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Necrotising Sarcoid Granulomatosis with Rares Localisations: Skin, Nose and Lung

Nadir Lokalizasyonlu Nekrotizan Sarkoid Granülomatoz: Deri, Burun ve Akciğerler

Lamiyae Senhaji, Mariem Karhate Andaloussi, Bouchra Amara, Mounia Serraj

Abstract

Necrotizing sarcoid granulomatosis (NSG) is a rare disease with non-specific clinical symptoms that may be confused with other conditions, leading potentially to delayed diagnosis. It is characterized histopathologically by sarcoid-like granulomas, vasculitis and varying degrees of necrosis. We present here the case of a 52-year-old male who presented with NSG in rare locations (the skin and nose), discussing not only the clinical, radiological and histopathological features of this rare disease, but also the treatment and prognosis.

Keywords: *Necrotizing sarcoid granulomatosis (NSG), skin, nose, lung.*

Öz

Nekrotizan sarkoid granülomatozis (NSG), nonspesifik klinik semptomlarından dolayı fazlaca ayırıcı tanı veya tanının gecikmesine yol açan nadir bir hastalıktır. Histopatolojik olarak sarkoid benzeri granülomlar, vaskülit ve değişken derecelerde nekroz ile karakterizedir. Nadir görülen NSG lokalizasyonları (deri ve burun) ile başvuran 52 yaşında bir erkek hastayı bildiriyoruz ve bu nadir hastalığın klinik, radyolojik ve histopatolojik özelliklerinin yanı sıra tedavi ve prognozunu da bu yazıda tartışacağız.

Anahtar Kelimeler: *Nekrotizan sarkoid granülomatozis, deri, burun, akciğer.*

Department of Pulmonology, University Hospital Center Hassan II, Fez, Morocco; Faculty of Medicine, Pharmacy and Dentistry of Fez, Sidi Mohamed Ben Abdellah University, Fez, Morocco

Göğüs Hastalıkları Bölümü, Üniversite Hastane Merkezi Hasan II, Fez, Fas; Fez Tıp, Eczacılık ve Diş Hekimliği Fakültesi, Sidi Mohamed Ben Abdellah Üniversitesi, Fes, Fas

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Correspondence (İletişim): Lamiyae Senhaji, Department of Pulmonology, University Hospital Center Hassan II, Fez, Morocco; Faculty of Medicine, Pharmacy and Dentistry of Fez, Sidi Mohamed Ben Abdellah University, Fez, Morocco

e-mail: lamiyae.senhaji@usmba.ac.ma

Granulomatous lung diseases have been broadly studied by pathologists, while NSG has attracted less attention among both pathologists and pneumologists. The histopathology pattern is between sarcoidosis and Wegener disease, while clinical and radiological features are non-specific. The present study investigates this little-known pathology, presenting the case of a patient diagnosed with NSG who developed rare extra-pulmonary symptoms.

CASE

A 52-year-old male with a history of pulmonary tuberculosis in 1999 and lymph node tuberculosis in 2018 (histology: granulomatosis without caseous necrosis) presented in 2019 with symptoms that had emerged 6 years earlier, including dyspnea and dry cough, and facial lesions that had appeared 2 months ago. A physical exam revealed crackles on auscultation and erythematous plaque on the face.

Thoracic CT revealed consolidation in the right Fowler segment and multiple bilateral nodules of different diameters that were associated with pleural effusion and mediastinal lymphadenopathy.

A pleural puncture revealed exudate and 2 biopsies carrying out an inflammatory charge without granuloma or caseous necrosis. The biopsy culture and Xpert MTB were both negative.

The endobronchial appearance was found to be normal on bronchoscopy, and the tracheobronchial secretions sent for bacterial and fungal analysis produced negative results. The patient underwent bronchoalveolar lavage, and the fluid was found to be paucicellular and to have a mixed cell population.

A biopsy of the skin lesions revealed a histological appearance suggestive of necrotizing and granulomatous vasculitis, compatible with Wegener disease.

A lesion in the nasal mucosa and perforation of the nasal septum was identified during an ENT examination, and the subsequent biopsy revealed necrotizing vasculitis with granulomatous lesions but an absence of caseating necrosis, suggestive of Wegener disease. The case was ANCA negative.

No treatment was started, and the patient was subsequently lost to follow-up, but presented again in 2023 due to the worsening of his dyspnea.

