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【 CASE REPORT 】

Clopidogrel-induced Eosinophilia with Hypercalcemia

Kazuhiro Yamada, Kazuhisa Asai, Misaki Yanagimoto, Risa Sone, Satsuki Inazu, Ryo Mizutani, Hideaki Kadotani, Tetsuya Watanabe, Yoshihiro Tochino and Tomoya Kawaguchi

Abstract:
There are few cases describing the association of eosinophilia with hypercalcemia, and drug-induced eosinophilia with hypercalcemia has not been reported. A 74-year-old man had been diagnosed with asthma 4 months earlier. He was admitted due to eosinophilia with hypercalcemia. Chest computed tomography showed a nodule in the left lung and mediastinal lymphadenopathy. By obtaining a detailed medical history, clopidogrel was suspected as the prime cause of eosinophilia. After the discontinuation of clopidogrel, the eosinophilia with hypercalcemia, lung nodule and mediastinal lymphadenopathy improved. Clopidogrel-induced eosinophilia can potentially cause hypercalcemia. Obtaining a detailed clinical history is important in diagnosing the cause of eosinophilia.

Key words: clopidogrel, eosinophilia, drug-induced eosinophilia, hypercalcemia

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Introduction

Eosinophilia is defined as a peripheral blood eosinophil count greater than 500 cells/μL. The causes of eosinophilia are numerous and include neoplasms, drugs, and infectious diseases, among others (1). Eosinophilia can affect all organs in the body, including the heart, digestive tract, lungs, nerves, skin, and kidneys. Eosinophilia can affect a single organ, as in eosinophilic pneumonias or eosinophilic esophagitis, or multiple organ systems simultaneously (2). Few reports have described the association of eosinophilia with hypercalcemia, and drug-induced eosinophilia with hypercalcemia has not been reported.

We herein report a case of clopidogrel-induced eosinophilia with hypercalcemia. Obtaining a detailed clinical history is important when determining the cause of eosinophilia.

Case Report

A 74-year-old man had been diagnosed with asthma 4 months earlier at a previous hospital. Despite treatment with inhaled corticosteroids and bronchodilators, his cough had not improved. He was admitted due to eosinophilia (1,188 cells/μL) and hypercalcemia (serum-corrected calcium 17.4 mg/dL) 13 days before transfer to our hospital. Saline and furosemide were given to decrease the calcium level. Chest computed tomography (CT) showed a nodule in the left lung, mediastinal lymphadenopathy, right pleural effusion, and bilateral lower lung infiltrates (Fig. 1). Eosinophilia with hypercalcemia caused by lung cancer was suspected, so he was referred to our hospital.

He was an ex-smoker (15 pack-years) with no known exposure to raw food. His medical history included myocardial infarction. He reported that he had not taken any new prescribed medications recently. On auscultation, there were no rales. He had erythema with blisters over the left upper limb and left lower limb. His white blood cell and eosinophilic counts were increased (31,200 cells/μL and 21,840 cells/μL). His serum alkaline phosphatase (ALP), bone alkaline phosphatase, and pro-gastrin-releasing peptide (ProGRP) levels were increased (1,469 U/L, 61.6 μg/L and 106.9 pg/mL, respectively). However, his serum carcinoembryonic antigen (CEA) and cytokeratin-19 fragment (CYFRA) values were within normal ranges (3.1 ng/mL and 2.2 ng/mL, respec-

Department of Respiratory Medicine, Osaka Metropolitan University Graduate School of Medicine, Japan
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Correspondence to Dr. Kazuhisa Asai, kazuasai@omu.ac.jp

