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CASE REPORT

Pulmonary Hyalinising Granuloma
A report of two cases

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الورم الرئوي الحبيبي الزجاجي
تقرير حالتين

امين كمونة، فاطمة اللواتية، اثيل كمونة، ناصر البوسعيدي، يعقوب المحروقي، صقر الطائي، نبيل اللواتي، راشد بن سيف العميري

ABSTRACT: Pulmonary hyalinising granuloma (PHG) is a rare fibrosclerosing inflammatory lung condition of unknown aetiology. It is characterised by solitary or multiple pulmonary nodules that are usually found incidentally while imaging the chest for other reasons. We report two cases of histologically proven PHG diagnosed at the Royal Hospital, Muscat, Oman. The first case was a 71-year-old male patient who presented in 2010 with a dry cough, weight loss and bilateral pulmonary nodules. The second case was a 58-year-old male patient who presented in 2012 and was found to have incidental bilateral pulmonary nodules on chest X-ray. Both patients were started on prednisolone and on follow-up the PHG nodules remained stable. Although there is no definitive treatment, PHG generally has an excellent prognosis.

Keywords: Granuloma; X-Ray Computed Tomography; Multiple Pulmonary Nodules; Lung; Case Report; Oman.

الملخص: الورم الرئوي الحبيبي الزجاجي هو نوع نادر من التهابات الرئة المتصفة بالتليف والتحجر والذي لا يعرف مسببه حتى الآن. يتميز الورم الرئوي الحبيبي الزجاجي بوجود عقدة رئوية وحيدة أو بوجود مجموعة من العقد الرئوية والتي عادة ما يتم اكتشافها عن طريق الصدفة أثناء تصوير الصدر لأسباب أخرى. نعرض هنا حالتين للورم الرئوي الحبيبي الزجاجي والتي تم إثبات تشخيصهما في المستشفى السلطاني، مسقط، سلطنة عمان عن طرق دراسة الأنسجة من العينات المأخوذة من العقد الرئوية. كانت الحالة الأولى في عام 2010 لرجل يبلغ من العمر 71 عاما كان يعاني من سعال وفقدان في الوزن ووجد لديه عقد رئوية. وكانت الحالة الثانية في عام 2012 لرجل يبلغ من العمر 58 عاما والذي وجد لديه بالصدفة عدة عقد في الرئتين اليسرى واليمنى. تم علاج المريضين بإستخدام البريدنيزولون. خلال المتابعة ظلت بقية العقد الروية ثابتة في الحجم من دون تغير. تبقى توقعات سير المرض ممتازة على الرغم من عدم وجود علاج أكيد للورم الرئوي الحبيبي الزجاجي.

الكلمات المفتاحية: ورم حبيبي؛ أشعة سينية مقطعية؛ عقيدات رئوية متعددة؛ رئة؛ تقرير حالة؛ عمان.

Pulmonary hyalinising granuloma (PHG) is a rare fibrosclerosing inflammatory lung disease which was first reported by Benfield *et al.* in 1962 and then characterised by Engleman *et al.* in 1977.[1,2]

Patients with PHG might have non-specific mild symptoms or be asymptomatic. The presence of PHG is usually discovered incidentally by chest X-ray or computed tomography (CT) scan performed for other reasons.[3] PHG is characterised by either unilateral or bilateral multiple pulmonary nodules which consist of extracellular, eosinophilic hyaline *lamellae*, surrounded by a collection of plasma cells, lymphocytes and histiocytes.[2–5] Although an exaggerated immune response to the antigenic *stimuli* by infection or autoimmune processes has been proposed as an aetiology, the exact pathophysiology of PHG remains unknown.[3]

On imaging, PHG presents as solitary or multiple pulmonary nodules that can mimic other more common pulmonary disorders, such as neoplastic and granulomatous conditions.[3] To the best of the authors' knowledge, these are the first cases of PHG reported in Oman.