At the thoracic level, multiple perihilar consolidations crossed by air bronchograms (Figure 1) were identified, associated with multiple nodules and micronodules in the subpleural and peribronchovascular arrangement (Figure 2) associated with calcified mediastinal adenomegaly (Figure 3), a bilateral pleural effusion of moderate abundance and low abundance pericardial effusion, along with Celio mesenteric adenomegaly at the abdominal level. Bronchoscopy and subsequent biopsies revealed granulomatosis with epithelial cells, but with neither giant cells nor caseous necrosis. The pleural liquid was transudative, and an ENT exam revealed the continued existence of the nasal septum perforation. A pulmonary function test revealed low FVC at 1.54 L (36%).

Cranial, cervical, thoracic and abdominal CT scans revealed mucosal thickening in the left maxillary sinus at the facia cervical level associated with the mucosal filling of the left ethmoidal cells and the left sphenoidal hemisinus without adjacent bone lysis (Figure 4).

Echocardiography revealed a medium pericardial effusion with no signs of constriction, while the results of a cardiac MRI were normal.

A laboratory exam revealed all ANA (-), soluble antigen (-), ANCA (-), rheumatoid factor and all bacterial and mucosal specimen findings to be negative.

The case was discussed at a multidisciplinary meeting, and after ruling out a diagnosis of tuberculosis, sarcoidosis and Wegener disease, the patient was diagnosed with necrotizing sarcoid granulomatosis with systemic localizations in the lung (consolidations and nodules on CT), bronchi (biopsy on bronchoscopy revealing a granulomatosis without caseous necrosis), pleura (exudative pleural effusion), heart (pericardial effusion), ENT (perforation to the nasal septum at the ENT examen with a CT showing mucosal thickening in the left maxillary sinus associated with mucosal filling of the left ethmoidal cells and the left sphenoidal hemisinus), lymph nodes (mediastinal lymphadenopathy and celio mesenteric adenomegaly) and skin (rheumatous plaque with a biopsy revealing necrotizing and granulomatous vasculitis). The patient started corticotherapy at a dose of 1mg/kg/day (60mg/day) for 6 weeks, after which degression was begun. During follow-up, the patient improved clinically (he is now asymptomatic and has gained 9 kg in weight), radiologically (disappearance of the pleural effusion, but persistence of the right paracardiac consolidation) and functionally (increased FVC, from 1.54 L before treatment to 2.08 L). The patient's follow-up is continuing due to the risk of relapse.

DISCUSSION

Granulomatous pulmonary conditions can develop alongside many diseases, and while they are most commonly associated with infectious diseases (tuberculosis, fungal diseases) and sarcoidosis, they may also develop alongside such other conditions as hypersensitivity pneumonitis, berylliosis, vasculitic granulomatous disease (GEP, GEPA), rheumatoid polyarthritis, bronchocentric granulomatosis, immunodeficiency (CVID, cancer), iatrogenic (foreign body, drugs) and, of course, necrotizing sarcoid granulomatosis (NSG) (1,2).

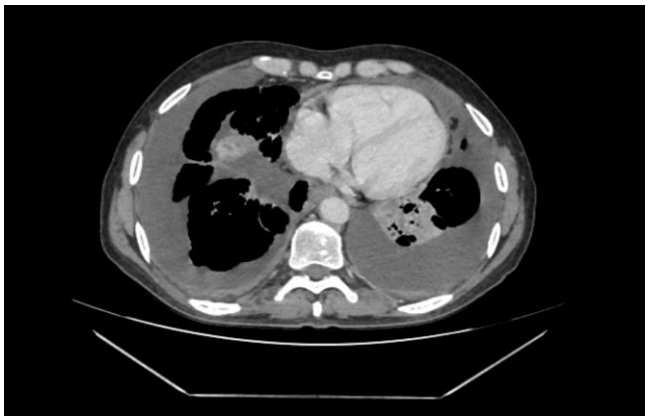

Figure 1: Thoracic CT, mediastinal section showing a moderately large bilateral pleural effusion with perihilar condensation focus

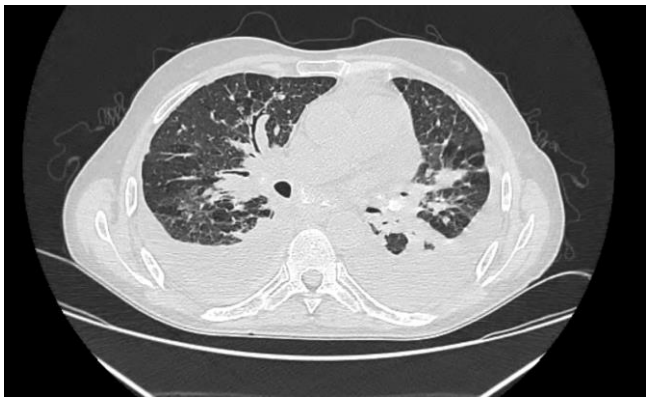

Figure 2: Thoracic CT, parenchymal section of multiple pulmonary nodules and micronodules