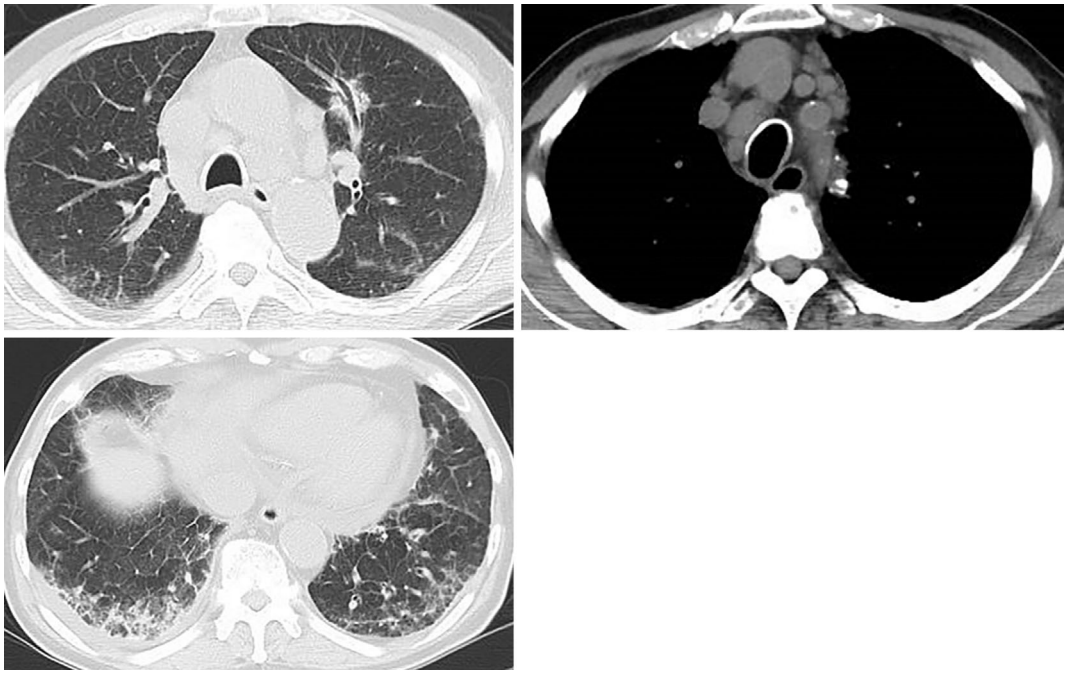

Figure 1. **Chest computed tomography shows a nodule in the left lung, mediastinal lymphadenopathy, right pleural effusion, and bilateral lower lung infiltrates.**

Table. **Results of Laboratory Investigations.**

Variables	Results	Normal reference range
White blood cells	31,200	4,300-8,000 /μL
Eosinophil	21,840	/μL
Neutrophil	3,744	/μL
Lymphocyte	1,872	/μL
Hemoglobin	9.7	12.4-17.2 g/dL
Platelets	1.9×10^5	18.0-34.0 /μL
CRP	1.24	0-0.40 mg/dL
Cre	2.88	0.50-1.10 mg/dL
Serum-corrected calcium	11.7	8.8-10.1 mg/dL
ALP	1,469	106-322 U/L
BAP	61.6	3.7-20.9 μg/L
T-bil	0.2	0.2-1.0 mg/dL
γ-GTP	13	13-64 U/L
$1,25(OH)_2$VitD	12	20-60 pg/mL
PTH-intact	25	10-65 pg/mL
PTHrP	<1.1	<1.1 pg/mL
ACTH	44.3	7.2-63.3 pg/mL
Cortisol	10.9	3.7-19.4 μg/dL
Parasite antibodies	Negative	
Ova and parasite test	Negative	
CEA	3.1	0.0-5.0 ng/mL
CYFRA	2.2	0.0-3.5 ng/mL
ProGRP	106.9	<81 pg/mL

CRP: C-reactive protein, Cre: creatinine, ALP: alkaline phosphatase, BAP: bone alkaline phosphatase, T-bil: total billirubins, γ-GTP: γ-glutamyl transpeptidase, $1,25(OH)_2$VitD: 1,25-dihydroxyvitamin D3, PTH-intact: parathyroid hormone-intact, PTHrP: parathormone-related peptide, ACTH: adrenocorticotropic hormone, CEA: carcinoembryonic antigen, CYFRA: cytokeratin-19 fragment, ProGRP: pro-gastrin-releasing peptide

tively), as were $1,25(OH)_2$VitD, intact PTH, and PTHrP (12 pg/mL, 25 pg/mL, and <1.1 pg/mL, respectively) (Table). The left upper limb blister was punctured, and the eosinophil percentage was high (59%). The right pleural effusion was punctured and showed no malignancy, but the eosinophil percentage was also high (59.5%). ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)-CT showed an intense abnormal FDG uptake in a nodule in the left lung, in the enlarged mediastinal lymph nodes, in the left scapula, and in the left acetabulum (Fig. 2).

