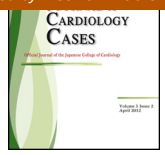
Journal of Cardiology Cases 10 (2014) 54–57

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase



Case Report

Increase in serum triglyceride was associated with coronary plaque vulnerability in a patient with rheumatoid arthritis

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ARTICLE INFO

Article history:
Received 30 July 2013
Received in revised form 25 February 2014
Accepted 24 April 2014

Keywords:
Acute coronary syndrome
Triglyceride
Tumor necrosis factor-α
Biomarker

ABSTRACT

Rates of morbidity and mortality from cardiovascular disease are high in patients with rheumatoid arthritis (RA); however, the mechanisms and biomarkers that reflect coronary plaque vulnerability have not yet been established. We present a case of acute coronary syndrome (ACS) presumably caused by exacerbation of chronic inflammation of RA, in which an abrupt increase in serum triglyceride was seen on the day of onset of ACS but not during effort angina. This case suggests that RA patients with an abrupt increase in triglyceride need intensive care including anti-platelet and statin therapy for the prevention of coronary plaque rupture.

<**Learning objective:** Triglyceride might be a sensitive biomarker of activated macrophages and plaque vulnerability in patients with RA. RA patients with an abrupt increase in triglyceride might need intensive care including anti-platelet and statin therapy for the prevention of coronary plaque rupture.>

Introduction

Rheumatoid arthritis (RA) is a chronic progressive inflammatory joint disorder. Vasculitis is the most serious complication of RA leading to severe extra-articular organ failure due to microvascular insufficiency, which can result in a fatal outcome [1]. Patients with RA suffer significant morbidity and mortality from cardiovascular disease (CVD) [2,3]. CVD associated with RA includes coronary artery disease, stroke, congestive heart failure, and peripheral arterial disease, which are presumably caused by chronic vasculitis due to endothelial dysfunction; however, the precise mechanism by which an inflammatory joint accelerates endothelial dysfunction has not been clarified [4]. In addition, biomarkers that reflect coronary plaque vulnerability have not yet been established. Here, we present a case of acute coronary syndrome (ACS) presumably caused by exacerbation of chronic inflammation of RA, in which an abrupt increase in serum triglyceride was seen on the day of onset of ACS.

Case report

A 72-year-old man was admitted to our hospital in August 2007 for sudden onset of chest pain at rest and was brought to the emergency room of our hospital by ambulance. He had a history of diabetes and hyperlipidemia for 25 years and a history of RA complicated with rheumatoid vasculitis for 18 years and had been prescribed 15 mg of prednisolone and 50 mg of azathioprine daily. A 12-lead electrocardiogram on admission showed elevation of ST in leads V2–4 and depression of ST in leads II and aVF (Fig. 1A). ACS was therefore suspected. Emergency coronary angiography showed 99% stenosis with thrombosis at the proximal left anterior descending coronary artery (Fig. 1B). Thrombus aspiration and implantation of a bare metal stent (3.0 mm × 30 mm)