NSG was first described by Liebow in 1973 in a study detailing 11 young adults who were presented with respiratory symptoms, all of whom were identified with nodular lesions by a CT scan and histological findings of granulomas, necrosis and vasculitis. He described three criteria for the diagnosis of the condition:

1. Histologically, a background of sarcoid-like granulomatous with marked granulomatous angiitis and varying degrees of necrosis,
2. Radiologically, multiple pulmonary nodules or ill-defined infiltrates but no enlarged hilar nodes, and
3. Clinically, symptoms of cough, fever, sweat, malaise, dyspnea and pleuritic pain, suggest a possible underlying infection but with minimal physical signs (3).

Today, however, there is considerable polemic questioning whether NSG is a disease in its own right, or merely a form of sarcoidosis, specifically a developed form of nodular sarcoidosis (NS). Those who concur with this train of thought claim that there is a degree of overlap between NSG and NS in clinical, radiological and also histopathological terms, as both present with pulmonary and systemic symptoms, as well as nodules, masses, cavitations and pleural effusion among their radiological features. Histopathology, necrosis occurs in classical sarcoidosis, with incidences of 6–35% reported in different studies. The necrosis is minute, spotty and involves a small central portion of granulomas. Granulomatous vasculitis is common in cases of sarcoidosis, and can involve arteries, veins or both. Many studies to date confirm it with reported incidences in the range of 42–69% (4). Therefore, some authors favor the term "sarcoidosis with NSG pattern" over NSG (4,5).

The etiology and pathogenesis of the condition remain unclear, although some authors suggest that certain infections and post-infection immune disorders are involved in the pathogenesis of NSG. Huang et al. (6) reported a reduced peripheral blood CD4/CD8 T cell ratio and increased lesion ratio indicating that the cells migrate from the blood to the organs, especially the lungs due to their large blood content, leading to their more frequent involvement, more frequent disorders and the subsequent formation of granulomas and vasculitis (3,6).

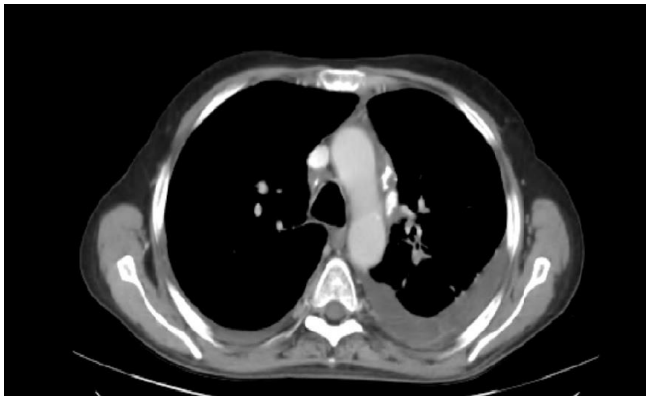

Figure 3: Thoracic CT, mediastinal section showing mediastinal lymphadenopathy

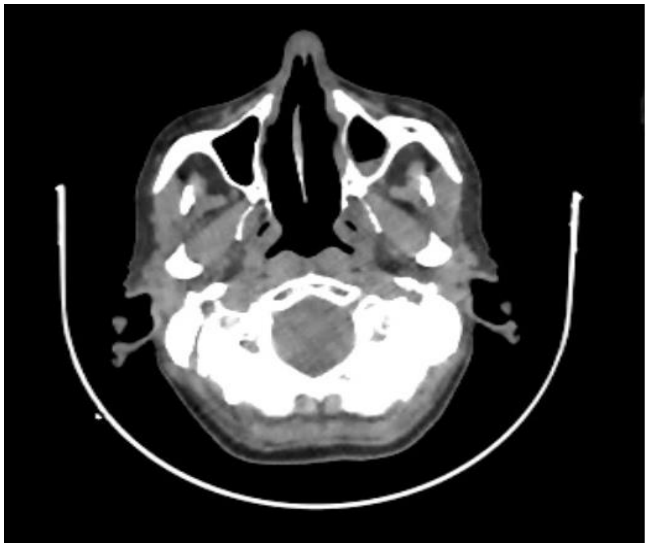

Figure 4: Cervical facia CT showing mucosal thickening in the left maxillary sinus with filling of the left ethmoidal cells, but without adjacent bone lysis