To make a definite diagnosis, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed. A lymph node of station 4R was punctured, and bronchoalveolar lavage was performed in right B5; the recovery rate was 35%. A transbronchial lung biopsy for the nodule in the left lung was not performed due to the patient's limited tolerance. The lymph node tissue was insufficient to confirm the lymph node structure, but substantial eosinophil infiltration was noted. The cytological findings did not indicate malignancy, and the percentage of eosinophils in the bronchoalveolar lavage fluid was 68%. To rule out a leukemic process, a bone marrow biopsy was also performed at the right ilium, which showed no malignancy, no chromosomal abnormalities, and numerous eosinophils and plasma cells. During an investigation for cancer, a detailed medical history was obtained, and it was determined that cilostazol and aspirin had been switched to clopidogrel six months earlier for post-myocardial infarction treatment, after which he had developed the asthma-like symptoms. Clopidogrel was thus suspected as the cause of the eosinophilia and was discontinued.

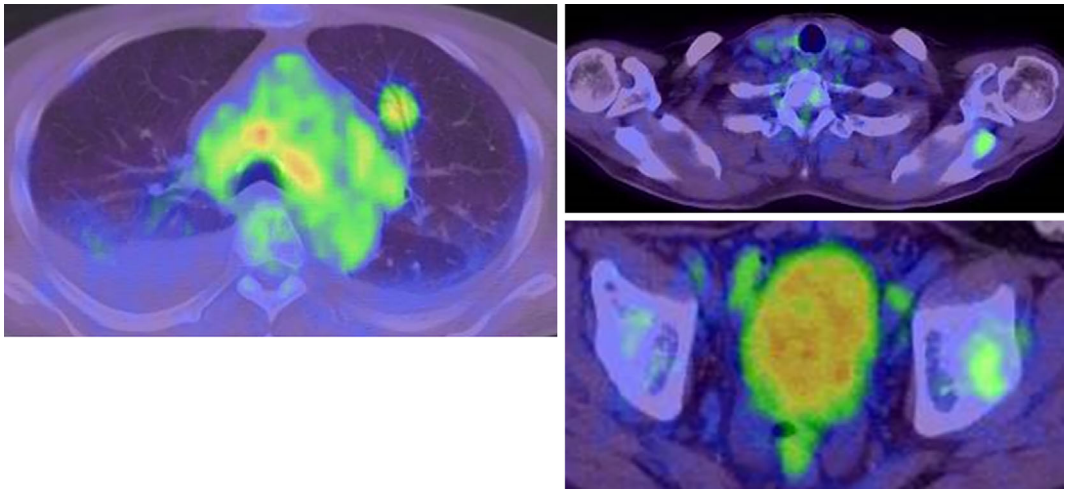

Figure 2. **^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography shows an intense abnormal ^{18}F-fluorodeoxyglucose uptake in a nodule in the left lung, in the enlarged mediastinal lymph nodes, in the left scapula, and in the left acetabulum (standardized uptake values: 4.8, 9.5, 3.4, and 3.4, respectively).**

