MÆDICA - a Journal of Clinical Medicine

CASE REPORT

MAEDICA – a Journal of Clinical Medicine
2022; 17(4): 990-994
https://doi.org/10.26574/maedica.2022.17.4.990

# Eosinophilic Pneumonia with Marked Peripheral Eosinophilia during the Course of Sarcoidosis

Shinichiro OKAUCHI[a], Gen OHARA[a], Yuika SASATANI[a], Hiroaki SATOH[a]

[a]Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, Mito-city, Japan

**ABSTRACT**

*Patients with sarcoidosis are known to have peripheral blood eosinophilia (PBE). However, most of them had PBE slightly above the upper limit of the normal range. Few patients had increased eosinophils in the bronchoalveolar lavage fluid (BALF), and eosinophilia in BALF enough to be diagnosed as eosinophilic pneumonia (EP) was extremely rare. We present herein a sarcoidosis case with PBE. There were fluctuations in peripheral eosinophils consistent with sarcoidosis disease activity, and peripheral blood eosinophils increased up to 50%, 12500/mm$^3$, although the patient was affected by cough variant asthma and multimodal therapies for breast cancer. Some case reports showed EP in patients with sarcoidosis. To our best knowledge, however, no sarcoidosis patient presented with such a high level of PBE. In this report, we would like to emphasize that there might be patients with sarcoidosis who have a marked increase in peripheral blood eosinophils.*

**Keywords**: sarcoidosis, peripheral blood eosinophilia, eosinophilic pneumonia.

## INTRODUCTION

Sarcoidosis is a systemic inflammatory granulomatous disorder of unknown etiology, commonly involving lymph nodes, lungs, spleen, skin, eyes and parotid glands. Although the precise mechanism is still unknown, sarcoidosis might be directly associated with peripheral blood eosinophilia (PBE) in some patients (1-3). That is, PBE in patients with sarcoidosis might not always indicate coexisting allergic diseases (1-3). Evaluation of bronchoalveolar lavage fluid (BALF) is often performed when diagnosing sarcoidosis, and increases in number and percentage of eosinophils in BALF have been reported (4-10). Patients with sarcoidosis usually do not have eosinophilia in BALF. Diagnosis of eosinophilic pneumonia (EP) is established by an increased proportion of eosinophils in the BALF (11, 12), but eosinophilia is usually absent in the BALF of patients with sarcoidosis. As far as we could research, there have been only four sarcoidosis patients with eosinophilic pneumonia (7-10). Of these, three were

*Address for correspondence:*
*Hiroaki Satoh, MD, PhD*
*Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, Miya-machi 3-2-7, Mito-city, Ibaraki, 310-0015, Japan*
*Tel: +81-29-231-2371; fax: +81-29-221-5137; email: hirosato@md.tsukuba.ac.jp*

*Article received on the 22nd of August 2022 si acceptat la publicare on the 7th of December 2022*

patients who were diagnosed with sarcoidosis and EP at the same time (7-9), and one patient developed EP 32 years after the diagnosis of sarcoidosis (10).

Here we report an interesting case of sarcoidosis who developed EP one year later the diagnosis of sarcoidosis with increased PBE up to 52%, 19300/mm$^3$. To our knowledge, this sarcoidosis patient is the first one with such an extreme increase in PBE. ❑

