Clopidogrel-induced Acute Interstitial Pneumonitis: a Case Report

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Case report

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Abstract

Background In patients with cerebral infarction resulting from intracranial arterial stenosis, combined administration of clopidogrel and aspirin may be needed for the thereafter ischemic attack. Clopidogrel has an inevitable adverse effect profile, and the most common complications are related to hemorrhagic propensity.

Case presentation A 79-year-old female patient had taken aspirin (100mg/d) for old cerebral infarction, and started taking the dual antiplatelet drug consisted of aspirin and clopidogrel (75mg/d) due to severe stenosis on both anterior cerebral arteries. Two weeks later, the patient presented dyspnea started 3 days ago, which had been worsened the last 24 h. Chest computed tomography on admission showed symmetric peribronchial ground glass opacity with reticulation in both lungs. Microorganism tests, including serology and bronchoalveolar lavage for infection, were all negative. Suspecting clopidogrel-induced acute interstitial pneumonitis, we withdrew clopidogrel and initiated steroid treatment. The patient's clinical signs and chest radiographs improved after steroid treatment, and she was discharged on the 21st day of hospitalization.

Conclusions Clopidogrel can induce acute interstitial pneumonitis as a rare complication. The present report shows the importance of recognizing this rare adverse effect of clopidogrel in clinical practice.

Background

Clopidogrel is a drug in wide use for secondary prevention of atherothrombotic complications in patients with myocardial infarction and ischemic stroke[1]. It inhibits platelet aggregation, thus increases the bleeding time and reduces blood viscosity by inhibiting adenosin diphosphate (ADP) action on platelet receptors[2]. In addition, it has an inevitable adverse effect similar to other anti-platelet agents, such as ticlopidine or aspirin. The most common adverse effect is increased risk of gastro-intestinal bleeding[3, 4]. However, clopidogrel has not been known to induce interstitial lung disease. Here, we report the rare adverse effect of clopidogrel-induced interstitial pneumonitis in a patient with cerebral infarction resulting from intracranial arterial stenosis.

Case Presentation

A 79-year-old female patient with prior cerebral infarction on the left basal ganglia admitted for an unveiled unruptured aneurysm on the right superior cerebellar artery (SCA), which was found on magnetic resonance imaging (MRI). She had taken an aspirin (100 mg/d) and atorvastatin (40 mg/d) since the occurrence of cerebral infarction as well as amlodipine (5 mg/d) and telmisartan (40 mg/d) for hypertension and metformin (1700 mg/d) for type 2 diabetes mellitus. There was neither history of autoimmune-related disease nor abnormal allergic reactions in her past medical history. Also, she had never smoked in her life.

Cerebral angiography displayed a small SCA aneurysm that had a broad neck with a maximum diameter of 2.62 mm and a neck diameter of 2.73 mm. Besides, it revealed a considerably narrowed vasculature on both anterior cerebral arteries (ACA), which can lead to a large territory infarction. Because the unruptured SCA aneurysm was small and unlikely to rupture, it was determined to be followed with periodical brain imaging. For disclosed severe stenosis on the ACA, she started taking the dual antiplatelet drug consisted of aspirin (100 mg/d) and clopidogrel (75 mg/d).

Two weeks later, she was readmitted to the hospital due to dyspnea that started 3 days prior. She complained of anorexia, nausea, dyspnea on exertion, and chest pain. The patient did not complain of cough, sputum, rhinorrhea, or chills. At the time of admission, she was hypoxic (pulse oximetry, 91% on room air), and a chest x-ray revealed features of bilateral infiltration after comparison to a chest x-ray obtained at the previous hospitalization (Fig. 1A, 1B). The patient's initial vital signs were as follows: blood pressure, 136/66 mmHg; pulse rate, 78 beats/min; respiratory rate, 20 breaths/min; and body temperature, 36.7°C. The initial arterial blood gas analysis revealed pH 7.422, PaCO2 38.3 mmHg, PaO2 57 mmHg, SaO2 88.1% (2 L/min of oxygen with nasal prong), and laboratory tests showed the following: hemoglobin, 11.5 g/dL; white blood cell count, 7,410 cells/μL (neutrophils, 65.1%; lymphocytes, 24.3%; monocytes, 9.0%; eosinophils, 0.9%; and basophils, 0.7%); platelet count, 327,000 cells/μL; and C-reactive protein, 1.6mg/dL. The other serum biochemistry results were within normal limits as follow: aspartate aminotransferase, 19 IU/L; alanine aminotransferase, 5 IU/L; total bilirubin, 0.7 mg/dL; alkaline phosphatase, 59 IU/L; total protein, 7.0 g/dL; albumin, 3.5 g/dL; blood urea nitrogen, 7 mg/dL; and creatinine, 0.57 mg/dL. Congestive heart failure was excluded by normal ultrasound cardiography results and a normal level of serum brain natriuretic peptide.