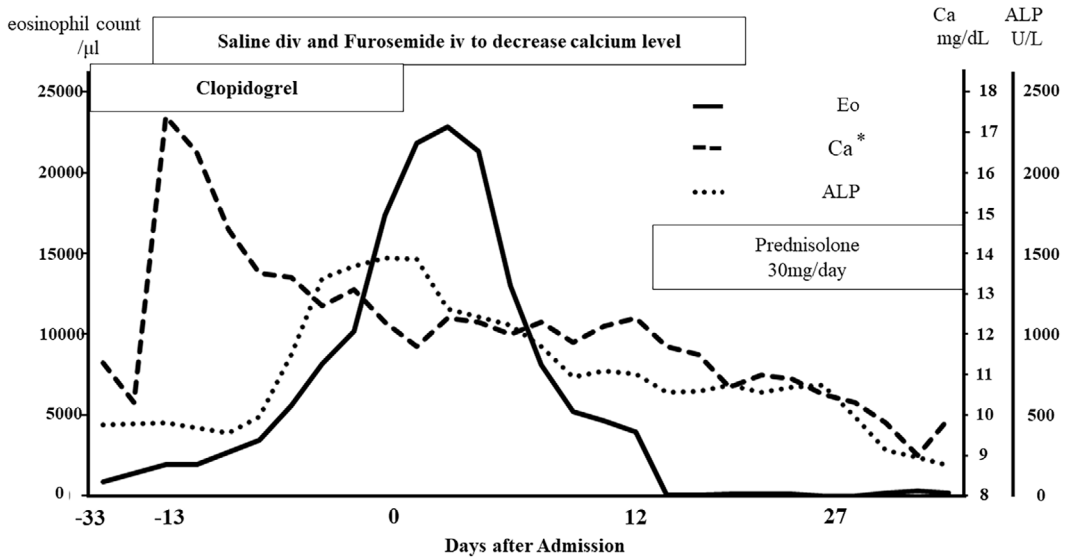

Figure 3. **The patient's clinical course. After the discontinuation of clopidogrel, the eosinophil count and ALP level decrease. After stopping the administration of saline and furosemide, the serum-corrected calcium level does not increase. *: serum-corrected calcium**

After the discontinuation of clopidogrel, his cough and erythema with blisters disappeared. His eosinophil count, serum-corrected calcium, and ALP levels also decreased rapidly. A drug-induced lymphocyte stimulation test for clopidogrel was positive, and he was diagnosed with clopidogrel-induced eosinophilia with hypercalcemia.

To accelerate his improvement, prednisolone was prescribed on admission day 13 (Fig. 3). One month after the discontinuation of clopidogrel, the ALP had decreased from 1,469 to 281 U/L, and serum-corrected calcium remained within the normal range without the administration of saline and furosemide. Chest CT showed that the size of the nodule and mediastinal lymphadenopathy had decreased, and the right pleural effusion and bilateral lower lung infiltrates had also improved (Fig. 4).

Discussion

In this case, two important clinical issues were identified: clopidogrel-induced eosinophilia can cause hypercalcemia, and obtaining a clinical history is important in diagnosing the cause of eosinophilia.

First, clopidogrel-induced eosinophilia can cause hypercalcemia. Eosinophilia can affect any organ in the body. The most common presenting manifestation of hypereosinophilic syndrome in a previous study was dermatologic (37%), followed by pulmonary (25%) and gastrointestinal (14%). Under 5% of patients had cardiac manifestations (3). Eosinophilia does not commonly occur with hypercalcemia, being quite rare. To our knowledge, three such cases have been re-

