased and a new pulmonary lesion was seen on the chest radiograph. Again, after increasing the prednisolone dosage, the symptoms disappeared, CRP fell into normal range and the chest radiograph showed rapid regression of the infiltrates.

Due to prednisolone side effects, different prednisolone sparing regimes where tried: Increased dosage of dapsone was abandoned due to arthralgias. On methotrexate treatment the lung lesions recurred and therefore infliximab treatment was started. The patient has now been followed for 3½ year after starting infliximab. Prednisolone, methotrexate and dapsone have been reduced and the patient has no respiratory complaints and a normal chest radiograph. Currently there is no activity in the skin.

Review

Data source and study selection

A PubMed search with the terms “pyoderma gangrenosum”, "lung” and "pulmonary” was performed. Papers were restricted to those published in the English language. Additional articles were identified by the reference lists of the identified papers.

Epidemiology

Epidemiological data on Pyoderma gangrenosum is mostly based on case reports and cohort studies. Pulmonary involvement is rare and only 29 previous cases have been reported (Table 1).

A population-based retrospective cohort study including 313 persons found an incidence rate of 0.63 per 100,000 person-year and a high mortality associated with PG. Fifty-nine percent were women [2]. In accordance with this we found that 18 out of 29 previous cases were women (Table 1). PG is most often diagnosed in the third to sixth decade, but debut is also described in children. We found 5 cases of children/adolescents with PG and pulmonary involvement.

Etiology

The etiology is unknown but approximately 50–70% of pyoderma gangrenosum cases are associated with an underlying systemic disease such as inflammatory bowel
disease, rheumatoid arthritis, hematologic diseases or malignancy.

This is also true for PG patients with pulmonary involvement, in which 19 out of 29 patients had an underlying disease. In six cases the patient’s previous medical history was not reported. Rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, proctitis, leukemia, multiple sclerosis, gastritis with vitamin B deficiency, monoclonal IgA-gammapathy, and diabetes mellitus have all been described in single cases in patients with pulmonary manifestation of PG. The pathogenic relation between PG and these diseases is not completely understood. It is, however, important that patients diagnosed with PG undergo thorough examinations to rule out comorbidity and if found, it is pivotal to treat the underlying disease.

Our two patients had been extensively examined without the identification of any underlying disease.

Clinical features

The skin lesions are usually painful and rapidly progressive while the pulmonary manifestations can be asymptomatic or present with continuous fever, dyspnea, cough, chest pain and hemoptysis.

The skin manifestations of PG are most frequently evident before pulmonary involvement. Lung involvement can occur simultaneously or from a few weeks up to several years after the diagnosis of cutaneous PG. Both our patients had cutaneous PG when the diagnosis of pulmonary involvement was made. Patient 1 had PG for a few months, and patient 2 for 9 years. Only 9 patients with pulmonary changes due to PG before appearance of skin lesions have been described (Table 1).

Elevated erythrocyte sedimentation rate (SR) and CRP is typically seen in PG as well as leukocytosis. IgA, IgG and IgM are elevated in 15% of patients with PG. There is, however, no specific laboratory assay diagnosing PG and most important is a broad blood-screening to rule out other diseases [3]. Although non-specific, p-ANCA is often positive in patients with PG whereas c-ANCA indicates Wegeners granulomatosis [4]. SR, CRP or leukocytes were elevated in 19 cases of PG with pulmonary involvement.

The most important differential diagnoses are lung cancer, lung abscess and Wegener’s granulomatosis. Histological examinations will exclude these diagnoses. In our cases the diagnosis of PG was confirmed by the clinical presentation with the pre-existing cutaneous PG, the absence of malignant cells, the lacking evidence of abscess and/or pneumonia and the rapid response to steroids. A neoplasm was excluded based on transthoracic needle biopsy with no malignant cells.

Radiological characteristics

Chest radiograph and CT scan often reveal a picture with infiltrates. Both single and multiple infiltrates have been described and the infiltrates are often cavitating. There is no predilection for any lung zone and cases of bilateral infiltrates have been reported. Other manifestations such as pleural effusion (5/29) and opacities (2/29) have also been described (Table 2).

Pathological characteristics

Histopathologic findings are non specific, but skin biopsy specimens can support the clinical diagnosis as well as rule out some differential diagnoses such as cancer. The main feature is predominant neutrophil infiltration. Ulcerative parts of the lesion will show tissue necrosis and inflammation around the vessels. Vasculitis and signs of infection is usually not seen. Finally, histological features can be inconsistent with PG despite obvious clinical findings.

Little is known about the pathogenesis. Neutrophil dysfunction including altered chemotaxis is thought to be a main feature. The effect of antineutrophilic agents such as dapsone supports this idea. The frequent coincidence with other auto-inflammatory diseases such as inflammatory bowel disease and arthritis supports the idea of an altered function of the immune system.