Empirical antibiotics (piperacillin/tazobactam 4.5g every six hours plus levofloxacin 75mg every 24 hours) were started after bacterial cultures were obtained because bacterial pneumonia could not be ruled out on the chest x-rays. Enhanced chest computed tomography (CT) revealed symmetric peribronchial ground glass opacity (GGO) with reticulation in both lungs (Fig. 1C, 1D).

On the second day of hospitalization, the patient experienced a transient fever (37.8°C). In addition, oxygen saturation could not be maintained via nasal prong 5L/min, so we supplied oxygen via high flow nasal cannula (Flow 30L/min, FiO2 35%). On hospital day 4, bronchoalveolar lavage (BAL) was performed to rule out diffuse alveolar hemorrhage and atypical pneumonia. Bacterial polymerase chain reaction (PCR), viral PCR, *Cytomegalovirus* PCR, *Pneumocystis jirovecii* PCR, fungal culture, and acid-fast bacilli smear were performed with the BAL specimens. BAL revealed a clear color fluid, and no microorganisms were detected from any of the examinations. The patient's clinical symptoms continued to deteriorate.

One day after BAL (day 5) and after ruling out all other possible causes of her symptoms, we suspected clopidogrel-associated interstitial pneumonitis. We changed superpirin to aspirin and initiated treatment with 1mg/kg/day of intravenous methylprednisolone. The patient's clinical signs and chest x-ray improved after withdraw of clopidogrel and addition of steroid treatment (Fig. 2A). The patient was

discharged on the 21st day of hospitalization with oral prednisolone 25mg/day. The oral steroid was tapered over a period of 6 months in the outpatient setting. A follow-up chest x-ray taken 6 months after discontinuation of steroids showed no recurrence, and the patient is currently doing well in daily life (Fig. 2B).

Discussion And Conclusions

We report a case of acute interstitial pneumonitis (AIP) that occurred after administration of clopidogrel and showed features of interstitial pneumonia on chest CT. These manifestations resolved after withdrawal of the culprit drug and treatment with prednisolone.

Clopidogrel is indicated for secondary prevention of atherothrombotic events[2]. The most common adverse effect is increased risk of bleeding. Thus, uncommon cases of clopidogrel-induced acute lung injury were associated with diffuse alveolar hemorrhage[5]. In the study of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE), fewer patients (4.5%) reported dyspnea in the clopidogrel with aspirin group than in the placebo with aspirin group[4]. Some case reports about adverse respiratory effects related to clopidogrel reported non-cardiogenic pulmonary edema[6, 7]. However, our case showed a type of AIP on chest CT.

The global incidence of drug-induced interstitial lung disease (DILD) is not clearly known, but 2.5-3% are drug induced[8, 9]. Anti-cancer drugs were the leading cause of DILD in most studies, accounting for 23–51% of cases, followed by disease-modifying anti-rheumatic drugs, antibiotics, non-steroidal anti-inflammatory agents, psychiatric medications, and anti-arrhythmic agents[10]. Although cases of DILD induced by anti-platelet agents have been rarely reported, most of them were secondary to aspirin or ticlopidine. The mechanism of DILD remains unclear, but previous reports have explained it as an allergic reaction or stimulation of neutrophil function, rather than direct toxicity from chemicals[11, 12]. Since clopidogrel structurally resembles ticlopidine, which is another thienopyridine anti-platelet drug[13], the mechanism of action of clopidogrel may be identical to that of ticlopidine. The previous cases of ticlopidine-induced lung injury showed a type of bronchiolitis obliterans organizing pneumonia (BOOP), which has aggressive symptoms and a longer recovery time[14, 15]. Our case also had the pattern of cryptogenic organizing pneumonia (COP) similar to case of ticlodipine-induced interstitial lung disease. This is consistent with that clopidogrel caused comparable finding on chest CT because its structure and mechanism of action were similar to ticlodipine.

The clinical presentation and course of AIP are similar to those of ARDS. Therefore, AIP should be distinguished from ARDS by the absence of identifiable predisposing factor and systemic involvement, such as multiorgan failure[16]. A case study reported patients with ARDS after first-dosing of clopidogrel, and rapid improvement with clearance of clopidogrel[17]. The patient was underwent a right sub-temporal craniotomy for placement of two clips to the aneurysm, leaving a 4 mm residual aneurysm, and planned medication of clopidogrel. Within hours of first-time dosing of clopidogrel, patient presented a dyspnea and syncope, and chest imaging showed severe pulmonary edema without a focal consolidation. Patient

was diagnosed with ARDS, but infectious and cardiogenic causes were ruled out. Upon cessation of clopidogrel, patient's mental status and pulmonary function improved. In our patient, it was possible to differentiate AIP from ARDS by chest imaging which revealed a type of AIP rather than pulmonary edema and exclusion of infectious causes using serology and BAL. In addition, our patient didn't have the risk factors for ARDS, such as a history of high-risk surgery, respiratory disease or smoking.

