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BRIEF COMMUNICATIONS

A case of persistent fever, cutaneous manifestations and pulmonary and splenic nodules: clinical experience and a literature review

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Abstract

Pyoderma gangrenosum (PG) is a rare and recurrent ulcerating, non-infectious, inflammatory dermatosis, with occasional concomitant extracutaneous manifestations. The pathogenesis and aetiology of PG are unknown. Moreover, early diagnosis is challenging because there are several visceral manifestations that may occur prior to the skin findings, such that misdiagnosis of PG as an infection is common. Here, we present a case of PG in which pulmonary and spleen lesions preceded the cutaneous manifestations. The correct diagnosis was made 6 months after multiple nodules were detected in the lung and spleen, based on the development of skin wound ulcers. To the best of our knowledge, this is the first report of PG in which pulmonary and splenic involvement preceded the appearance of skin lesions, without systemic disease. The patient was followed up for 5 years, during which time complete clinical and radiographic resolution was confirmed. This case demonstrates the challenges in the diagnosis of PG and the importance of using multiple diagnostic methods to determine the cause of unexplained clinical manifestations.

A 32-year-old Chinese man presented with a 1-year history of recurrent cough and a 3-month history of low-grade fever with small amounts of blood-streaked sputum. He had been hospitalised at a community medical institution for diagnosis and treatment, with the latter consisting of a combination of cefaclor and clarithromycin. However, after 1 month, there was little clinical improvement of his symptoms. On admission to our hospital, he presented with a peak temperature of 37.8°C and an aggravated cough productive of yellow, blood-stained sputum. He did not have chest pain, dyspnoea or haemoptysis. He denied recent travel, weight loss, a possible sexually transmitted disease and alcohol or tobacco use. He had no unusual exposure history, and his medical history was unremarkable.

His temperature was 37.6°C, and his blood pressure, heart rate and respiratory rate were normal. Oxygen saturation was 98% on room air. He had no skin lesions, and his chest and abdominal examinations were unremarkable.

A complete blood count revealed a white blood cell count of 15.7×10^9/L, 76% neutrophils, a haemoglobin level of 111 g/L, an erythrocyte sedimentation rate of

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60 mm/h and a C-reactive protein level of 9.15 mg/L. His serum albumin was 31.4 g/L, and globulin level was 36.7 g/L. Urinalysis results were normal, as were liver and renal function tests and electrolyte levels. His *Aspergillus* antigen test, fungal serologies, human immunodeficiency virus and syphilis enzyme-linked immunosorbent assay were negative, and tuberculosis (TB) skin test were weakly positive. The bacterial, mycobacterial and fungal blood cultures were sterile.

A chest radiograph revealed multiple nodules in both lungs. Initially, the patient was diagnosed with pneumonia and started on empirical antibiotics, consisting of moxifloxacin. Two weeks after his admission, a new chest radiograph revealed that the nodules had become smaller, but there was little improvement of his fever and cough. A computed tomography (CT) scan without contrast medium (Fig. 1) and bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy of the posterior basal segment of the left lower lung were performed.

Examination of the bronchial mucosa revealed a reddish mucosa. The histopathologic analysis and special staining revealed an inflammatory granulomatous disease, although TB and a fungal infection were excluded. Acid-fast and weak acid-fast staining was negative, as was the TB culture. Tests for fungi and bacteria in the BAL fluid were negative.

The serological results, including antinuclear antibody (Ab), antineutrophil cytoplasmic Ab, rheumatoid factor, Sm Ab, SS-A/SS-B Ab, ribonucleoprotein Ab, Scl-70 Ab, Jo 1 Ab, and anti-double-stranded DNA Ab, were also negative. His plasma DNA results for cytomegalovirus and Epstein–Barr virus were negative. No valvular vegetation was seen on three-dimensional transthoracic echocardiography.

Despite consultations among expert respiratory and haematology physicians, as well as surgeons, the diagnosis was uncertain. Infectious disease, lymphadenoma and vasculitis were considered. Video-assisted thoracoscopic surgery to obtain lung and splenic biopsies was ruled out due to the associated risks. The patient was administered vancomycin and fluconazole as diagnostic treatment, but neither drug improved the recent worsening of his cough or his recurrent fevers. Repeat CT scan showed an increase in the number of pulmonary nodules, located within cavitary lesions, and an enlarged spleen containing multiple nodules that were circular in shape on the enhanced images (Supporting Information Fig. S1). The patient's temperature rose to 39°C and a festering skin wound occurred at the site of bone marrow aspiration. Cytologic examination and culture of the purulent secretion produced negative results, except for many aggregates of neutrophils. Bone marrow analysis was normal. The patient was started on intravenous moxifloxacin for continuous hyperpyrexia and to treat the festering wound. His symptoms dramatically improved after 10 days, and he was discharged with a normal temperature. He remained on moxifloxacin.

