Case report

Successful corticosteroid treatment of necrotizing sarcoid granulomatosis associated with tracheal lesion recurred after a surgical lung biopsy

Go Makimoto a,*, Keita Kawakado a, Masamoto Nakaniishi a, Tomoki Tamura a, Yumiko Sato b, Shoichi Kuyama a

a Department of Respiratory Medicine, National Hospital Organization Iwakuni Clinical Center, 1-1-1 Atago-machi, Iwakuni-City, Yamaguchi, 740-8510, Japan
b Department of Pathology, National Hospital Organization Iwakuni Clinical Center, 1-1-1 Atago-machi, Iwakuni-City, Yamaguchi, 740-8510, Japan

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ABSTRACT

Necrotizing sarcoid granulomatosis (NSG) is a rare disease that presents with nodular lung lesions and necrosis. The pathology is consistent with sarcoidosis, but the necrosis can lead to a diagnosis of tuberculosis. Herein, we report a rare case of NSG that recurred four years after the initial diagnosis was made by surgical lung biopsy. A 51-year-old woman was initially referred to our hospital for the evaluation of multiple lung nodules. The pathological evaluation of a lung biopsy showed granulomas with necrosis and the infiltration of lymphocytes; thus, she was diagnosed with NSG. The lung nodules gradually improved after the diagnosis and we continued to follow her even though she did not require treatment. Four years after her initial diagnosis, she complained of back pain. Upon evaluation, we found that multiple lung nodules had recurred. Bronchoscopy also revealed a tracheal polypoid lesion, which showed granulomas with necrosis pathologically. Therefore, we diagnosed her with the recurrence of NSG. After the corticosteroid therapy, multiple lung nodules drastically improved. NSG patients should be carefully followed-up over several years, even if they do not require treatment.

1. Introduction

Necrotizing sarcoid granulomatosis (NSG) was first reported by Liebow in 1973 [1]. NSG is a rare disease characterized by sarcoidosis-like granulomas and vasculitis with necrosis [2]. To date, approximately 200 cases have been reported in the world [3–5]. The clinical presentations of NSG include pulmonary symptoms, such as cough, dyspnea, chest pain, and extrapulmonary symptoms, such as general fatigue, fever, and weight loss [2,3]. There has not been any report of a tracheal lesion with NSG.

The pathogenesis of NSG has not been fully elucidated. Some reports hypothesize that NSG is a subtype of sarcoidosis with vascular inflammation [6–8]. Churg et al. reviewed 12 NSG cases and concluded that the clinical characteristics of NSG are not similar to that of other angiocentric granulomatosis. They also suggested that NSG could be the complement of nodular sarcoids [6]. On the other hand, some reports have suggested that NSG is independent of sarcoidosis. Chittock et al. reviewed seven cases of NSG and concluded that NSG is distinguishable from sarcoidosis as a clinicopathologic entity, and that pleural involvement is a frequent finding [9].

Previous reports have found that the prognosis of NSG is generally good [2,3]. Most NSG patients respond to corticosteroid therapy [2,10], and some patients have recovered naturally without corticosteroid treatment [2,4]. On the other hand, several patients have been reported to have relapsed several years after the first episode [2,11]. Researchers have not identified predictive factors or markers associated with the relapse of NSG.

We herein report a case of NSG that recurred four years after the initial diagnosis with multiple nodular shadows of the lung and a tracheal lesion, which responded corticosteroid treatment.

2. Case report

A 51-year-old woman presented at another hospital four years ago with complaints of fever and back pain. A chest computed tomography (CT) image showed multiple nodular shadows (Fig. 1A), so she was referred to our hospital for further evaluation. She had no history of asthma, had never smoked, and had no significant family history.
Fig. 1. Computed tomography images of the multiple lung nodules of necrotizing sarcoid granulomatosis. The first episode of NSG (A), 4 years after the surgical lung biopsy at the time of regular follow-up (B), the second episode of NSG 3 weeks after the regular follow-up (C) and 3 months after the corticosteroid treatment (D).
Although she had a low-grade fever, her physical examination, including chest auscultation, was normal. Her laboratory findings were as shown in Table 1 (left column), which included no significant elevation of tumor markers. We performed lung biopsies of the left upper lobe using video-assisted thoracic surgery. The histological evaluation of the lung specimen showed the infiltration of lymphocytes and granulomas with necrosis (Fig. 2A). There were no findings suggesting mycosis or acid-fast bacillus infection, and the specimen was negative for M. tuberculosis PCR. Therefore, we diagnosed her with NSG. Subsequently, the multiple nodular shadows, and her fever and back pain, gradually improved. We continued to follow her even though she did not require treatment.