Pulmonary involvement of PG is rare and histopathologic findings are non-specific. Most frequently, neutrophilic inflammation is seen in lung biopsies/BALF. Neutrophilic inflammation was found in 12 out of 19 cases (Table 3).

In case 1 a transthoracic needle biopsy showed granuloma which has been reported in 2 previous cases [5,6].
Treatment

The treatment of PG is immune modulation generally by the use of prednisolone, azathioprine, or ciclosporine [7]. Because of the rarity of PG there is no standard protocol and the choice of therapy is mostly based on case studies. Prednisolone has been the mainstay of treatment and typically, a rapid response is observed within days to weeks [6,8–22]. Such a rapid response is never seen in Wegener’s granulomatosis, rheumatoid arthritis, abscesses, cancer and fungal infections. Therefore, a rapid steroid response can indirectly support the diagnosis of PG. In case 2, a rapid response to prednisolone treatment was observed. The patient had several chest radiographs with infiltrates disappearing in relation to prednisolone treatment and the infiltrates reappeared after steroid tapering, but not in the same location. Migrating infiltrates have to our knowledge not been described before.

Due to the long term side effects of corticosteroid treatment other immune-modulating agents are often used in combination with steroid. Ciclosporine has been used in most cases for the treatment of PG in combination with corticosteroids or as mono-therapy [23]. Several case reports of PG with lung involvement showed a rapid response on this treatment [5,24] just as we experienced with patient 1, who had rapid regression of the pulmonary infiltrate with ciclosporine and prednisolone.

Dapsone can also be used in the treatment of PG and help reduce exposure to corticosteroids. Dapsone was used as mono-therapy in a case report by Fukuhara et al. with a response within 2 months [25]. Ze-Hu et al. describes the combination of steroid and dapsone in treatment of PG with lung involvement with a response of only 2 days [26].

Although prednisolone seems to be the mainstay in the treatment of PG with pulmonary involvement, a few case reports describe patients with no or inadequate response to steroids. Rajan et al. presented a 4 month-old girl with progressive skin lesions and cough. Leucocytes and C-reactive protein were elevated. The patient quickly developed upper airway obstruction requiring intubation and ventilatory support. Prednisolone had no effect. Ciclosporine and later dapsone were tried also without effect and at last infliximab 5 mg/kg was initiated. After the introduction of infliximab, no further lesions appeared and the old lesions healed [27].

Infliximab is a biological agent that blocks tumor necrosis factor-α (TNF-α). One randomized, double blinded, placebo-controlled trial on the treatment of cutaneous PG with infliximab exists. The study included 30 patients with cutaneous PG. They were randomized to receive infliximab at a dose of 5 mg/kg or placebo. After 2 weeks of treatment significantly more patients in the infliximab group had improved (46% [6/13]) compared to the placebo group (6% [1/17]). At week 2, all patients with no improvement (23/30) were treated with open label infliximab. At week 4 and 6 69% of the patients receiving infliximab had improved or were in complete remission. No response to treatment was observed in 31% of the patients. This trial showed a rapid and significant improvement on cutaneous PG when treated with infliximab [7].

Long-term course

PG is a chronic dermatosis with a high recurrence rate. However, data on the long-term outcome of PG with pulmonary involvement is sparse and no follow-up studies have been done. In our experience the prognosis is good since both our patients have experienced no relapse of pulmonary PG 3 1/2 years after they started treatment. They both experienced side effects to their initial treatment and in both cases alternative treatment regimes were found with no relapse of pulmonary PG.

Conclusion

Pyoderma gangrenosum (PG) is an ulcerative, destructive, non-infectious, neutrophilic disease that primarily affects the skin. Pulmonary involvement is a rare condition and only 29 cases have been described in the literature previously. We present two unique cases of pyoderma gangrenosum with pulmonary involvement.

Pulmonary manifestation of PG is a diagnostic challenge and exclusion of other conditions such as Wegener’s granulomatosis, malignancy and infection is mandatory.

With the exception of the study by Brooklyn et al. [1] there are no randomized controlled trials of the treatment of PG and the choice of therapy is often empirical. As seen in both our cases a rapid response to steroid treatment is characteristic for PG and prednisolone is typically the first choice of therapy. Other immune-modulating agents such as ciclosporine and dapsone are also used as mono-therapy or in combination with systemic steroid. Biological agents such as infliximab have shown promising results and should also be considered in the treatment of PG with visceral involvement.

Contribution to the study

Conception and hypothesis delineation: MG, OH, EB, KA. Data acquisition, analysis and interpretation: MG, OH, EB, AA. Writing the article or substantial involvement in its revision: MG, FS, KF, OH, EB, KA.

Conflict of interest

None declared.

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References