However, 4 months later the patient was rehospitalised because of an elevated temperature. Tuberculin skin testing was performed but within 48 h a deep, necrotic lesion appeared at the testing site (volar aspect of the right arm). Active TB was the most likely diagnosis and the lesion was treated locally. In addition, the patient was treated for suspected TB (oral rifampicin, isoniazid, pyrazinamide and sulfanilamide), but his condition steadily deteriorated. A rapidly progressing ulceration developed not only at the tuberculin skin testing site but also at every injection site. With disease progression, necrosis swelling, and oedema developed on his face and calves (Fig. 2). Bacterial and mycobacterial cultures of his sputum and skin secretions were negative. A skin biopsy was performed on his arm. The histologic sections showed thinning of the epidermis, thickening and fibrinoid degeneration of the dermal vascular wall, and infiltration of neutrophilic debris (including from the cell nuclei) into the vessel walls and perivascular space (Fig. 3).

By a process of exclusion the final diagnosis was pyoderma gangrenosum (PG) at multiple sites, with predominant involvement of lungs, spleen and skin.

Discussion

This case describes a patient who complained of fever and productive cough. The CT scan revealed multiple pulmonary and splenic nodules. None of the laboratory tests yielded pathognomonic findings, and there were no specific pathologic changes allowing a definitive diagnosis. Histopathologic analysis of the transbronchial biopsy sample revealed an inflammatory granulomatous disease. The diagnosis of PG was made 6 months after multiple nodules were detected in his lung and spleen and was facilitated by the occurrence of the skin wound ulcers. Our literature search failed to identify a report of PG without systemic disease, in which pulmonary and splenic involvement preceded the appearance of skin lesions.

PG is a rare but recurrent ulcerating, noninfectious, inflammatory dermatosis whose pathogenesis and aetiology are unknown. The neutrophilic dermatosis characteristic of PG is accompanied by necrotic ulceration, in which the ulcers have an irregular mucopurulent base and an erythematous radiance.[1] There are no diagnostic histopathological changes in PG, the aetiology of which is widely believed to be immunological. Visceral involvement is rare,[2] as are neutrophilic infiltrates in sites other