## CASE REPORT

A 68-year-old woman was referred to our hospital due to bilateral hilar and mediastinal lymphadenopathy with ground glass opacities (GGOs) in both upper lobe of the lung (Figure 1-A and -B). She was diagnosed with cough variant asthma one year before, which had been well controlled with inhalation corticosteroid/long-acting beta-2 agonist (ICS/LABA). She had never traveled to areas with a high prevalence of parasites. The patient had never been abroad. The patient had no abdominal pain, no weight loss or fever. The liver and spleen were not palpable, and the patient had no sensory impairment or paralysis. Neither skin eruption nor ulceration was found. Laboratory data revealed increases in peripheral eosinophil counts (34.0%, 2414/mm$^3$), total serum IgE levels: 509.3 IU/L (normal: 0-295), serum angiotensin converting enzyme activity: 33.5 IU/L (normal: 8.3-21.5), and soluble interleukin-2 receptor: 3932 U/mL (normal: 0-459). Stool examination was negative. Bronchoalveolar lavage fluid results were as follows: total cell counts 1.7 × 105/mm$^3$, macrophages 52%, eosinophils 16%, and lymphocytes 32%, with a high CD4/8 ratio (26.2), and no evidence of microbial culture. Transbronchial lung biopsy (TBLB) revealed non-caseous granulomatous tissue containing multinucleated giant cells. In the TBLB specimen, only a small number of eosinophils were found. Based on these findings, she was diagnosed as having sarcoidosis. She was asymptomatic, and was not received prednisolone (PSL). A chest computed tomography (CT) scan, which was taken one month after the diagnosis of sarcoidosis, confirmed the disappearance of the ground-glass opacities and the shrinkage of the mediastinum and bilateral hilar lymph nodes (Figure 1-C). Peripheral blood eosinophilia normalized after two months. During the examination at this admission, bilateral breast cancer was discovered, and preoperative chemotherapy, resection, and postoperative irradiation were performed. One year later, a bronchoscopy was performed once again due to the appearance of infiltrative opacities in the upper lobes of both lungs on chest CT scan (Figure 1-D). Bronchoalveolar lavage fluid results were as follows: total cell counts 2.7×105/mm$^3$, macrophages 22%, eosinophils 61%, and lymphocytes 15%. We diagnosed EP developed during the clinical course of sarcoidosis. This time, we administered PSL, 20 mg daily. The opacities were promptly reduced and the increased peripheral eosinophils returned to normal, and bilateral hilar and mediastinal lymph nodes had shrunk. PSL was tapered over two years and one month, and administration was terminated. At the termination of PSL therapy, PBE had already reappeared, and re-enlargement of the mediastinal and bilateral hilar lymph nodes was confirmed. Peripheral blood eosinophilia increased up to 50%, 12500 /mm$^3$ appeared four months after the end of PSL administration. Prednisolone 30 mg was administered again. BHL and PBE disappeared within a month. There were no asthma attacks. During the clinical course, no sign and symptom suggestive of hypereosinophilic syndrome developed. Bone marrow aspiration and

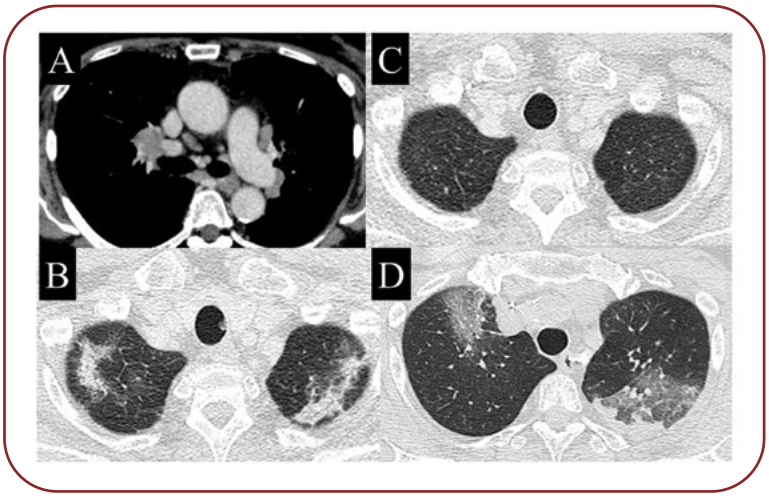


**FIGURE 1.** Chest CT scan at the first presentation revealed bilateral hilar and mediastinal lymphadenopathy (A) with ground glass opacities (GGOs) in both upper lobe of the lung (B); CT one month after the first admission showed disappearance of ground glass opacities (C); appearance of infiltrative opacities in the upper lobes of both lungs was found on the chest CT scan one year after the first visit (D)