Case One

A 71-year-old male patient was referred to the Royal Hospital, Muscat, Oman, in 2010 for the further work-up of lung lesions found on a chest CT scan. He had diabetes and hypertension and complained of a six-month history of dry cough associated with weight loss. There was no history of smoking, haemoptysis, anorexia or fever. On physical examination, there were bilateral palpable supraclavicular lymph nodes, but an otherwise unremarkable systemic examination. Laboratory tests were normal, including complete blood count, renal function test, liver function test, rheumatoid factor and antinuclear antibody. Chest X-ray showed bilateral pulmonary nodules and further evaluation

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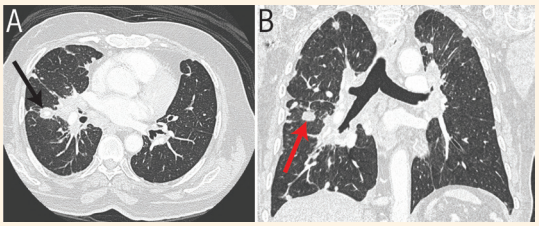

Figure 1: High resolution computed tomography scans of the chest of a 71-year-old male patient (case one) in (**A**) axial and (**B**) coronal views showing bilateral pulmonary nodules (black and red arrows) and central calcification in the right upper lobe nodule (red arrow).

with a chest CT scan revealed bilateral pulmonary nodules and masses associated with nodular interlobular septal thickening, along with extensive bilateral hilar and mediastinal lymphadenopathy. Some pulmonary nodules showed central calcification [Figure 1]. There was a small right-sided pleural effusion. Findings from the chest CT scan were suggestive of a metastatic process from an unknown primary source. F-18-fluordeoxyglucose positron emission tomography/CT (FDG-PET/CT) was performed; however, no extrathoracic lesion could be seen. The decision was made to obtain a tissue sample from the lung nodules.

Bronchoscopy was performed and bronchoalveolar lavage (BAL) was tested. Findings were negative for malignant cells and acid-fast *bacilli* (AFB). The tuberculosis (TB) culture from bronchial lavage was also negative. Subsequently, CT-guided biopsy of the pulmonary nodule was performed. Microscopic examination of the obtained tissue sample using haematoxylin and eosin stain showed a thick relatively acellular eosinophilic collagen bundle with *lamellar* arrangement that formed a *storiform* pattern [Figure 2]. The Congo red stain for amyloid was negative. Histopathological findings were consistent with PHG.

The patient was started on prednisolone 30 mg for two months and then 5 mg for another ten months. The PHG nodules remained stable on follow-up; however, the patient developed prostate cancer after three years following the diagnosis of PHG.

Case Two

A 58-year-old male patient with a known history of paraparesis due to myelopathy since 2009 presented to the neurology clinic at the Royal Hospital, in 2012 with a history of painless haematuria, significant weight loss and generalised abdominal pain. The patient had no history of smoking. Physical examination was normal except for rhonchi on the left lung and stable neurological deficits. Urine analysis was positive for blood, leukocytes and protein. Other laboratory tests were normal, including complete blood count and renal and liver function tests.

Abdominal ultrasound showed diffuse bladder wall thickening and trabeculation with a moderate right hydroureteronephrosis; no renal *calculi* were detected. The patient was treated as having a urinary tract infection; however, his chest X-ray showed bilateral multiple pulmonary nodules and masses [Figure 3]. CT scans of the abdomen, chest and pelvis were performed for further work-up and showed multiple pulmonary nodules and masses, some of which were calcified [Figure 4]. There were also multiple enlarged mediastinal lymph nodes and some had evidence of calcification with no identifiable primary source. Based on the CT findings, radiological differential diagnoses included lymphoma and metastasis from an unknown primary and histopathological correlation was recommended. Bone scan showed no evidence of bone metastasis. Both the AFB test and TB culture were negative.

