Acute coronary vasospasm in a patient with eosinophilic granulomatosis with polyangiitis following NSAID administration

A case report

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Abstract
Eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss syndrome) is a rare systemic disease characterized by a small-vessel necrotizing vasculitis. Cardiac manifestations are broad-ranging and are associated with a poor prognosis. Coronary vasospasm is uncommon.

Here, we report a case of an acute coronary vasospasm in a patient with EGPA after corticosteroids withdrawal and nonsteroidal antiinflammatory drug (NSAID) introduction. This patient was initially misdiagnosed as bradykinin-mediated angioedema. A 30-year-old man presented with recurrence of abdominal pain and acute dyspnea. NSAID administration for pain during a flare was followed by coronary vasospasms leading to cardiac arrest. Corticosteroid treatment was recently interrupted by the patient.

This case reports a rare cardiac complication of EGPA. NSAID might contribute to coronary vasospasm by eosinophilic degranulation in EGPA. Moreover, corticosteroid compliance must be emphasized among patients who display EGPA with high cardiac risk to prevent fatal issues.

Abbreviations: COX-1 or COX2 = cyclooxygenase type 1 or 2, CysLT = cysteinyl leukotriene, ECG = electrocardiogram, EGPA = eosinophilic granulomatosis with polyangiitis, LT4 = leukotriene B4, NSAID = nonsteroidal antiinflammatory drug.

Keywords: ANCA, coronary vasospasm, eosinophilic granulomatosis with polyangiitis, NSAID

1. Introduction
Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic small-vessel necrotizing vasculitis. Its most frequent manifestations are late-onset asthma, chronic rhinitis, and sinus polyposis associated with eosinophilia. Cardiac involvement is the main cause of mortality.[1] Cardiac manifestations are very diverse but coronary vasospasm is uncommon. Here, we report a case of an acute coronary vasospasm in a patient with EGPA after corticosteroids withdrawal and nonsteroidal antiinflammatory drug (NSAID) introduction. This patient was initially misdiagnosed as bradykinin-mediated angioedema. Few coronary vasospasms have been reported in patients with symptomatic EGPA during both active and passive phases of the disease. To our knowledge, this is the first case describing acute coronary vasospasm leading to cardiac arrest during corticosteroid interruption and following NSAID administration in EGPA.

2. Case report
A 30-year-old man without significant medical history presented with a 5-month history of recurrent abdominal pain and dyspnea. A trigeminal neuralgia was diagnosed 7 months earlier because of left hemifacial paroxysmal pain. The patient used NSAID occasionally in the early symptom phase as pain killers without adverse effect.

From April to August 2013, he suffered from intense crisis of acute abdominal pain localized on the upper and lower left quadrants, followed by hypoxemic acute dyspnea with cough and sometimes wheezing. Nasofibroscopy revealed no laryngeal cause but noticed nasal polyps. CT-scan revealed peribronchial infiltrates and submucosal edema of the esophagus and the stomach with a small peritoneal effusion. Moderate hyperclosinophilia was found (1.29 × 10⁹/L). Antihistaminic drugs were ineffective. The recurrence of abdominal pain, mucosal edema, and atypical dyspnea with laryngeal component suggested a diagnosis of nonhistaminergic angioedema. Quantitative and functional assay of C1-inhibitor and complement assay were normal. Thus, bradykinin-mediated angioedema was suspected. Oral tranexamic acid and prophylactic treatment with human C1-esterase inhibitor twice a week was initiated as it seemed to be effective on abdominal symptoms. Icatibant was administered during attacks as a rescue medication. C1-esterase inhibitor treatment was stopped 1 month later after another
abdominal attack. Moreover, assay of kinin metabolism was normal thus dismissing the diagnosis of bradykinin-mediated angioedema. Asthma was diagnosed as the patient sometimes experienced wheezing and inhaled salbutamol was slightly effective on symptoms. Oral corticosteroid therapy was initiated as the diagnosis of vasculitis was suspected. On September 2013, the patient was admitted to the Emergency department with localized abdominal pain. Corticosteroid therapy was stopped 12 days before as the patient was out of medication. One hour after NSAID (ketoprofen) administration, he presented with angina pectoris followed by ventricular fibrillation and cardiac arrest. One defibrillation biphasic shock of 150J enabled to restore sinus cardiac activity. Active-life support lasted about one minute. Electrocardiogram (ECG) displayed significant anterosepto-lateral ST elevation with an inferior mirror image (Fig. 1). Troponin was initially elevated at 2.33 μg/L (N < 0.1 μg/L). Eosinophils were 1.34 × 10^9/L. Coronary angiography revealed a tight spasm of the anterior interventricular branch of the left anterior descending artery and of the right coronary artery (Fig. 2). Spasms were reversed after intracoronary injection of glycerin trinitrate. Nine days after cardiac arrest, cardiac MRI disclosed a small-scale anteromedial cardiac infarction without any ventricular dysfunction or without vasculitis, myocarditis, and pericarditis. Repetitive anti-neutrophil cytoplasmic antibodies (ANCA) measurements were negative and complement assay was normal. Serum tryptase levels and screening for parasites were normal. Neither FIP1L1-PDGFRα myeloid mutant nor lymphoid clone was found. Histological analysis of esophagus, stomach, colon tissue, and temporal artery did not show evidence of vasculitis. Nasal mucosa biopsy of polyps revealed eosinophilic infiltrates. The patient met 4 of the 6 American College of Rheumatology diagnostic criteria required for EGPA: asthma, parasinusal abnormalities, neuropathy, extravascular eosinophils. Blood eosinophilia could not be taken in consideration as it was below the threshold of 10% of total white blood cell count. An implantable cardioverter defibrillator was implanted 15 days after cardiac arrest. High dose intravenous corticosteroids (1 mg/kg/day) and immunosuppressive therapy by intravenous cyclophosphamide (600 mg/m² monthly during 3 months, then 700 mg/m²) were initiated. After 6 months, cyclophosphamide was switched to azathioprine (2.5 mg/kg). General symptoms markedly improved. Daily oral prednisone (10 mg) and azathioprine therapy was pursued 30 months without relapse. The patient fully recovered neurologically after cardiac arrest. He was discharged 23 days after entering the hospital.

