

Case Report

Advanced Coronary Atherosclerosis and Fatal Myocardial Infarction in Mild Dyslipidemic, Low Risk Young Man: A Case Report With Literature Reviewed

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Abstract

Acute Myocardial infarction (AMI) at a young age (below 45 years) is rare and difficult to predict. We reported a fatal myocardial infarction from advanced atherosclerosis in a healthy young man who had no other major coronary risk factors except mild hypercholesterolemia. Thus, all available systemic risk scores identified him as a low risk candidate for developing a cardiovascular event. Autopsy revealed advanced atherosclerosis in all three major coronary arteries causing acute and old myocardial infarction. Thick epicardial adipose tissue and myocardial bridging of the mid left anterior descending artery were also noted. He frequently used etoricoxib to treat knee and back pain for consecutive five years. Potential mechanisms of sudden death from atherosclerosis, myocardial bridging, epicardial adipose tissue and selective COXIB are discussed in more detail below.

Keywords: sudden death, young myocardial infarction, premature atherosclerosis, mild hypercholesterolemia, myocardial bridging, epicardial adipose tissue, COX 2 inhibitor

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Acute myocardial infarction (AMI) at young age, below 45 years, is rare and little known in clinical practice. Most victims are male and share common conventional coronary risk factors including cigarette smoking, a family history of premature coronary artery disease (CAD), dyslipidemia, hypertension, diabetes mellitus and being overweight or obese.¹⁻⁵ We reported a fatal AMI from advanced atherosclerosis in a relatively young man who had none of the aforementioned risk factors except dyslipidemia which was well controlled. Thus, all systemic risk score identified him as a low risk candidate for developing future cardiovascular disease and precluded primary prevention.

Case Report

A 43-year old man, regular tennis player, had been well, with a physically active life style for decades. In 2010, at the age of 39 years, he was diagnosed with hypercholesterolemia, with a total cholesterol of 260 mg/ dl. With dietary control, regular exercise i.e. swimming every day, jogging on weekend and simvastatin 10 mg/day, his lipid was well under control, see Table 1. At the same time, he was diagnosed with a herniated disc (L4-5 level) and spinal canal stenosis so surgery was recommended. He used to smoke cigarettes, for a year, and stopped seventeen years earlier. Preoperative physical examination was unremarkable; body mass index (BMI) was 25, BP was 110/70 mmHg and pulse rate was 76 beats per minute. Chest film was normal. Screening ECG showed regular sinus rhythm, normal QTc and had Q wave in lead III, see Figure 1. The total cholesterol was 164 mg/dl, triglyceride was 50 mg/dl. His father drank alcohol and had died during sleep in his mid 30's. His brother and one uncle also had dyslipidemia (no details available) but none of them had known cardiovascular diseases.

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In Jan 2011, microdiscectomy and foraminostomy were uneventfully performed and allowed him to play tennis for two hours a day instead of swimming. Serial blood test showed fasting glucose of 91 mg/dl, total cholesterol of 177 mg/dl, triglyceride of 47 mg/dl, HDL-cholesterol of 78

mg/dl and LDL cholesterol of 96 mg/dl. In 2013, after having developed his own business, he exercised less, gained 6 kg and felt dyspnea on exertion. Cardiac check-up was scheduled but he did not come. From 10/2013-11/2014, he had ten OPD visits for pain of knee and back and took etoricoxib 90 mg daily. Two weeks prior to the event, he had chest discomfort but was still able to play two sets of tennis regularly. In December 2014, after having finished the first set, he felt dizzy and suddenly collapsed on the court. Resuscitation was performed by bystanders and later by paramedics but they failed to restore spontaneous circulation so he expired in the field.

