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Case Report

Clarithromycin-induced eosinophilic granulomatosis with polyangiitis: A case report

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ABSTRACT

A 75-year-old man presented to our hospital with chronic sinusitis, bronchiectasis, and chronic lower respiratory tract infections. He began taking erythromycin in August, X-2. The chronic lower respiratory tract infection gradually worsened, and clarithromycin was started on May 11, X. He became aware of fever and numbness in his lower legs on June 4, X. The sign occurred soon after oral clarithromycin and blood tests showed an elevated eosinophil count and C-reactive protein (CRP) levels, positive MPO-ANCA antibodies, and positive for drug-induced lymphocyte stimulation test (DLST); we diagnosed eosinophilic granulomatosis with polyangiitis (EGPA) associated with clarithromycin administration.

1. Introduction

Eosinophilic Granulomatosis with Polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is characterized by chronic sinusitis, bronchial asthma, and marked eosinophilia. Microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) belong to the class of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, whereas only approximately 30% of cases are ANCA-positive [1]. Compared to ANCA-negative patients, ANCA-positive cases have more vasculitis symptoms, such as peripheral neuropathy, renal impairment, mucous membrane, eye, ear, nose, and pharyngeal lesions, and less cardiomyopathy [2]. Several drugs (leukotrienes, inhaled steroids, omalizumab, cocaine, and some macrolide antibiotics) have been reported to be associated with the development of EGPA [3–7]. However, no reports of clarithromycin-induced EGPA exist. Herein, we report a case of EGPA induced by oral clarithromycin.

2. Case presentation

In August X-2, a 75-year-old man was referred to our hospital because of abnormal chest computed tomography (CT) imaging, which showed lobular central granular shadows and bronchial wall thickening in the bilateral lower lobes (Fig. 1A).

Respiratory function tests showed mixed impairment with Forced Expiratory Volume % in 1 s (FEV1%) of 58% and Vital Capacity as percent of predicted (%VC) of 65.9%. The flow volume curve was convex downward, and obstructive disease was suspected. At this point, the exhaled nitric oxide (NO) level was below the sensitivity level. Nasal endoscopy revealed no obvious eosinophilic sinusitis; however, sinus CT showed soft shadows in both maxillary sinuses and the anterior ethmoidal sinus, raising suspicion of chronic sinusitis (Fig. 1B). Sputum cytology performed on July X-1 showed no predominant increase in eosinophils, with an eosinophil ratio of

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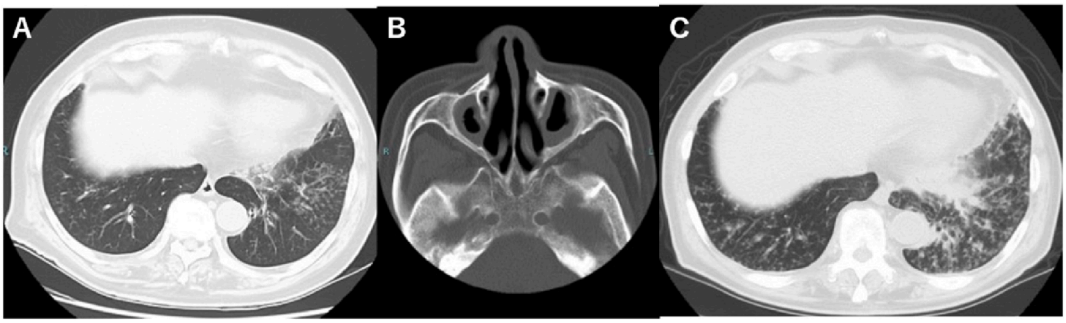

Fig. 1. A: August, X-2, chest CT scan showed lobular central granular shadows and bilateral bronchial wall thickening in the lower lobes.
B: July, X-1, sinus CT showed soft shadows in both maxillary sinuses and anterior ethmoidal sinuses, raising the suspicion of chronic sinusitis.
C: February, X, bilateral granular shadows worsened slightly on CT imaging.
CT, computed tomography.