This case report has several limitations. First, clopidogrel readministration for accurate diagnosis was not performed because of probability of reoccurrence of serious adverse reaction similar to this event. Second, we did not conduct surgical or transbronchial lung biopsy (TBLB) because of possible several complications including bleeding and deterioration of hypoxia. However, we suspected drug-induced AIP based on chest CT findings, which showed interstitial pneumonia, and lack of changes in drug history other than addition of clopidogrel. Finally, the patient clinically improved only after withdraw of clopidogrel and initiation of steroid treatment.

Identification of drug-induced lung disease is difficult because the clinical, radiological, and histological findings are nonspecific. Therefore, physicians must employ rapid decision making to recognize any possible correlation with each drug in use and development of related inflammatory lung damage. This case report suggests that patients receiving clopidogrel may develop AIP, although its occurrence is rare. This is a substantial finding considering the wide use of clopidogrel as an antithrombotic agent.

Abbreviations

AIP acute interstitial pneumonitis

ADP adenosin diphosphate

SCA superior cerebellar artery

ACA anterior cerebral artery

MRI magnetic resonance imaging

CT computed tomography

BAL bronchoalveolar lavage

GGO ground glass opacity

PCR polymerase chain reaction

DILD drug-induced interstitial lung disease

ARDS acute respiratory distress syndrome

BOOP bronchiolitis obliterans organizing pneumonia

COP cryptogenic organizing pneumonia

Declarations

Ethics approval and consent to participate

The patient's written consent has been obtained for this publication. The study was approved by the ethics committee of Kyung Hee University Hospital at Gangdong (IRB No. KHNMC 2020-07-027).

Consent for publication

The patient's written consent has been obtained for this publication.

Availability of data and materials

The data that support this case report are available from the corresponding author on reasonable request, since respecting the Ethics Committee to protect patient confdentiality.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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Not applicable

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Figures

Figure 1.