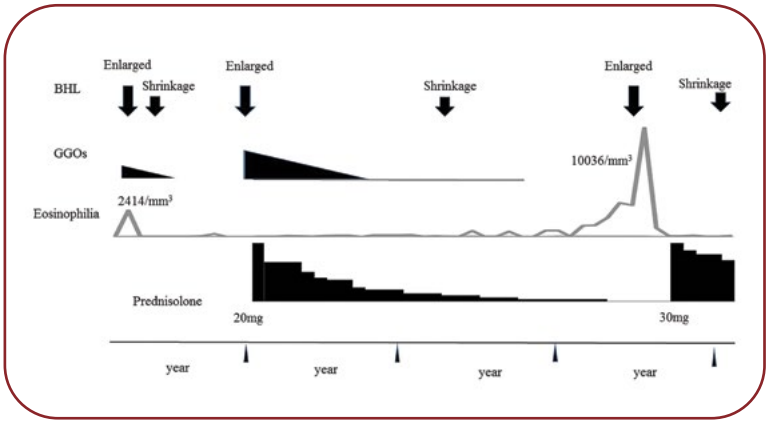


**FIGURE 1.** Clinical course of the patient. BHL: bilateral hilar lymphadenopathy, GGOs: ground glass opacities

genetic testing could not be performed because the patient did not want to do. PSL has gradually reduced to 10 mg daily. Seven months have passed since the re-exacerbation, but the patient is fine. Clinical course was shown in Figure 2. ❑

## DISCUSSION

Peripheral blood eosinophilia is defined as an increase in the number of eosinophils above the normal values observed in healthy individuals (3, 13). In the Guide of the British Hematology Society it is explained that patients with sarcoidosis can have mild PBE (1). The frequency of PBE in sarcoidosis has been reported to vary and could reach up to 25% (1). In a study of Renston *et al* on sarcoidosis patients, the PBE frequency was found to be 41% of them when the threshold value was 4% (3). In a study by Takahashi *et al* investigating 178 sarcoidosis patients, the frequency of PBE to be 35.4% when the PBE threshold value (>4%) was used (10). They explained that the presence of PBE was not only associated with the accompanying allergic disease (*e.g.*, asthma, allergic rhinitis) (10). Several researchers indicated that PBE could be directly associated with sarcoidosis (1, 3, 10). Other diseases associated with PBE include parasitic diseases, hematological disorders, non-hematological tumors, and bronchial asthma. Fecal worm egg test was negative in this patient. Bone marrow aspiration could not be performed due to the patient's refusal, but there were no abnormal blood findings other than eosinophils for over three years. This patient was found to have a complication of breast cancer. However, changes in breast cancers and PBE were inconsistent. Among patients with sarcoidosis, 15-19% were reported to have bronchial asthma (14, 15). In our patient, peripheral eosinophils at the time of diagnosis of sarcoidosis were 34%, 2414/mm$^3$, and maximum peripheral eosinophils increased up to 50%, 12500/mm$^3$, which was returned to normal with prednisolone. The possible involvement of cough variant asthma in PBE in this patient could not be ruled out. However, cough variant asthma in this patient was controlled by ICS/LABA inhalation. There was no concordance between PBE and condition of cough variant asthma in this patient and she had no major asthma attack during the clinical course. Considering the clinical course (Figure 2), the progression of sarcoidosis and PBE appeared to be linked, and it was determined that these two conditions were related.

