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In-Stent Restenosis Exacerbated by Drug-Induced Severe Eosinophilia after Second-Generation Drug-Eluting Stent Implantation

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Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 83
Final Diagnosis: In-stent restenosis
Symptoms: Chest discomfort
Medication: —
Clinical Procedure: Cardiac catheterization
Specialty: Cardiology

Objective: Unusual clinical course

Background: In-stent restenosis (ISR) is still a recognized clinical problem in the era of drug-eluting stent (DES). Some previous studies have suggested that circulating eosinophils play an important role in both restenosis and thrombosis after DES implantation. However, the contribution of eosinophils to the pathogenesis of ISR has not yet been concisely clarified.

Case Report: We present the case of an 83-year-old male Japanese patient with ISR exacerbated by drug-induced severe eosinophilia. He had previous histories of coronary stent implantations by DES and was referred to our hospital because of erythema with severe eosinophilia (maximum was 6500/μl [48% of total white blood cell count]). Around the same time, the patient developed ISR, for which a stent was deployed 2 years earlier. Arterial wall injury due to the increase in circulating eosinophils was verified in several findings, such as the increase of D-dimer and brain natriuretic peptide. In addition, the histology of the resected tissue from erythema demonstrated that the nuclei of endothelial cells were swollen where eosinophils and lymphocytes heavily infiltrated into the extravascular space, suggesting the presence of vascular injury. This injury due to the increase in circulating eosinophils may have a marked impact on the pathologic process of ISR in DES implantation.

Conclusions: Just a few anecdotal reports are available of ISR occurring in the setting of hypereosinophilia. The clarification of the mechanism in this patient provides a new effective therapeutic strategy against ISR in the setting of DES implantation.

MeSH Keywords: Coronary Restenosis • Drug-Eluting Stents • Eosinophilia

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Background

Although stenting is an effective method against coronary artery stenosis, in-stent restenosis (ISR) is still a recognized clinical problem. The implantation of a drug-eluting stent (DES) significantly lowers the rate of restenosis as compared with a bare metal stent; however, the exploration of effective strategies against restenosis is still an important issue in the clinical setting of DES. Some previous studies have suggested that circulating eosinophils play an important role in both restenosis and thrombosis after DES implantation [1–4]. However, the contribution of eosinophils to the pathogenesis of ISR has not yet been concisely clarified. We report on our experience with a representative case of ISR that was exacerbated by drug-induced severe eosinophilia.

Case Report

An 83-year-old Japanese man presented with uncomfortable chest pain and was admitted to our hospital in October 2011. Coronary angiography revealed 3 vessel diseases – 90% stenosis in segment 2 and segment 14, and 75% stenosis in segment 6. Then, 6 everolimus-eluting stents (EES) were implanted into the above-mentioned stenotic lesions. Six months after this coronary intervention, the patient had *de novo* stenosis in segment 1 and segment 4. Additional stentings were successfully performed, with 2 EES in segment 1 and segment 4. The patient's uncomfortable chest pain dramatically improved after these interventions. In December 2012, we confirmed that no in-stent restenosis (ISR) or *de novo* stenotic lesions were observed (Figure 1A).