Four years after her initial diagnosis, she came to our hospital for regular follow-up without any symptoms and abnormal chest CT shadows (Fig. 1B). Three weeks after that, she complained of acute back pain and high fever (＞38 °C) for a few days. She returned to our hospital for further evaluation. Her body temperature was 38.0 °C. There were no remarkable findings on a physical examination, including chest auscultation or skin lesions. Her laboratory findings were as shown in Table 1 (right column). Although the antinuclear antibody was elevated, antihistidyl-tRNA synthetase antibody; RNP, anti-ribonucleoprotein antibody; Scl-70, anti-scleroderma-70 antibody; Jo-1, anti-histidyl tRNA synthetase antibody; PR3-ANCA, proteinase-3-anti-neutrophil cytoplasmic antibodies; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibodies; s-IL2R, soluble interleukin-2 receptor; Ag, antigen; QFT, QuantiFERON; CEA, carcinoembryonic antigen; CYFRA, cytokeratin 19 Fragment; ProGRP, pro-gastrin-releasing peptide.

Both chest radiography and CT showed multiple nodular shadows in both the lung fields. These shadows consisted of irregular margins and a hypovascular central area, which suggested necrosis (Fig. 1C), although there was no cavity formation. The sputum culture revealed no significant bacteria, including acid-fast bacilli. A Gallium-67 scan image demonstrated the increased uptake in the multiple lung nodules (Fig. 3A). A bronchoscopy was performed for further diagnosis. Transbronchial biopsy of nodular shadow revealed the infiltration of lymphocytes and macrophages in the alveoli. Samples of bronchoalveolar lavage fluid showed an elevated lymphocyte proportion (31.3%), and CD4/CD8 ratio was within the normal limit (3.19).

The bronchoscopy revealed a small nodular lesion in the trachea (Fig. 3B). The biopsy sample of this lesion revealed infiltration of lymphocytes and granulomas with necrosis (Fig. 2B), which was similar to the surgical lung biopsy obtained four years ago. The specimen was also negative for M. tuberculosis PCR. Therefore, we diagnosed her with the recurrence of NSG.

As her back pain, high fever, and chest radiography worsened, we initiated corticosteroid therapy with oral prednisolone 40 mg/day. Her symptoms dramatically improved within a week, and the multiple nodular shadows in both lung fields resolved almost completely after three months (Fig. 1D). Oral prednisolone was gradually decreased to 15

| Table 1 | Laboratory data on the first (left) and the second (right) episode. |

| Peripheral blood | Peripheral blood |
|------------------|------------------|
| WBC 5600 /μL | WBC 7000 /μL |
| Ne 58.4 % | Ne 71.5 % |
| Ly 28.3 % | Ly 15.2 % |
| Mo 10.1 % | Mo 9.7 % |
| Eo 2.8 % | Eo 3.3 % |
| Ba 0.4 % | Ba 0.3 % |
| RBC 414 *10^6/μL | RBC 445 *10^6/μL |
| Hb 12.4 g/dL | Hb 13.5 g/dL |
| Plt 26.5 *10^9/μL | Plt 32.7 *10^9/μL |

| Serology | Serology |
|---------|---------|
| CRP 0.13 mg/dL | CRP 1.88 mg/dL |
| ACE 10.6 IU/L | ACE 8.0 IU/L |
| KL-6 176 IU/ml | Lysozyme 7.4 IU/ml |
| IgG 1291 mg/dL | KL-6 153 mg/dL |
| IgE <10 IU/L | IgE 1146 IU/ml |
| ANA ≥1280 | IgG 63 |
| SS-A – | ≥1280 |
| SS-B – | – |
| RNP – | SS-B – |
| ScI-70 – | RNP – |
| Jo-1 – | ScI-70 – |
| Centromere 183 | Jo-1 – |
| PR3-ANCA <1.0 | Centromere 173 |
| MPO-ANCA <1.0 | PR3-ANCA <1.0 |
| s-IL2R 771 IU/ml | MPO-ANCA <1.0 |
| Aspergillus Ag 0.2 | s-IL2R 806 |
| Cryptococcus Ag – | Aspergillus Ag 0.0 |
| QFT – | Cryptococcus Ag – |
| Tumor marker | Tumor marker |
| CEA 1.5 ng/ml | CEA 1.5 ng/ml |
| CYFRA 1.2 mg/ml | CYFRA 1.2 mg/ml |
| ProGRP 62 pg/ml | ProGRP 62 pg/ml |