A 2016 metanalysis by Karpathiou et al. (7) including all cases of NSG reported in the English language over the last 43 years (130 reported cases) revealed a median age of 42 years (range 8–68) at the time of diagnosis, a predominance among females (62%), and presentations with cough, dyspnea, fever, chest pain or weight loss. In a case presented by Huang et al. (6), hemoptysis was the main symptom. In other cases, the patients have been asymptomatic, with the discovery of a mass in the lung leading to an investigation, resulting in the NSG diagnosis. The condition may also be associated with such extrapulmonary manifestations as skin erythema nodosum, uveitis and central nervous system (CNS) involvement. Liver, stomach, kidney, heart, nose and spleen involvement are rarely reported (8,9). The case described herein presented with pulmonary symptoms, as well as skin and nose involvement, and actually lymphadenopathy because of the misdiagnosis of lymph node tuberculosis even if the histopathology didn't show caseous necrosis. This fact has been reported in several studies in which patients were started on TB treatment but were subsequently reassessed due to a lack of response, and diagnosed with NSG (10). Our patient underwent antibacillary treatment with clinical stabilization for 1 year.

Radiographic imaging (CT scan) revealed multiple nodules with peribronchial and subpleural distributions in the mid or lower lung fields, while other radiographical manifestations included solitary nodules or masses mimicking lung tumors, leading to an FD/ PET scan in some cases and a surgical biopsy to confirm the diagnosis (5,11,12). Diffuse infiltrates, cavitations, some mediastinal lymphadenopathy (less than sarcoidosis), and pleural effusion or diffuse pleural thickening may also be seen in some cases (13). The pulmonary lesions match our patients'. Our patient also had lesions in the sinus, which are a very rare manifestation.

NSG is diagnosed based on the identification of histopathologically confirmed non-caseating epithelial cell granulomas, granulomatous vasculitis and necrosis. Diagnosis can be difficult in small specimens and mostly requires a surgical biopsy, or assessment of a surgically removed mass. That said, culture, bacteriological and mucosal tests should be carried out to exclude differential diagnoses, especially infections, as well as laboratory exams to eliminate vasculitis granulomatosis diseases, autoimmune diseases, DCIV and other possible candidates (ANA, ANCA, RF, dosage of immunoglobulin) (14). Several specimens showing granulomatous and necrotizing vasculitis were identified in the presented case, while infections in the bronchoalveolar lavage and vasculitis granulomatosis and autoimmune diseases were excluded based on the patient's ANA and ANCA negativity.

The pulmonary function test results reported in several studies include reports of normal pulmonary function, while others mention obstructive–restrictive ventilation deficits, commonly restrictive ventilatory deficits, and frequently, reduced DLCO. All of these conditions improve with treatment. Our patient had a restrictive ventilatory defect that improved after 6 weeks of corticotherapy.

NSG is a disease that can resolve with or without treatment (8). Patients are usually started on corticotherapy at a dose of 1mg per kg per day for an average of 6 months, and usually have a very good response within 2 to 4 weeks. Relapses have been reported upon dose reduction, spurring increased doses or the addition of immunosuppressors such as methotrexate to the protocol to counter the reduction (13). Immunosuppressants may also be needed in some systemic forms of the condition, or in cases that do not respond to corticotherapy. Such situations have been described in a few cases in literature (pulmonary NSG, ocular or neural location) in which the adjunction of cyclophosphamids or similar therapies was required to improve symptoms or to allow a reduction in corticotherapy doses. One described case required cerebral radiation (9). Our patient responded very well to the corticotherapy, but a long follow-up is needed to confirm full resolution or to identify any relapses.

In general, the prognosis of patients with NSG is favorable, and the patient in the present study was no exception. Patients can get better with or without any treatment, although a few may develop complications and die. Studies have reported a poor prognosis, especially in cases with an extended follow-up. A multicentric follow-up study assessing patients followed up for 18–114 months reported the death of one patient due to central nervous system infection, two patients due to lung cancer and four patients due to relapse (6). Other reported deaths are attributed to pneumonia or hemoptysis (9). As such, long-term follow-up is recommended, with further examinations whenever a new pulmonary consolidation, nodule or cavitation appears along with a worsening of symptoms, along with a biopsy (14).

CONCLUSION

NSG is a rare disease that is usually benign but may sometimes have a mortal course. Many organs can be involved, and several features are shared with sarcoidosis. More data-driven studies are required in the future to provide a better understanding of etiology and the associated risk factors for recurrence.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - L.S., M.K.A., B.A., M.S.; Planning and Design - L.S., M.K.A., B.A., M.S.; Supervision - L.S., M.K.A., B.A.,

M.S.; Funding - L.S., M.S.; Materials - L.S., M.S.; Data Collection and/or Processing - L.S.; Analysis and/or Interpretation - L.S., M.S.; Literature Review - L.S.; Writing - L.S.; Critical Review - L.S., M.K.A., B.A., M.S.

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