An autopsy study was performed the next day. No pathological cause of death was found in any other organ except the heart. Cardiac weight was above average,⁶ 425 gm, and the organ was covered by epicardial adipose tissue (EAT), mostly over anterior and some around apico- basal part of the

left ventricle (see Figure 2A&B). The pericardium and all valves were normal. New and old myocardial infarction areas were noted in postero-septum and posterior wall, as evident by fibrosis intervening with hemorrhagic infarction, see Figure 5. Under light microscope, most myocytes were hypertrophic and had changed edematous, especially at cardiac rim. Evidence of contraction band necrosis was documented, see Figure 5A. All three epicardial coronary arteries were occupied by advanced calcified atheromatous plaque. The left anterior descending artery (LAD) lumen was narrowed, ranging from 50% to over 90% stenosis, see Figure 3A&B. The mid LAD artery embedded, 10 mm, under myocardium for 20 mm in length, but was free from atherosclerotic disease, see Figure 3C. The circumflex (Cx) artery had calcified eccentric plaque causing 80% luminal stenosis, see Figure 4A. The right coronary artery (RCA) had 50-80% luminal stenosis, see Figure 4B.

Table 1: Summary of all available lipid profiles, exercise and medication from 2010-2014

Data	2010	2011	2012	2013	2014
Total Chol (mg/dl)	260	177	195 - 205	180	190
LDL- Chol (mg/dl)	NA	96	NA	NA	NA
HDL-Chol (mg/dl)	NA	78	NA	NA	NA
Triglyceride (mg/dl)	NA	47	NA	NA	NA
Simvastatin 10 mg	Yes	Yes	Yes	Yes	No
Exercise	Swimming Jogging	Swimming Jogging	Tennis	Tennis	Tennis
Etoricoxib	Yes	Yes	Yes	Yes	Yes

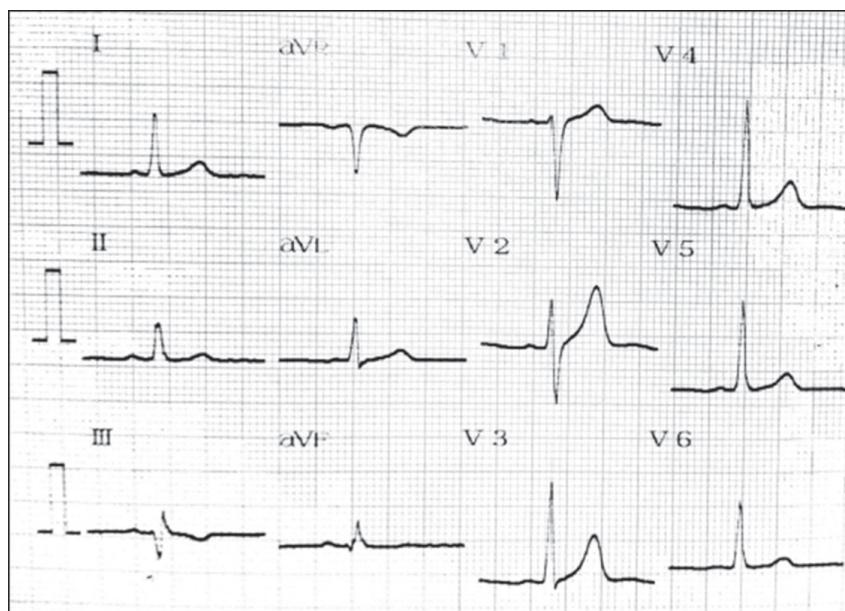


Figure 1: Pre-operative ECG in 2011 showed sinus rhythm with significant Q wave in lead III. Relative tall T wave was noted in V2 and V3. The QTc was within normal range.