2%. Because the patient had no asthma attacks or symptoms, eosinophilic inflammation was not observed, inhaled steroids were not initiated, and the patient was followed only with erythromycin (400 mg). Subsequently, the bilateral granular shadows worsened slightly on CT imaging (Fig. 1C). A sputum culture test confirmed the presence of *Pseudomonas aeruginosa*. Considering that the chronic lower respiratory tract infection was poorly controlled, erythromycin was discontinued, and clarithromycin 400 mg tablets were started on May 11, X. On May 2, X, just before the start of the treatment, a blood sample showed a white blood cell count of 12190/μL, eosinophils 0.9% 109.7/μL, C-reactive protein (CRP) 2 mg/dL, and a mild inflammatory reaction due to chronic lower respiratory tract infection was observed, whereas eosinophils were not elevated. On June 4, he developed a fever, leg edema, and numbness in his lower extremities. On June 14, the patient visited our hospital, and respiratory symptoms remained the same. However, he had bilateral leg edema and numbness in both lower extremities. Blood samples showed markedly elevated eosinophils and an inflammatory reaction with leukocytes 24060/μL, eosinophils 43% 10345/μL, and CRP 11.1 mg/dL. He stopped taking clarithromycin, although his symptoms did not improve on June 21. Blood samples showed a white blood cell count of 28150/μL, eosinophils 53% 14919/μL, CRP 12.6 mg/dL, and MPO-ANCA positive (423 IU) (Table 1).

5/2, the eosinophil count did not increase immediately before starting oral clarithromycin. 6/14 After the initiation of oral clarithromycin, markedly elevated eosinophil levels and an elevated inflammatory response were observed. 6/21 No decrease in eosinophil count or inflammatory response was observed after the discontinuation of clarithromycin. Blood samples were positive for MPO-ANCA. 7/19–9/20 After starting prednisone, his inflammatory response and eosinophil count decreased, and ANCA levels tended to decline.

WBC, white blood count; CRP, C-reactive protein; MPO-ANCA, On June 21, he was started on oral prednisone (30 mg). An additional close examination revealed a gait disturbance due to decreased tactile sensation and hyperalgesia, and marked loss of bathyesthesia in his lower extremities. Nerve conduction studies (NCS) showed decreased compound muscle action potential, and motor nerve conduction velocity in the posterior tibial, peroneal, and sural nerves were not evoked potentials. These neurological findings and the abnormalities found in the NCS were compatible with mononeuritis multiplex. He had a gait disturbance that appeared to be caused by neuropathy. The patient was diagnosed with EGPA after scoring 12 points on the ACR2022 classification criteria [8]. As no eosinophils or eosinophilic airway inflammation were seen before the start of clarithromycin, we suspected clarithromycin-induced EGPA because of the rapid onset of symptoms after the start of clarithromycin. Subsequently, a drug-induced lymphocyte stimulation test (DLST) was performed, which confirmed a positive result for clarithromycin with a stimulation index of 189% as in Japan, the index of 180% or higher is considered positive. Following this result, we suspected that the patient was allergic to clarithromycin. Clarithromycin was not administered again due to the possibility of recurrence.

After starting prednisone, his fever resolved, his general condition improved, his inflammatory response and eosinophils decreased, and ANCA levels tended to decrease (Table 1). His neuropathy persisted; a 300 mg subcutaneous injection of mepolizumab was added on July 26, X. However, the neurological symptoms persisted; therefore, on October 4, X, intravenous immunoglobulin

Table 1
Changes in parameters: WBC, eosinophil count, CRP, and MPO-ANCA.

X-year/month/date	5/2	6/14	6/21	7/19	8/23	9/20
Laboratory data.						
WBC(/μL)	12190	24060	28150	16650	13700	12530
Eosinophil fractionation(%)	0.9	43	53	7.5	0.1	0.2
Eosinophil count(/μL)	109	10345	14919	1248	13	25
CRP(mg/dL)	2.1	11.2	12.6	4.8	1.2	1.1
MPOANCA(IU)			423	172	26.7	16.4
Treatment and dosage						
Prednisone (mg)			30	30	20	15
Mepolizumab (mg/month)					300	300

(IVIG) was added on October 4, X, and the neurological symptoms started to improve. Currently, prednisone is tapered on an outpatient basis. No change was observed in the lung lesions following treatment for EGPA.