However, the patient was referred to our hospital because of itching over his entire body in August 2013. Physical examination showed that edematous erythema had developed in all 4 limbs and the trunk, and a blood test revealed a marked increase in eosinophil count, from 437/μl in December 2012 to 2670/μl in July 2013, with a maximum of 6500/μl in August 2013 (48% of total white blood cell count). Based on laboratory data, hepatic and renal function did not change; however, the levels of brain natriuretic peptide and D-dimer significantly increased as compared with those at baseline (brain natriuretic peptide: 81.4→192.9 pg/ml, D-dimer: 1.7→13.4 μg/ml). The level of immunoglobulin E also increased to 456 IU/ml. For diagnosis of erythema, a skin biopsy was performed, and diagnoses of malignant lymphoma and erythroderma were excluded. In addition, the specific causes of eosinophilia (e.g., solid tumor, infections caused by parasites, bronchial asthma, angioedema with eosinophilia, eosinophilic pneumonia, and atopic dermatitis) were not detected. Finally, we assumed that the cause of erythema and eosinophilia was drug allergy; therefore, medication (propranolol, nicorandil, clopidogrel, rosuvastatin, and valsartan) was stopped. After we changed the drugs, erythema and the increase in eosinophil count improved gradually, and abnormalities in laboratory data were normalized. Around the same time, the patient developed typical exertional chest pain again in September 2013. However, although a 12-lead electrocardiogram was unremarkable, coronary angiography revealed severe ISR in segment 6, in which a stent had been deployed 2 years earlier (Figure 1B). The intravascular ultrasound finding of neointimal hyperplasia progression was observed, and plain balloon angioplasty was successfully

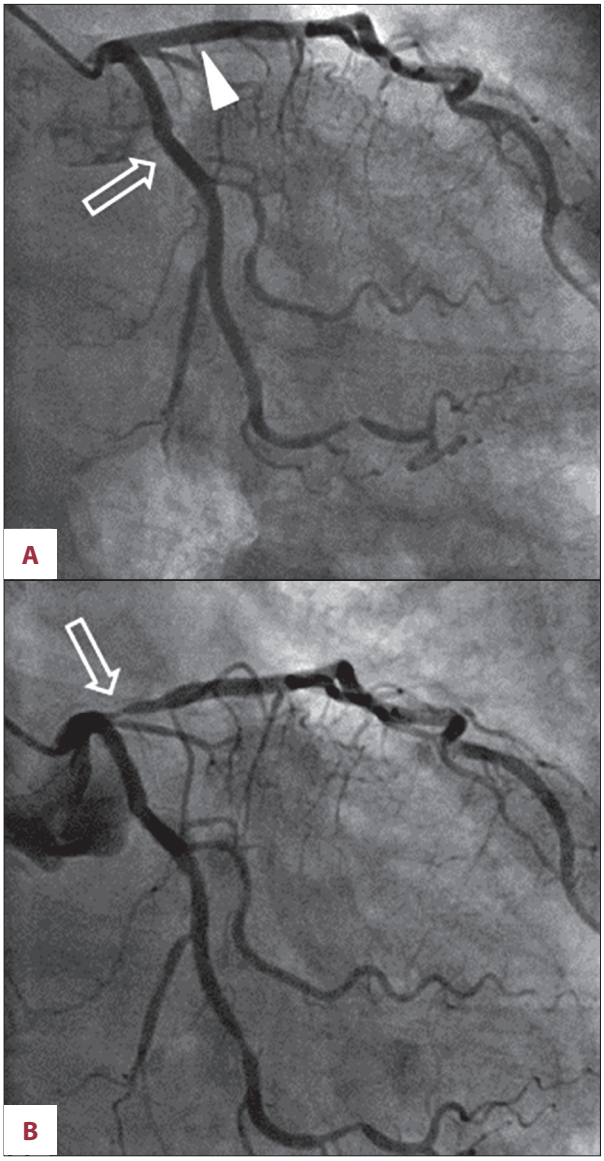

Figure 1. Coronary angiography in December 2012 (**A**) and in December 2013 (**B**). (**A**) Everolimus-eluting stents (EES) were successfully inserted in segment 6 (arrow head) and segment 13 (arrow) in October 2011. No in-stent restenosis lesions were detected in December 2012. (**B**) In-stent restenosis in segment 6 (arrow) was detected after eosinophilia due to drug allergy.