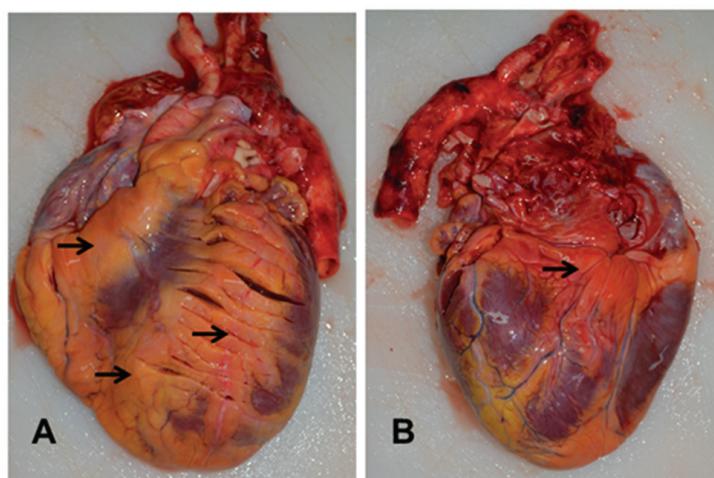


Figure 2: The heart weight was above normal range, 425 gm. It was covered by the thick yellowish epicardial adipose tissue (EAT, black arrow), mostly over anterior (A), apico-basal parts of the left ventricle (B).

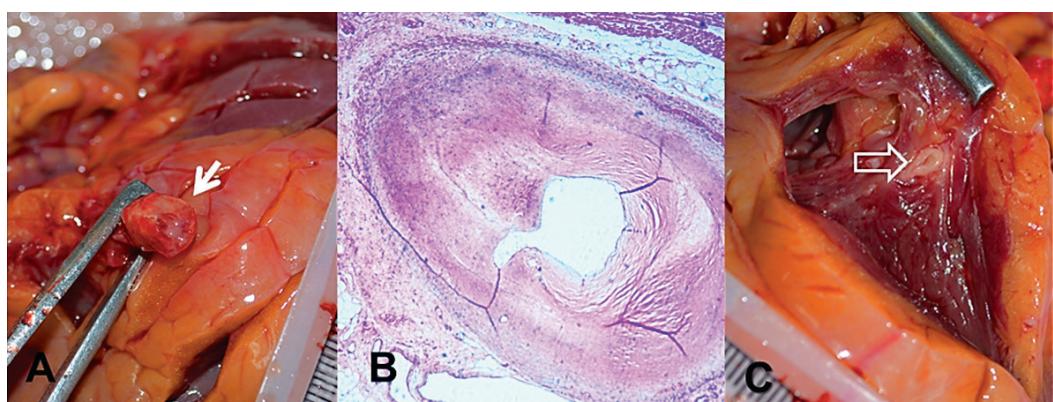


Figure 3: The lumen of the proximal left anterior descending artery (LAD) was occupied by atherosclerotic plaque (white arrow, A) causing over 90% luminal stenosis, as shown in histological section B. The mid LAD embedded, 10 mm deep into myocardium (bridging or tunneled) for 20 mm length, and was free from atherosclerotic lesion (arrow, C). The epicardial adipose tissue (EAT) overlying the proximal LAD was obviously thickened, see Figure A & C.

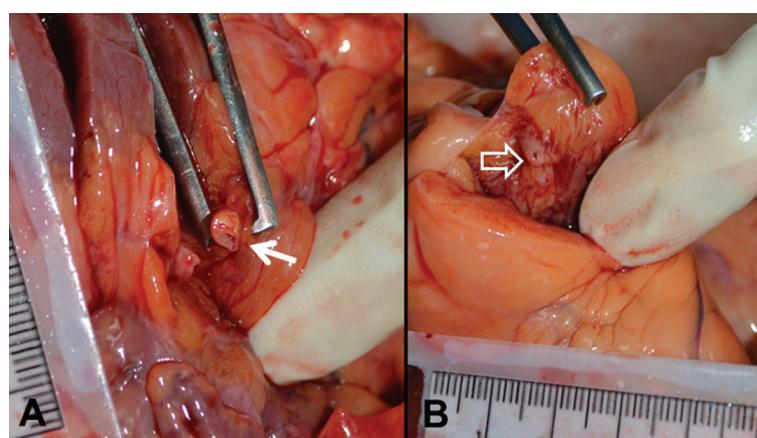


Figure 4: Cross section profile of the circumflex artery showed severe eccentric atheroma causing 80% luminal stenosis (A). The right coronary artery had concentric plaque with 50-80% luminal stenosis along its course (B).