3. Discussion

Most patients with cardiac involvement of EGPA do not display any circulating ANCA. Existence of ANCA-negative EGPA hypothesizes the role of eosinophilic infiltrates in some organ-specific symptoms, such as cardiac, gastrointestinal, and pulmonary manifestations, associated with a low frequency of vasculitis histology as compared to ANCA positive patients. Indeed, we only found eosinophilic infiltrates in nasal mucosa. Previous episode of left trigeminal neuralgia could have been the first manifestation of EGPA in our patient.

To date the pathophysiology of coronary vasospasm in EGPA has not been elucidated. Eosinophilic infiltration of the arterial wall is suspected to drive a segmental vasoconstriction through the release of chemokines and eicosanoid inflammatory mediators. Human coronary arteries express several subtypes of leukotriene receptors, mostly BLT1 which binds Leukotriene B4 (LTB4) but also cysteinyl leukotriene (CysLT) receptor 1. CysLT receptor 1 and BLT1 are upregulated in smooth-muscle cell by proinflammatory stimuli diseases. In a vasculitis like EGPA, we could consider CysLT and leukotriene B4 (LTB4) to be responsible of vessel smooth muscle cells constriction through eosinophil chemotraction and local inflammation. Besides, local eosinophil accumulation has been reported to be enhanced with leukotriene through paracrine activation. Thus, NSAID might exacerbate this segmental eosinophilic-mediated vasoconstriction process.

NSAID do not directly increase the synthesis of CysLT and LTB4. Nevertheless they decrease the synthesis of prostaglandin E2 which inhibits the production and the release of CysLT and LTB4 by eosinophils and mast cells. By analogy, In aspirin-exacerbated respiratory disease, basal low expression level of COX-2 make subjects very sensitive to non selective COX inhibitors. Indeed, the removal of constitutive COX-1 activity by drugs permits eosinophil activation which leads to broncho-spasm. Such a mechanism could be considered for EGPA.
In addition, discontinuation of systemic corticosteroids has been presumed to trigger EGPA flare.\[^7\]

Despite nasal polyps and asthma, the diagnosis of aspirin-induced asthma was dismissed as attacks occurred without any use of aspirin or NSAID. Kounis syndrome is defined as allergic reactions accompanied by cardiac symptomatology.\[^8\]\[^8\] In our case, the patient used ketoprofen and ibuprofen a few times as self-medication when he experienced acute trigeminal neuralgia pain at the beginning of the medical history but he stopped because of their ineffectiveness. He had never suffered from chest pain or dyspnea when he used NSAID which was not in favor of a Kounis syndrome. Moreover, he had not experienced other symptom than angina pectoris after ketoprofen administration before cardiac arrest.

In summary, NSAID could precipitate coronary vasospasm by eosinophilic degranulation in EGPA. Moreover, corticosteroid compliance must be emphasized among patients who display EGPA with high cardiac risk to prevent fatal issues.

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