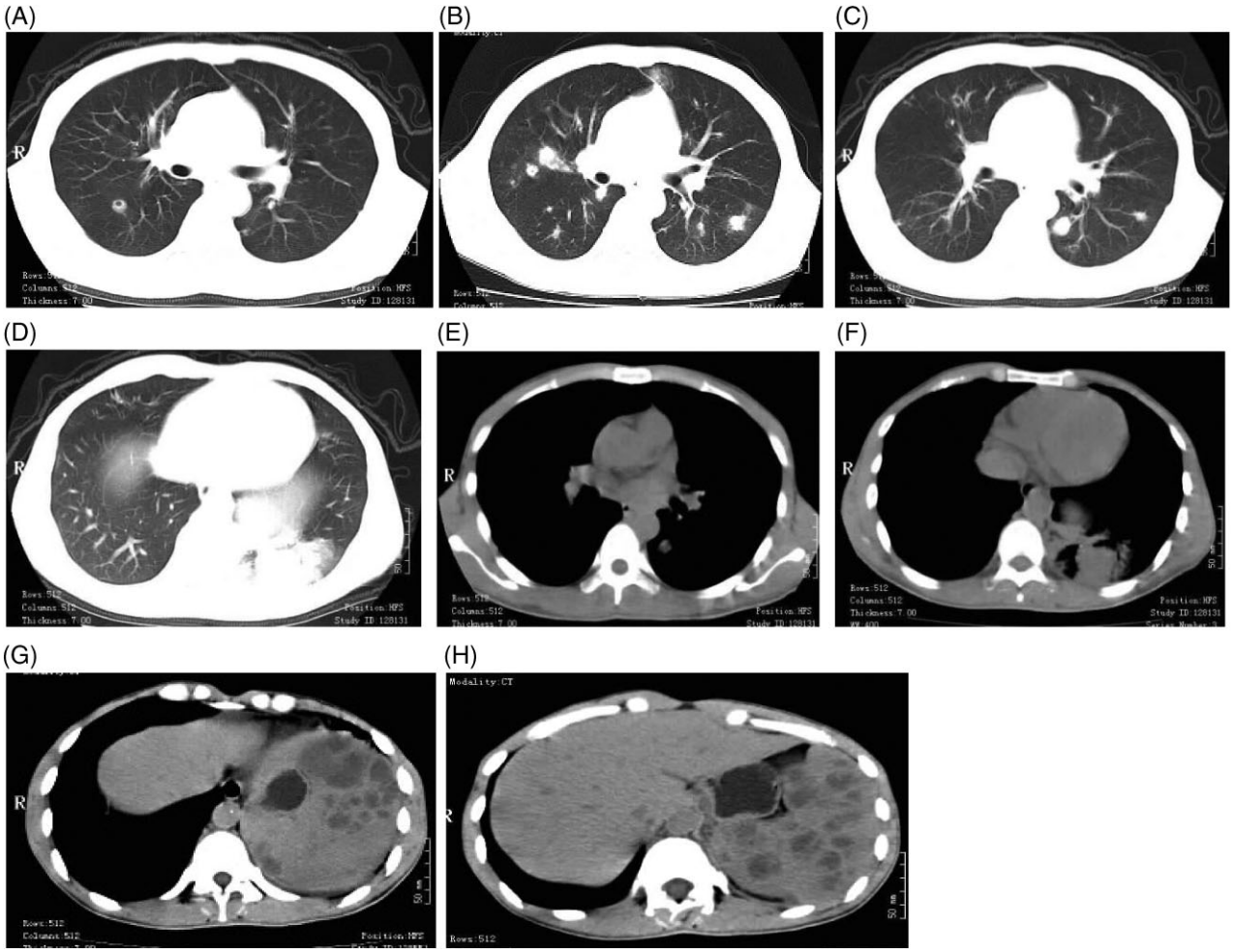

Figure 1 (A–C) chest computed tomography (CT) scans revealed multiple, bilateral poorly defined and peripherally distributed pulmonary nodules. Some foci showed internal cavitation. (D) consolidation lesion in left lower lung lobe. (E,F) CT in mediastinal windows showed cavitating image and consolidation lesions in left lower lung lobe. (G,H) revealed enlarged spleen with the presence of mutiple nodules.

than the skin, with the lungs being the most frequently involved organ.[3] The spleen is also seldom involved, although there are reports of patients presenting with splenic abscesses and haematological malignancy.[4] Some reports have shown that females are more susceptible to the disease, while others have determined an equal male: female distribution.[5,6] An epidemiological study estimated that an incidence of PG in a standardised European population of 6 per million per year,[7] but the incidence in China has not been accurately determined.

Approximately 50% of PG patients have an underlying systemic disease.[8] The skin lesions often develop prior to visceral involvement. While extracutaneous manifestations are rare, they may include scleritis and orbital, splenic, and hepatic involvement.[9] Only 32 cases of pulmonary involvement have been reported in the literature.[10–12]

Diagnosis of PG featuring by pulmonary involvement is challenging. Pulmonary manifestations present as recurrent cough, fever, chest pain, dyspnoea and haemoptysis. Bacterial, mycobacterial and fungal cultures of blood, sputum and BAL fluid are negative.[12–14] Imaging findings include multiple pulmonary nodules, lung abscesses, pleural effusion, cavitary consolidations, unilateral lung shadows and interstitial pneumonitis.[15] Lung biopsy shows noninfectious granulomatous inflammation with neutrophilic infiltration.[16] Owing to the lack of diagnostic laboratory tests and histopathological findings indicative of PG, it is often misdiagnosed as an infection, lung cancer or Wegener's granulomatosis.