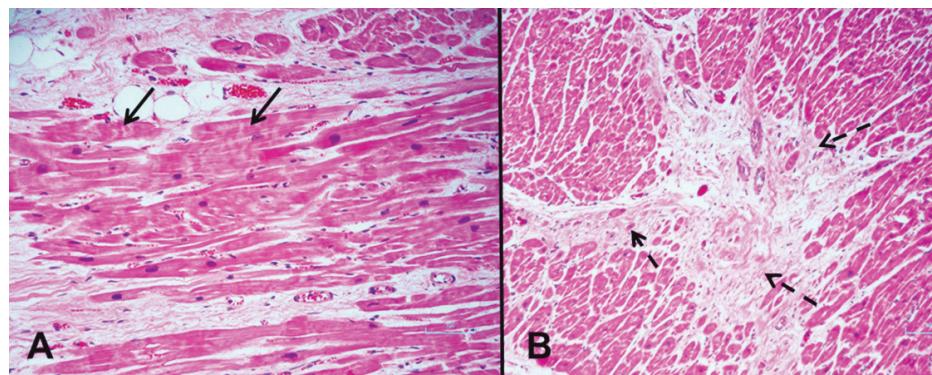


Figure 5: A dark red, cross striation (black arrow, A) of myocytes, (contraction band necrosis) was noted. Area of fibrotic scar (dashed black arrow) of previous myocardial infarction was shown in B.

Discussion

The cause of death

AMI occurred at a young age, below 45 years old, which is quite rare and accounts for only 5.7-7% of total AMI cases.¹⁻⁵ In general, the etiologies of young AMI cases could be classified in four groups: ^{7,8} 1) atheromatous coronary artery disease (CAD); 2) non-atheromatous CAD i.e. vasculitis, coronary dissection, myocardial bridging; 3) hyper-coagulable states ; and 4) AMI related to substance misuse. History provided by his wife confirmed that he never used cocaine or any other substance and had no hyper-coagulable conditions. There was no evidence of vasculitis or spontaneous coronary dissection on examination. The presence of advanced atheromatous CAD in all coronary arteries (Figure 3A&B and 4A), the scar and the contraction band necrosis located in postero-septum of the left ventricle (Figure 5A&B) indicated that the cause of death was AMI on top of an old myocardial scar. Both ischemic myocardium and the scar could serve as an arrhythmogenic substrate for ventricular arrhythmia and led to sudden cardiac death.⁹

COX-2 inhibitor and adverse cardiovascular effect

In addition, our case often took the selective non-steroidal anti-inflammatory drug, etoricoxib 90 mg/day to treat knee and back pain for five consecutive years, Table 1. It is known that COX-2 inhibitors predominantly suppress the formation of prostaglandin I₂, the cardiac-protective cyclooxygenase product in endothelium. It inhibits platelet aggregation, provides vasodilatation, and prevents the proliferation of vascular smooth-muscle cells in vitro.^{10,11} Although the cardiovascular safety of selective cyclooxygenase-2 (COX-2) drugs had previously been reported but the data remained controversial and conflicting.^{12,13} A recent meta-analysis of 31 trials involving 116,429 patients, followed up with more than 115,000 patient years, supported the excessive cardiovascular risk of COX-2 inhibitor.¹⁴ Studied patients were allocated to naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib,

rofecoxib, lumiracoxib, or placebo. Compared with placebo, Etoricoxib (rate ratio, RR, 4.07, 95% CI 1.23 to 15.7) and diclofenac (RR 3.98, CI 1.48 to 12.7) were associated with the highest risk of cardiovascular death. Rofecoxib was associated with the highest risk of myocardial infarction (RR 2.12, 95% CI 1.26 to 3.56), followed by lumiracoxib (RR 2.00, 95% CI 0.71 to 6.21). Ibuprofen was associated with the highest risk of stroke (RR 3.36, 95% CI 1.00 to 11.6), followed by diclofenac (RR 2.86, 95% CI 1.09 to 8.36).¹⁴ In fact, two AMI Thai cases had been previously reported by our group and one in each case had taken celecoxib and etoricoxib a few days before having events.¹⁵ Although we still could not prove how much etoricoxib contributed to AMI in this case, it has been recommended not to use COX2 inhibitors in known cardiovascular disease patients.^{16,17} Only in case of need it should be used within a short period and a low dose aspirin should be added to reduce thromboxane A2 production.¹⁷