Abbreviations: WBC, white blood cells; Ne, neutrophils; Ly, lymphocytes; Mo, monocytes; Eo, eosinophils; Ba, basophils; RBC, red blood cells; Hb, hemoglobin; Plt, platelets; CRP, C-reactive protein; ACE, angiotensin-converting enzyme; KL-6, Krebs von den Lungen-6; IgG, immunoglobulin G; IgE, immunoglobulin E; ANA, antinuclear antibodies; SS-A, anti-Sjogren’s-syndrome-related antigen A; SS-B, anti-Sjogren’s-syndrome-related antigen B; RNP, anti-ribonucleoprotein antibody; ScI-70, anti-scleroderma-70 antibody; Jo-1, anti-histidyl tRNA synthetase antibody; PR3-ANCA, proteinase-3-anti-neutrophil cytoplasmic antibodies; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibodies; s-IL2R, soluble interleukin-2 receptor; Ag, antigen; QFT, QuantiFERON; CEA, carcinoembryonic antigen; CYFRA, cytokeratin 19 Fragment; ProGRP, pro-gastrin-releasing peptide.
mg/day over three months without any recurrence.

3. Discussion

We report a rare case of NSG that recurred four years after the first episode accompanied with tracheal nodular lesion. This case is rare for two reasons: first, a recurrence of NSG after four years has not been reported, and second, the manifestation of a tracheal nodular lesion of NSG is novel.

Relative to sarcoidosis, NSG is a relatively rare disease with approximately 200 cases reported in the literature [5]. The clinical presentation of NSG includes pulmonary and/or systemic symptoms (i.e., fever, weight loss, night sweats, malaise). Several organs have been reported to be involved, including eye, skin, lymph node, liver, spleen, and lacrimal gland [5]. Although a few sarcoidosis cases have been reported with tracheal polypoid lesions [12,13], there have been no reports of NSG accompanied by tracheal lesions.

Very few reports describe the recurrence of NSG. However, Quaden et al. discuss recurrence in their review of 14 patients with NSG [2]. In this report, the mean follow-up time was 54.6 months (range 18–114), and four patients recurred after the first diagnosis and treatment. Recurrent cases all underwent initial treatment (corticosteroid therapy or surgical resection), and the mean interval between the first treatment and relapse was 32 months (range 24–43 months). Out of the four recurrent cases, two cases occurred after the first surgical resection. Both cases spontaneously improved without treatment. No predictive factors of relapse, such as biological, radiological, or functional markers, have been found.

The current case presented with systemic symptoms of high fever and back pain. We found granulomas with necrosis in both the surgical biopsies at initial diagnosis and the transbronchial biopsy at the recurrence. The NSG recurred more than four years after the first episode and did not improve spontaneously. We treated the patient with corticosteroid therapy with satisfactory results.

The current case also showed high titer of antinuclear antibody and anti-centromere antibody. On the clinical course, however, she showed no significant signs of scleroderma. Therefore, she did not meet the diagnostic criteria for systemic sclerosis. Although there have been no previous reports discussing about the association between NSG and autoimmune disease, Judson M.A. et al. reported about the concomitant sarcoidosis and a connective tissue disease [14]. In this report, out of the total 68 patients with diagnoses of both sarcoidosis and autoimmune disease, systemic sclerosis was the most common autoimmune disease (29/68). Therefore, NSG may also have some association with autoimmune diseases such as systemic sclerosis. Further studies are needed to analyze this association.

In conclusion, we are reporting a case of NSG, associated with a tracheal lesion, which recurred after a surgical lung biopsy. NSG generally has an excellent response to corticosteroid treatment, but exceptionally severe neural involvement leading to death has also been reported [2]. A more data-driven basis for understanding the etiology, such as risk factors of recurrence or severe outcome, is needed in the future. In the meantime, we recommend the careful follow up of NSG patients for an extended period, even if they had full resolution after the first treatment.
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Declaration of competing interest

The authors declare no conflicts of interest.

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Fig. 3. (A) Gallium-67 scan image before corticosteroid therapy demonstrated the increased uptake in the multiple lung nodules. (B) Endobronchial nodule of necrotizing sarcoid granulomatosis.