Bronchoscopy was performed and BAL was negative for malignant cells as well as for AFB. The TB culture from the bronchial lavage was also negative. Pulmonary nodules were further evaluated with a CT-guided lung biopsy and the histopathological report was inconclusive. Subsequently, a right thoracoscopic

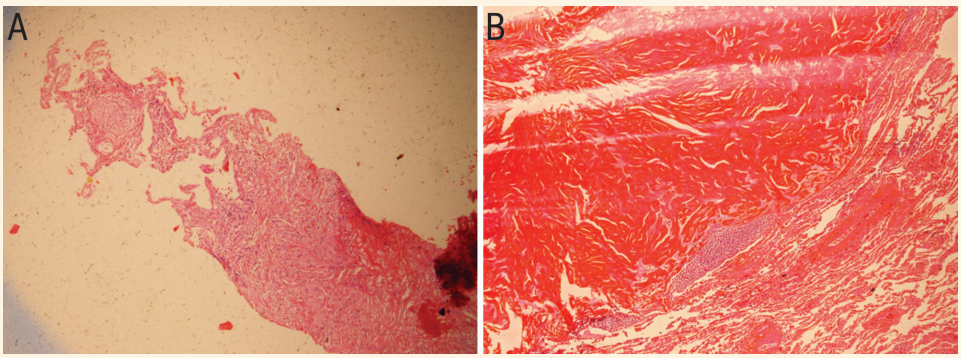

Figure 2: Haematoxylin and eosin stains of a pulmonary hyalinising granuloma nodule tissue sample obtained from a 71-year-old male patient (case one). **A:** Lung core biopsy at x5 magnification showing fascicles of collagen. **B:** Lung wedge biopsy at x2 magnification showing keloid-like collagen surrounded by a rim of lymphocytes.

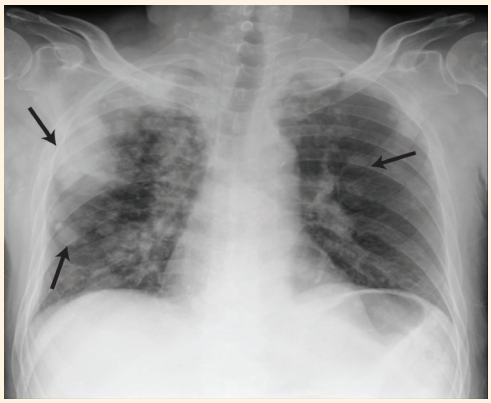

Figure 3: Coronal chest X-ray of a 58-year-old male patient (case two) showing bilateral pulmonary nodules and masses (black arrows), predominantly in the right lung.

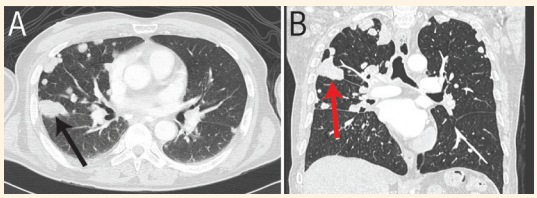

Figure 4: High resolution computed tomography scans of the chest of a 58-year-old male patient (case two) in (**A**) axial and (**B**) coronal views showing bilateral pulmonary nodules (black and red arrows) and central calcification in the right upper lobe nodule (red arrow).

lung biopsy and nodular excision were performed. Histopathological findings of the excised tissue were consistent with PHG.

The patient was counselled about the benign nature of the diagnosis and treated with prednisolone, initially 30 mg for three months and then gradually decreased over another three months. The patient was followed-up for five years and the pulmonary nodules remained stable. However, the patient developed Hodgkin's lymphoma five years following the diagnosis of PHG.

Discussion

PHG is a rare benign pulmonary disorder that is characterised by single or multiple pulmonary nodules. It is more predominant in males, with a mean age of 44.6 years (range: 15–83 years) at presentation.[3] Patients with PHG can present with mild and non-specific symptoms such as cough, fever, fatigue, dyspnoea and pleuritic chest pain. However, up to 25% of patients might be completely asymptomatic, with the pulmonary lesions detected incidentally while imaging the chest for other reasons. In the current cases, the first patient had a history of cough for six months associated with weight loss, while the second patient had pulmonary nodules that were detected incidentally while the patient was being evaluated for abdominal complaints.