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http://dx.doi.org/10.1016/j.jccase.2014.04.009
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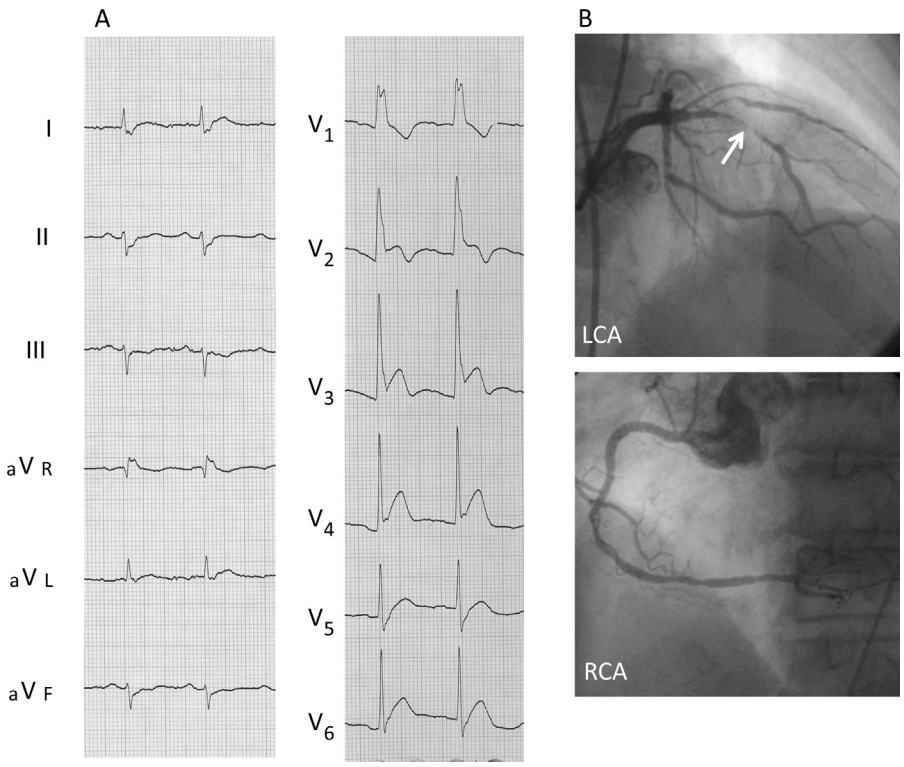

Fig. 1. (A) Twelve-lead electrocardiogram on admission. (B) Emergency coronary angiography showed 99% stenosis with thrombosis at the left anterior descending coronary artery (arrow). LCA, left coronary artery; RCA, right coronary artery.

were performed successfully, and creatine kinase peaked at 2627 U/L. Pathohistology of the thrombus showed accumulation of CD68-positive and CD3-negative inflammatory cells, indicating macrophage-dominant accumulation of inflammatory cells (Fig. 2).

Hyperlipidemia and diabetes had been controlled well with 10 mg of atorvastatin and insulin therapy, respectively. RA had been controlled with an adrenocortical steroid and immunosuppressant. However, the patient had gradually felt exacerbation of joint symptoms several months before the onset of ACS. The results of C-reactive protein (CRP) and rheumatoid arthritis particle agglutination (RAPA) tests showed elevation on the day of onset of ACS. Other inflammatory diseases including bacterial endocarditis, tumor, liver disease (acute and chronic hepatitis), and rheumatic fever were excluded from the medical interview and from laboratory and echographic findings. Of note, well-controlled fasting triglyceride had gradually increased 5 months before the onset of ACS and peaked at 626 mg/dL at the onset of ACS without any over-caloric intake (Fig. 3).