Although PBE is not uncommon in sarcoidosis patients, there are few reports of EP development in sarcoidosis patients (7-10). The diagnosis of EP is based on eosinophilia in the BAL rather than peripheral blood (11, 12). To our best knowledge, only four patients with sarcoidosis developed EP (7-10). With regard to the onset of EP in this patient, there might be three possibilities. Chest CT at the time of diagnosis of sarcoidosis pointed out GGOs along the pleura in both upper lobes, which disappeared without any specific treatment. This is the first possible time for PE onset. However, increase of eosinophils >25% was not confirmed in BALF performed at the time of diagnosis of sarcoidosis. Breast cancer was also discovered at the same time as the diagnosis of sarcoidosis, and the patient received multimodal treatment. Irradiation was also included in the treatment. Although it was out of the irradiation field, it was considered that radiation was involved in the onset of EP, and EP developed at this time. This was the second possibility. Patients who have actually developed EP even outside the irradiation field after breast cancer radiotherapy have been reported (16), and the mechanism of onset of EP is also of interest. A third possible time of onset was the re-exacerbation of mediastinal and bilateral hilar lymphadenopathy and the appearance of GGOs one year after the diagnosis of sarcoidosis. Although she had no PBE, she had undergone treatments for breast cancer, including chemotherapy, so it was possible that PBE never appeared. Regarding the time of EP onset, the

**TABLE 4.** Maximum peripheral blood eosinophilia and eosinophils in the bronchalveolar lavage fluid in sarcoidosis patients with eosinophilic pneumonia

| Authors | Maximum peripheral blood eosinophilia (%) | BALF, total cell, eosinophil (%) | Reference No. |
|---|---|---|---|
| Tani *et al* | 663/mm$^3$, 13% | 5.5 x 10$^5$/mL, not described | 7 |
| Shijubo *et al* | 891/mm$^3$, 11% | 19.6 x 10$^5$/mL, 94.2% | 8 |
| Nakano *et al* | 980/mm$^3$, 14% | 13.8 x 10$^5$/mL, 24.9% | 9 |
| Takahashi *et al* | 869/mm$^3$, 10% | Not described, 15.2% | 10 |
| Present study | 19300/mm$^3$, 52% | First time: 17.0 × 10$^5$/mL, 15.0% | |
| | | Second time: 27.0 × 10$^5$/mL, 61.0% | |

BALF: bronchoalveolar lavage fluid

third possibility was evaluated to be the most plausible.

Table 1 shows the characteristics of our patient and the four patients with EP reported previously. Three patients were diagnosed with sarcoidosis and EP at the same time. As observed in our patient, only one patient reported by Takahashi *et al* developed EP more than many years after the diagnosis of sarcoidosis (17). Interestingly, they reported a case of sarcoidosis with a concomitant increase in PBE and BALF (17). In our patient, BALF was obtained twice, but increase of eosinophils was only observed at the second time of BAL. Five patients in Table 1, including ours, received moderate doses of corticosteroids. EP improved rapidly in all patients. The mechanism for the increase in eosinophils in BALF in patients with sarcoidosis is unknown. Tani *et al* (7) and Shijubo *et al* (8) measured several cytokines in BALF and showed the possibility of the relationship between EP and increasing cytokines. Tani *et al* (7) and Shijubo *et al* (8) measured several cytokines in BALF and showed the possibility of the relationship between EP and increasing cytokines. There also were case reports inferring the relationship between sarcoidosis and EP from the clinical course (7, 17). In these patients, changes in BHL, changes in PBE, and response to PSL of them were consistent, indicating a clear association between sarcoidosis and PBE activity. Further evidence needs to be gathered to clarify the link between the activities of these two pathological conditions. ❑

## CONCLUSION

Patients with sarcoidosis might develop EP during the clinical course. Some of them could have a very high proportion of PBE. Peripheral eosinophilia might fluctuate with sarcoidosis disease. ❑

*Ethical statement: This study was approved by the institutional ethics committee of our institute (NO22-04). Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.*

*Conflicts of interest: none declared.*

*Financial support: none declared.*

*Authors' contributions: SO and HS designed the study. SO, GO, YS and HS collected the data. SO and HS analyzed the data and prepared the manuscript. All authors approved the final version of the article.*

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