Although the cause of PHG is unknown, it has been associated with infection and autoimmune and neoplastic disorders.[3,4,6–12] Lhote *et al.* reported a series of five PHG cases and reviewed 135 cases in the literature; they found that 19 cases were associated with infectious causes, of which TB was the most common infection. In the same study, 17 cases were associated with auto-immune disease and an association with mediastinal and retroperitoneal fibrosis was found in 19 and 12 cases, respectively.[3] Therefore, it has been proposed that PHG might be caused by an abnormal immune response to all of the above conditions. Chapman *et al.* reported a case of PHG and found elevated serum immunoglobulin (Ig)G4 and tissue IgG4-postive plasma cell in the PHG and concluded that PHG is part of IgG4 related-sclerosing disease.[12] In the current cases, neither of the patients were tested for IgG4 level.

In Lhote *et al.*'s study, PHG was found to be associated with solid tumours in six cases, including breast Paget's disease, lung adenocarcinoma, meningioma, anaplastic astrocytoma, thyroid carcinoma and basocellular carcinoma.[3] Ren *et al.* reported an association between PHG and lymphoma.[13] The current patients had developed two different malignant tumours on follow-up: the first patient developed prostate cancer, while the second developed Hodgkin's lymphoma. This suggests a possible association between PHG and the future development of malignancies, which needs to be further explored.

On chest X-ray and CT, PHG is characterised by solitary or, more often, multiple randomly distributed, unilateral or bilateral pulmonary nodules and/or masses without preferential distribution. The PHG nodules are usually well-defined and homogeneous, ranging in size from several millimetres to 5 cm in diameter, with an average diameter of 2 cm. They can calcify but rarely cavitate. Up to 60% of PHG lesions show increased metabolic activity using FDG-PET/CT.[3–12,14–16]

Radiological findings in PHG can mimic other nodular pulmonary disorders such as neoplastic and granulomatous processes; hence, radiological differential diagnosis should include sarcoidosis, rheumatoid nodules, Wegener's granulomatosis, TB and amyloidosis, as well as primary or metastatic tumours of the lung.[3,9,10,12,15] Therefore, histopathological examination is required to diagnose PHG and differentiate it from other nodular pulmonary disorders.

In the present two cases, the radiological findings of both patients are similar to those reported in the literature, with bilateral randomly distributed pulmonary nodules, some of which showed calcification. Both

patients had mediastinal lymphadenopathy, with some lymph nodes in the second patient showing central calcification.

Microscopically, PHG lesions are composed of a concentric dense network of hyalinised collagen that is centred in the perivascular lymphoplasmacytic infiltrate located in the centre of PHG lesions.[3,6,8–10,12,16]

The prognosis for patients with PHG is generally excellent. On follow-up, PHG shows a variable course with some nodules changing size and some remaining stable. Multiple lesions usually show a more rapid growth rate compared to single lesions.[3,12]

There is no definitive treatment for PHG. Although radiological and symptomatic improvement or even successful resolution of the nodules with the administration of glucocorticoids has been reported, the effect of corticosteroids remains unclear.[3,5] Surgical resection in patients with a solitary PHG nodule has been reported as a cure.[3,4,12] The current two patients received oral prednisolone; however, the nodules remained stable in size on follow-up chest CT scan.

Conclusion

PHG is a rare fibrosclerosing inflammatory pulmonary disease that can mimic other nodular pulmonary disorders such as neoplastic and granulomatous processes; therefore, it should be included in the differential diagnosis of pulmonary nodules or masses. Few reported cases of PGH in the literature developed extra-pulmonary malignancy on follow-up, however, this was the case for both current patients. There is a possible association between PHG and the future development of malignancy, which needs to be further explored and should warrant close follow-up of patients with proven PHG.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

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