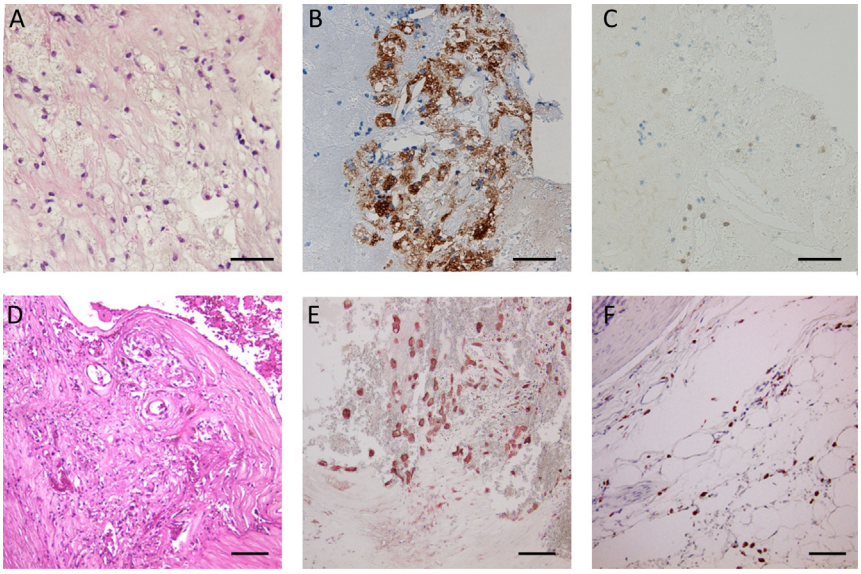

Fig. 2. Aspirated thrombus from the coronary artery shows accumulation of macrophage-dominant inflammatory cells. (A) Hematoxylin and eosin. (B) Immunohistochemistry for CD68. (C) Immunohistochemistry for CD3. The coronary artery from necropsy showed accumulation of CD68-positive inflammatory cells in neointima and pericoronal adipose tissue. (D) Hematoxylin and eosin staining of neointima. (E) CD68 staining of neointima. (F) CD68 staining of pericoronal adipose tissue. Black bar in A–F 100 μm.

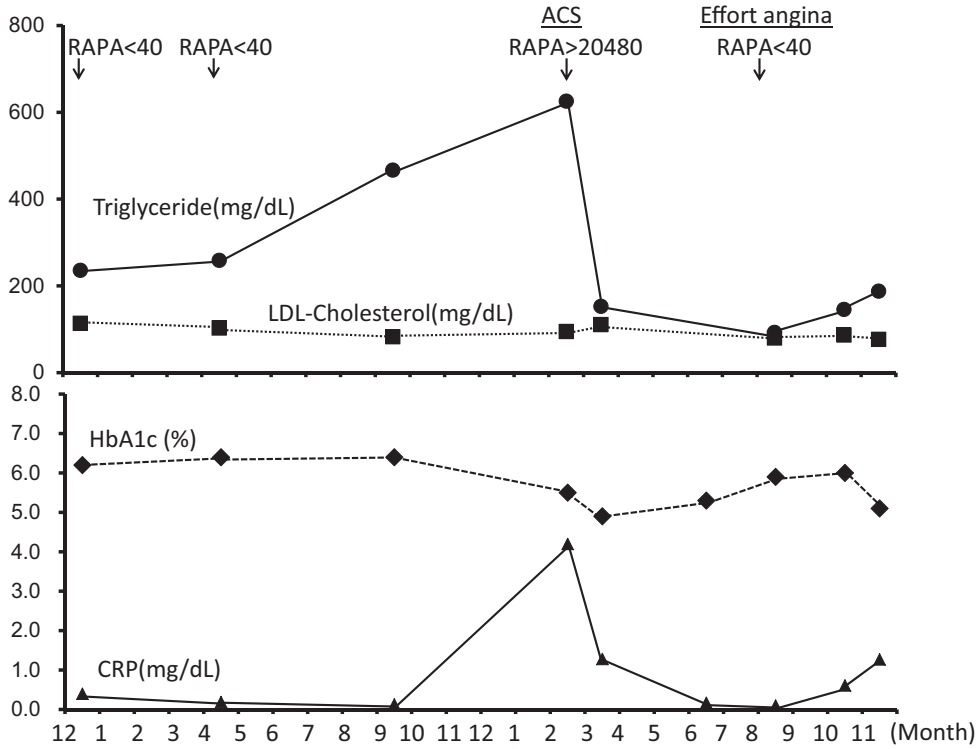

Fig. 3. Biomarkers during the clinical course of the onset of acute coronary syndrome and effort angina. RAPA, rheumatoid arthritis particle agglutination; ACS, acute coronary syndrome; LDL, low-density lipoprotein; HbA1c, glycated hemoglobin A1c; CRP, C-reactive protein.

CRP was decreased by 0.59 mg/dL and low-density lipoprotein cholesterol and triglyceride were decreased by 100 mg/dL and 148 mg/dL, respectively, with 2 mg of pitavastatin instead of atorvastatin, and the patient was discharged from the hospital with no complications. Six months later, he was hospitalized with stable effort angina. Coronary angiography showed 90% stenosis at the middle portion of the circumflex artery, and stent implantation was performed successfully. Elevations of inflammatory markers and triglyceride were not detected. Six months after the previous coronary angioplasty, the patient died from panperitonitis with septic shock from perforation of a gastric ulcer. Pathohistology of the right coronary artery from necropsy showed accumulation of CD68-positive inflammatory cells in neointima and pericoronal adipose tissue, indicating the existence of chronic coronary vasculitis involving adipose tissue.