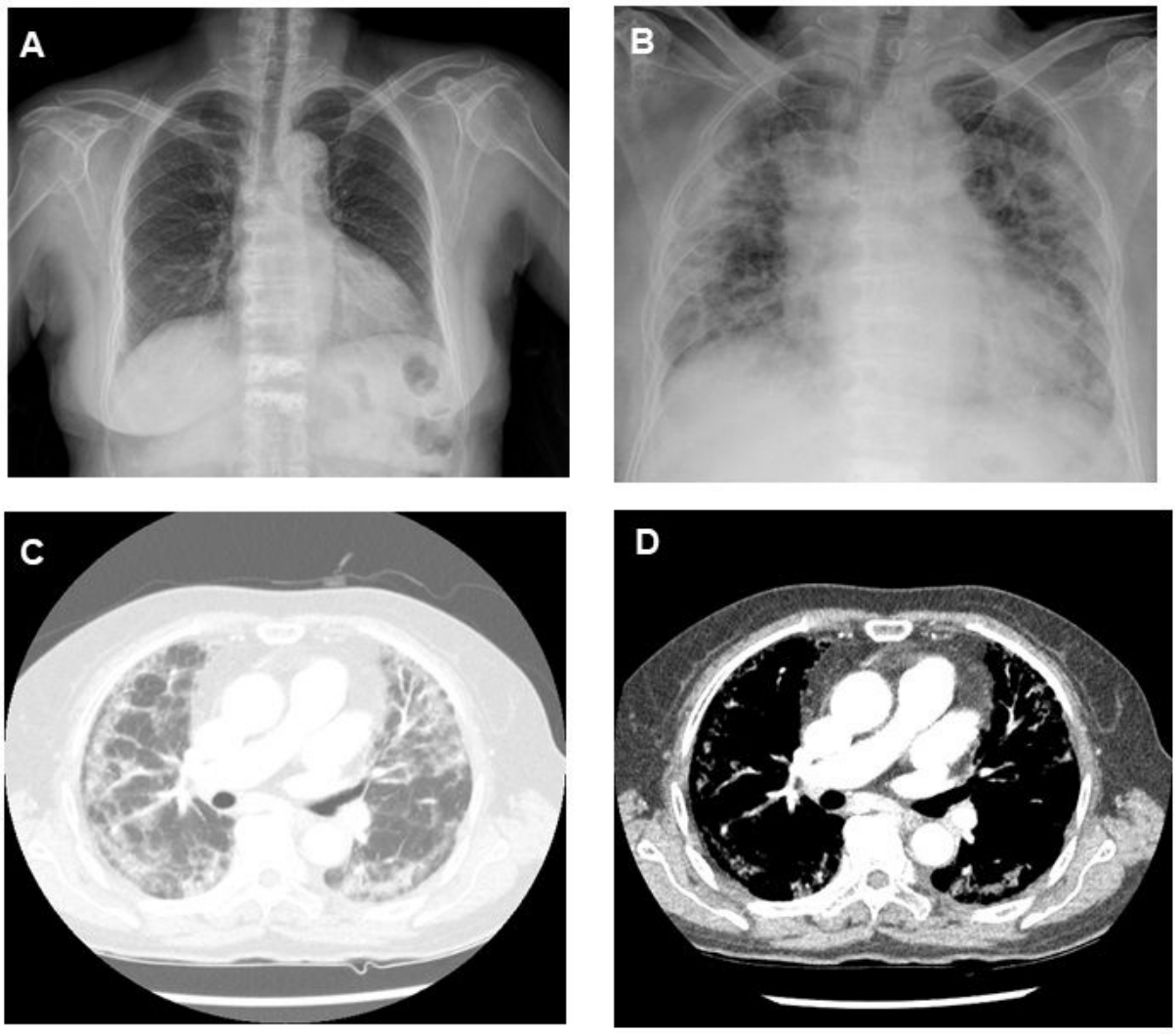

Figure 1

Chest radiographs of the patient. Chest x-rays of the patient taken at 2 months before (A) and at admission (B). Lung window (C) and mediastinal window (D) on Chest CT of patient at admission. The chest radiographs demonstrate symmetric peribronchial GGO with reticulation in both lungs. There is no significant endobronchial lesion and no bilateral axillary LN enlargement.

Figure 2.

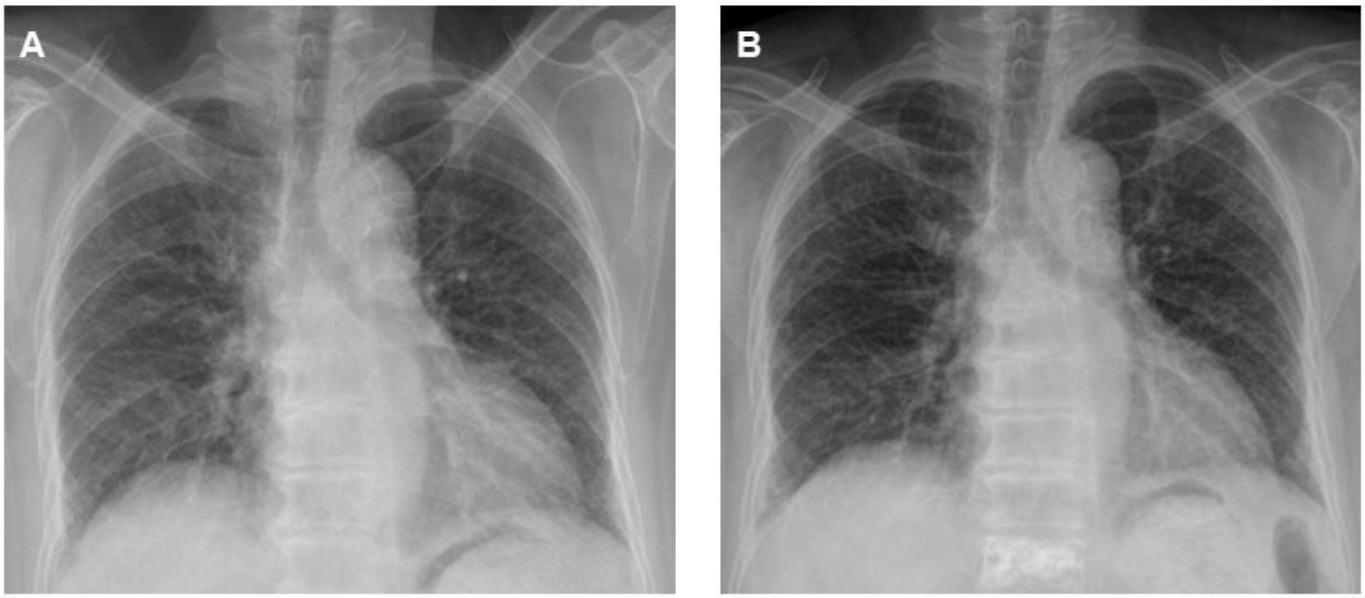

Figure 2

Chest x-ray taken on discharge (A) and 6 months after discontinuation of steroid (B). Note the disappearance of peribronchial GGO with reticulation in both lungs on the discharge radiograph and lack of deterioration at 6 months after discontinuation of the steroids.

Supplementary Files

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- CAREchecklist.pdf