Written informed consent was obtained from the patient to publish this case report.

3. Discussion

This case demonstrated that oral clarithromycin induces EGPA. Few cases of macrolide-induced EGPA have been reported to date, with only two caused by azithromycin and roxithromycin [6,7]. In one case, a patient with a history of atopy developed arthralgia, fever, rash, and dysesthesia five days after azithromycin administration, with increased peripheral blood eosinophil counts [6]. Another patient with a history of asthma was admitted to the hospital 14 days after receiving roxithromycin for fever and myalgia with increased peripheral blood eosinophil counts and polyneuritis [7]. The patient had a history of EGPA caused by macrolide antibacterial agents, as similar symptoms appeared when he had taken azithromycin one year earlier. Both patients had MPO-ANCA-negative EGPA, and polyneuritis was observed, requiring steroid therapy and drug discontinuation. However, the neurological deficits persisted for a long time after treatment.

EGPA typically develops in three stages. The prodrome (bronchial asthma or sinusitis) typically lasts 8–10 years, with an eosinophilic phase, and a vasculitis phase [9]. Using the Safety Surveillance Database, Martin et al. reported that the prevalence of EGPA per million person-years was 6.8 person-years in the general population and 1.8 person-years in non-asthmatic patients compared to 64.4 person-years in asthmatic patients [10]. Therefore, EGPA is considered an asthma-related disease. The patient's respiratory status was stable, and no obvious asthma complications were seen. We considered clarithromycin-induced EGPA for the following three reasons. 1st, no previous reports on clarithromycin-induced EGPA exist; however, reported to be induced by macrolide antibacterial agents. The acute onset of EGPA within a short period after oral administration of other macrolides is similar to that of clarithromycin. 2nd, Eosinophilic inflammation, which was absent before the start of treatment, was induced soon after clarithromycin administration. 3rd, Although the symptoms were too severe to re-initiate treatment, the positive DLST of clarithromycin in the blood sample led us to believe that the patient had clarithromycin-induced EGPA. There have been no reports of DLST or EGPA. DLST has more than 85% specificity for drug allergies and may be helpful when performed based on a thorough medical history [11].

Interleukin-5 (IL-5) plays an important role in the pathogenesis of EGPA [12]. It is important to investigate the impact of clarithromycin on IL-5 production in lymphocytes, rather than only assessing lymphocyte proliferation through DLST. While lymphocyte activation, as assessed by DLST, may contribute to the development of EGPA, it is not sufficient to induce EGPA. No reports of DLST in macrolide-induced EGPA exist, and it may be effective when re-administration is considered risky, as in this case, and further findings are warranted.

MPO-ANCA positivity is expected in drug-induced vasculitis [13]. A positive MPO-ANCA result was observed in this case. Furthermore, whether the positive result was induced by drug administration is unclear because the patient had no vasculitis symptoms before the onset of symptoms, and MPO-ANCA was not measured. In EGPA, ANCA-positive cases have more vasculitis symptoms, such as peripheral neuropathy; renal dysfunction; mucosal, ocular, and otorhinolaryngological lesions; and less cardiomyopathy than negative cases. This case was also consistent with the usual MPO-ANCA-positive EGPA in that peripheral neuropathy was mainly prominent.

In this case, EGPA was induced with oral clarithromycin. Therefore, we believe that clarithromycin-induced EGPA should be considered even in patients without asthma or eosinophilic inflammation.

4. Conclusion

- EGPA was induced by oral clarithromycin.
- DLST may be useful in diagnosing drug-induced EGPA.

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Consent

Written informed consent was obtained from the patient for the publication of this case report.

Data statement

Needed data can be made available on request.

Author contributions and authorship

Yoshio Nakano: conceptualization, methodology, data curation, writing- original draft preparation. Daisuke Sekinada: visualization, investigation. Gen Masuda: writing-reviewing and editing. Chihiro Nishio: supervision. Koji Nishida:supervision. Norio Okamoto: supervision. Gohma Iwao: supervision. Yoshiki Esa: diagnosis of neurology.

Declaration of competing interest

None.

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