Discussion

Inflammatory biomarkers are useful measures of synovial inflammation, and alteration in inflammatory biomarkers is a predictor of clinical response to therapy. Premature mortality in RA largely due to CVD is associated with the number of inflamed joints. Tumor necrosis factor (TNF)-α plays an important role in the development of not only synovitis but also CVD in RA. It has been reported that endothelial dysfunction is associated with systemic inflammation and that anti-TNF-α therapy, which is widely used for synovitis, improves endothelial function [5]. Therefore, TNF-α-mediated systemic inflammation should be suppressed in RA patients to prevent the development of CVD in addition to controlling classical risk factors.

The high incidence of CVD in RA patients cannot be explained only by the accumulation of classical risk factors, and it has therefore been believed that there is another pathway responsible for accelerated atherogenesis in RA patients. The mechanisms by which TNF-α mediates inflammation of a joint have been reported to involve increases in triglyceride level and plaque vulnerability [6]: TNF-α is released from activated macrophages at inflamed joints of synovitis, and then abundant circulating TNF-α reduces endothelial lipoprotein lipase activity, leading to a decrease in triglyceride catabolism and increase in circulating triglyceride level. In addition, TNF-α stimulates adipocyte lipolysis and increases release of free fatty acid from peripheral tissues, which augments triglyceride synthesis in the liver, leading to an increase in circulating triglyceride levels. Moreover, activated macrophages release matrix metalloproteinase, which accelerates plaque vulnerability. This hypothesis may explain the TNF-α-driven abrupt increase in serum triglyceride levels and increased vulnerability of coronary plaque leading to ACS (Fig. 4). The concept is consistent with a report showing that a high triglyceride level is related to a high level of systemic inflammation in RA patients [7]. In

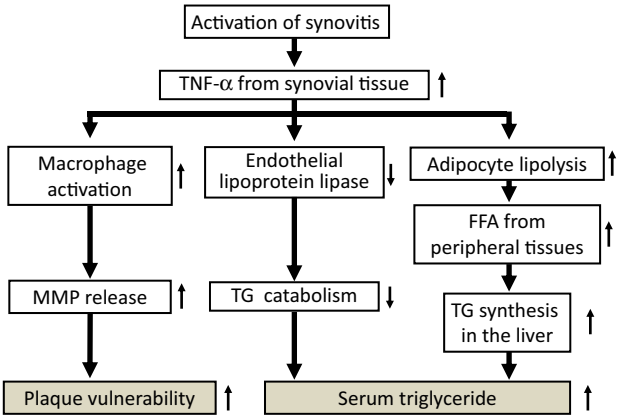

Fig. 4. Presumed mechanisms by which activation of synovitis accelerates plaque vulnerability and increases serum triglyceride. TNF-α, tumor necrosis factor-α; MMP, matrix metalloproteinase; TG, triglyceride; FFA, free fatty acid.

our case, an abrupt increase in triglyceride was seen with exacerbation of RA on the day of ACS onset even though other lipid markers including low-density lipoprotein cholesterol had been controlled; however, the change was not seen during effort angina, indicating that an abrupt increase in triglyceride could be a predictor of plaque rupture of coronary arteries. Therefore, triglyceride might be a sensitive biomarker of activated macrophages and plaque vulnerability, and an abrupt increase in triglyceride level might predict the onset of ACS in patients with RA. Although large-scale clinical studies are needed to confirm the hypothesis, RA patients with an abrupt increase in triglyceride might need intensive care including anti-platelet and statin therapy for the prevention of coronary plaque rupture.

CRP level did not parallel with triglyceride level before the onset of ACS in our case, and it is therefore unknown whether the degree of plaque vulnerability was related to disease activity of RA represented by CRP. There is no evidence to support our speculation because we could not measure TNF-α level, and large-scale clinical studies with measurements of triglyceride, CRP, and TNF-α are therefore needed to confirm the hypothesis.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

This work was supported in part by JSPS KAKENHI Grant Number 25461131.

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