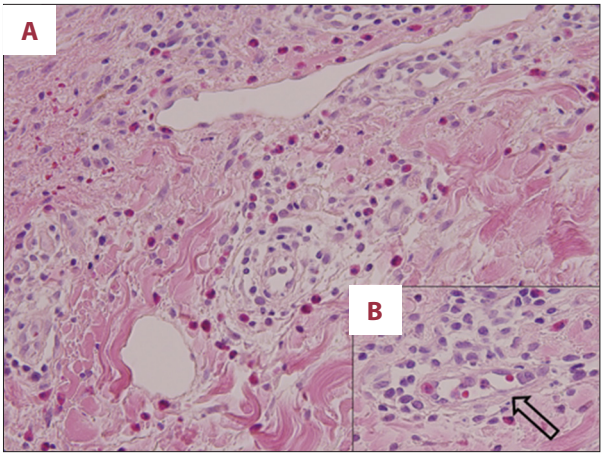

Figure 2. Histology of the resected tissue from abdominal erythema with hematoxylin-eosin staining. (**A**) Histology comprised dermal shallow layer with perivascular infiltration of many eosinophils and lymphocytes. (**B**) Inflammatory cell infiltration clearly extended to a vascular wall (arrow). Nuclear swelling of vascular endothelial cells was also observed.

administered against the stenosis. After this procedure, the patient's chest discomfort was promptly alleviated.

Discussion

Eosinophil granulocytes are approximately 12–15 μm in diameter, with prominent eosinophilic staining, and consist of an array of cytotoxic granule cationic proteins such as eosinophilic cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin [5]. These granules have can induce tissue damage and dysfunction by degranulation following activation by an immune stimulus. They also create reactive oxygen species such as peroxidase, elastase, cytokines, and an abundance of RNases. They are only present in the blood in small numbers (100–400/μl); therefore, the presence of more than 500/μl in blood is considered to be eosinophilia. The increase in eosinophil count due to a variety of eosinophilic syndromes can cause tissue damage or organ dysfunction in the cardiovascular system, such as endomyocardial fibrosis and intraventricular thrombosis [6].

The association between hypereosinophilia and vascular disease has not been well established. Few reports are available of coronary events occurring in the setting of hypereosinophilia, and they demonstrated that the increase in eosinophil count could lead to aggravated vasospasm [7,8]. In contrast, in this patient, ISR was assumed to be exacerbated by severe drug-induced eosinophilia.

In this patient, arterial wall injury due to the increase in circulating eosinophils was verified in several points. The histology of the resected tissue from abdominal erythema demonstrated that the nuclei of endothelial cells were swollen where eosinophils and lymphocytes had heavily infiltrated into the extravascular space (Figure 2A, 2B). In addition, some eosinophils were observed to be infiltrated into the subendothelial space (Figure 2B). The increase in D-dimer levels may also reflect the increased activity of thrombosis and fibrinolysis, which is further evidence of vascular injury [9]. These findings suggested that the increase in circulating eosinophils directly induced arterial wall injury, and this injury may have accelerated some pathologic ISR processes in this patient [10–12].

The association between the vascular injury due to eosinophils and ISR after DES implantation has been reported previously [1]. Eosinophil-derived cytotoxic agents contributed to the progression of ISR, and the eosinophilic inflammatory stimulus triggered by the polymer of DES is also assumed to be an important factor of ISR in DES implantation. Of interest, eosinophils infiltrating surrounding stent struts have been described after bare metal stent implantation, and eosinophils appear to be even more involved in DES than in BMS restenosis [13]. On the other hand, Gabbasov et al. demonstrated the frequency of restenoses after stenting is related to high peripheral blood eosinophil content, suggesting the increase in eosinophil count itself may be a risk factor for the progression of ISR after stent deposition [14]. Indeed, bronchial asthma, the pathologic process to which eosinophils are closely related, was exacerbated by the increase of eosinophil contribution [15]. The injury due to the increase in eosinophil count may also exhibit a marked impact on the pathologic process of ISR in DES implantation.

Conclusions

In this patient, we assumed that ISR was exacerbated by drug-induced severe eosinophilia. Just a few anecdotal reports are available of ISR occurring in the setting of hypereosinophilia. The clarification of the mechanism in this patient will provide a new effective therapeutic strategy against ISR in the setting of DES implantation.

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