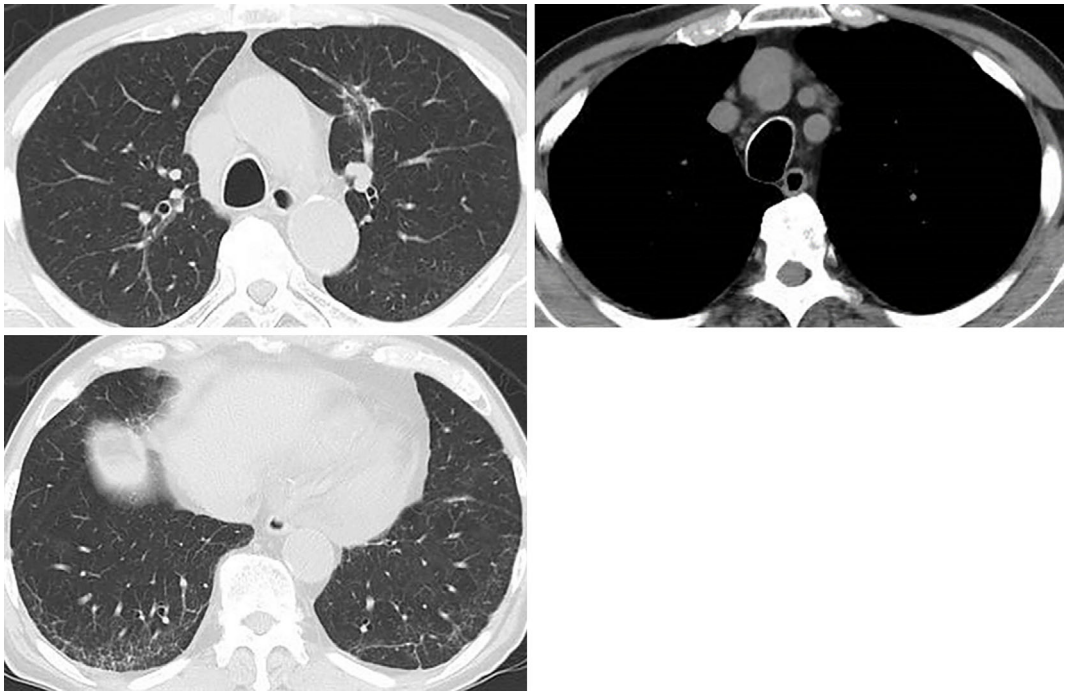

Figure 4. One month after the discontinuation of clopidogrel, chest computed tomography shows that the size of the nodule in the left lung and the mediastinal lymphadenopathy are decreased, and the right pleural effusion and bilateral lower lung infiltrates are improved.

ported: hypereosinophilic syndrome, eosinophilic fasciitis, and eosinophilic myocarditis (4-6). With respect to P2Y12 inhibitors, including clopidogrel, many cases of hypersensitivity reactions have been reported (7), but none have included eosinophilia and hypercalcemia. To our knowledge, this is the first case report of clopidogrel-induced eosinophilia with hypercalcemia.

Second, obtaining a clinical history is important in diagnosing the cause of eosinophilia, as the potential causes are numerous, including neoplasms, drugs, infectious diseases, etc. (1). While lung cancer is rarely associated with eosinophilia (8, 9), it is often associated with hypercalcemia (10). In the present case, lung cancer was initially suspected as the cause of the eosinophilia with hypercalcemia. When making a diagnosis, the clinical history often provides the most important clue for discovering the cause of eosinophilia (11). A clinician confronted with a patient presenting with eosinophilia must determine whether or not the eosinophilia is secondary to a common and treatable underlying condition, such as parasitic infections or adverse drug reactions (12). In this case, although eosinophilia with hypercalcemia was rare and lung cancer was suspected as the cause, by obtaining a detailed medical history, the cause of eosinophilia with hypercalcemia was diagnosed correctly. Without the detailed medical history, EBUS-TBNA or a transbronchial biopsy would have been unnecessarily performed repeatedly in an attempt to detect lung cancer.

The mechanism underlying the development of eosinophilia with hypercalcemia in the present case was unclear. After the discontinuation of clopidogrel, the patient's condition rapidly improved. He refused invasive examinations for a bone biopsy at the left scapula or left acetabulum. However, in this case, the serum-corrected calcium and ALP values improved along with the eosinophil count. Given the eosinophil infiltration into the lung, pleural effusion, and lymph nodes, we speculated that eosinophils had also infiltrated the bone tissue and caused hypercalcemia. CCL11 is a chemokine within the CC subfamily that is produced by a variety of cell types (13); CCL11 binds to the chemokine receptor CCR3, which is expressed in eosinophils (14). By interacting with CCR3, CCL11 stimulates the migration of eosinophils (15). In bone tissue, osteoblasts express CCL11, and osteoclasts express CCR3 (16). In the present case, as a possible mechanism, bone tissue might have recruited eosinophils in the peripheral blood. The eosinophilic infiltration into bone tissue and inflammation might have caused the hypercalcemia, as the FDG uptake showed.

Conclusion

Clopidogrel-induced eosinophilia can cause hypercalcemia, and obtaining a clinical history is important when determining the cause of eosinophilia. We must be aware that eosinophilia can occur with hypercalcemia and that drugs should be suspected as a potential cause. Further reports are needed to determine how often eosinophilia is associated with hypercalcemia and to clarify the mechanism underlying the involvement of eosinophilia with hypercalcemia, including pathological findings.

The authors state that they have no Conflict of Interest (COI).

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