The cavitary lung lesions and spleen lesions seen in our patient were probably extracutaneous manifestations of PG. Treatment with oral prednisolone 40 mg/kg/day produced a good response, as the follow-

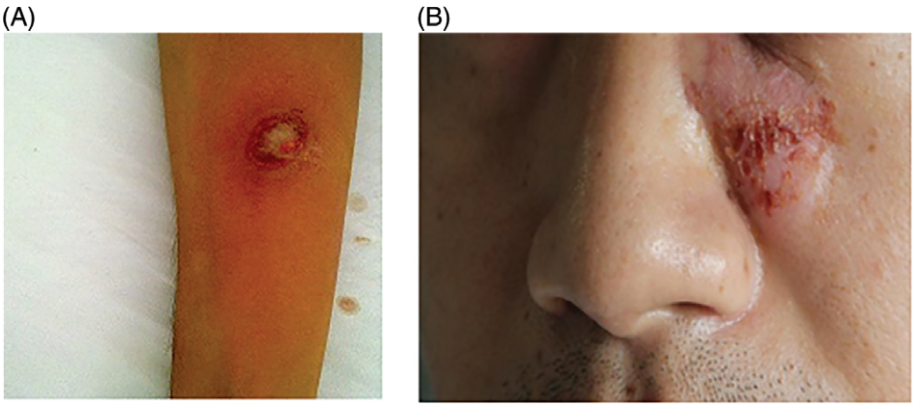

Figure 2 Necrotic lesions appeared at the testing site (volar aspect of the right arm [A]) and his face (B).

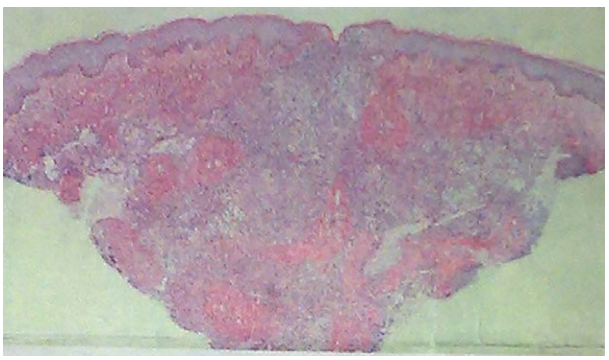

Figure 3 Histology showed polymorphonuclear neutrophil infiltration in the dermis and hypodermis, vasculitis and fibrinoid necrosis suggestive of pyoderma gangrenosum (PG) (haematoxylin and eosin stain; original magnification ×4). Immunohistochemistry showed CD45RO(+++), CD3(+), CD20(–), CD79a(–), CD30(++), MPO(+++). CD43(++).

up CT scan performed 3 months later showed regression of the lung and spleen lesions (Fig. S2A,B), The skin lesions healed but left scars. The dose of prednisolone was tapered to 10 mg/kg/day and gradual improvement in his clinical and radiological status was observed, but cessation of prednisolone therapy resulted in recurrent skin ulceration. Follow up continued for 5 years, during which time the patient had complete clinical and radiographic resolution (Fig. S2C,D). The effectiveness of glucocorticoid therapy confirmed the diagnosis.

Treatment of PG is mostly based on case studies, as there is no standard therapy. High-dose prednisolone is currently the preferred treatment. If prednisolone fails, methylprednisolone therapy can be considered, along with dapsone, azathioprine, infliximab, or cyclosporine. Related bacterial infections can be treated with antibiotics.[17]

Our patient with PG had lung, spleen and skin involvement, with the pulmonary and splenic lesions preceding the cutaneous manifestations. As demonstrated in this case, in the absence of cutaneous histopathology findings, a definite diagnosis of pulmonary and spleen lesions is difficult. Antibiotics and anti-TB treatment were ineffective in our patient and even invasive diagnostic examinations failed to lead to the correct diagnosis. The differential diagnosis of pulmonary nodules, skin lesions, and splenic lesions should include TB, fungal infections, malignancies such as melanoma and lymphoma, collagen vascular diseases and vasculitis. To diagnose PG repeated biopsy may be necessary to achieve a correct description of its histopathology. The present case shows that a variety of diagnostic methods may be needed to determine the cause of seemingly inexplicable, simultaneous disease manifestations.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Figure S1. Repeated computed tomography (CT) scan showed pulmonary nodules within cavitary lesions more than before, but consolidation lesions in left lower lung lobe improved. Abdominal CT revealed an enlarged spleen with the presence of mutiple nodules, which were enhanced as circular.
Figure S2. (A,B) Computed tomography (CT) scan showed improving state of pulmonary and spleen nodules after prednisolone performed 3 months later. (C,D) Scans showed the disappearance of the lung and spleen lesions after treatment with oral prednisolone for 5 years.