Role of myocardial bridging in sudden death

In the autopsy study, the tunneled mid LAD artery, so-called myocardial bridging (MB), was also noted, Figure 3C. The prevalence of MB varied widely in the literature, from 0.5-12% by angiography,^{18,19} to 26% by CT coronary angiogram,²⁰ and up to 58% in some autopsy studies.²¹ MB had been considered a benign anatomical variant since the long term prognosis was excellent. Krammer and colleague²² reported the excellent five-year survival rate, 97.5%, in 81 MB cases. In the 11 ± 3 year study of 28 cases of isolated MB in the LAD artery, the survival rate was very high, 98%, and the few deaths that occurred in this report were not relevant to MB.²³ However, acute myocardial infarction,²⁴⁻²⁶ ventricular septal rupture,²⁷ paroxysmal AV block,²⁸ ventricular tachycardia during exercise²⁹ or even sudden death³⁰ had been reported in MB cases. Recently, Hostiuc S et al.,³¹ performed a meta-analysis of 21 MB studies and found that MB was associated with major adverse cardiac events, OR = 1.52 (95% CI: 1.01–2.30), and myocardial ischemia, OR = 3.00 (95% CI: 1.02–8.82), but not with acute myocardial infarction, cardiovascular death, ischemia (identified using imaging

techniques), or positive exercise stress testing. In summary, MB could have significant cardiovascular consequences (MACE, myocardial ischemia) in three ways; 1) by direct systolic compression of the tunneled artery causes delayed relaxation and reduces blood supply,³²⁻³⁴ 2) by induced atherosclerosis of the proximal segment prior to the MB,³⁵⁻³⁷ as found in this case, and 3) enhanced vasospasm.³⁸ In other autopsy studies, the length (20-30 mm) and the depth of MB (2-3mm) were considered pathologic anatomy for sudden death.⁸ In our case, the length and the depth of MB segment were 20 mm and 10 mm respectively, so it could easily produce myocardial ischemia during exertion and contributed to sudden cardiac death.

Current risk predictor failed to predict this case

The reported common coronary risk factors of young AMI cases were male gender, cigarette smoker, family history of premature atherosclerosis, dyslipidemia, diabetes mellitus, obese, overweight, and hypertension.¹⁻⁵ Our case had none of these conditions except mild hypercholesterolemia which was under control. His LDL cholesterol was 96 mg/dl in 2011 and was considered to be safe by the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.³⁹ However, it was not clear what caused the sudden death of his father who died at night in his sleep after drinking alcohol. The patient did not have tendon xanthoma and his cholesterol was not unusually high, so it was less likely for him to have familial hypercholesterolemia.⁴⁰ With no other risk factors, he was classified as a low risk candidate for developing future CVD events by the current risk score including the Atherosclerotic Cardiovascular Disease (ASCVD), Thai CV risk score, World Health Organization (WHO) and the modified Coronary Risk Chart (CVD Risk Score: <http://caprecvdrisk.com/CVDRiskScore/>).⁴¹⁻⁴⁴ In retrospect, the inferior Q wave on ECG and the coronary calcium score would have been suitable indicators to predict his event.

AMI with no conventional coronary risk factors

All of these risk calculators required conventional risk factors include gender, age, current smoker, blood pressure, serum lipid for calculation so they failed to predict the cardiovascular death in this reported case. It is known that 15-40% of population could have CAD or AMI with no major risk factors. Knot and colleagues analyzed 122,458 CAD cases that had been enrolled in 14 international randomized trials and found that 15.4% of women and 19.4% of men still had CAD without having the four major conventional risk factors, i.e. cigarette smoking, diabetes mellitus, hyperlipidemia and hypertension.⁴⁵ In Southern China (Hakka) population, Zhang et al.,⁴⁶ studied coronary risk factors of the first AMI 1,382 cases. The authors found that 31.1% and 40.6% of non-elderly men and women had AMI with normal LDL, HDL and triglyceride levels. This led to the next question: how could advanced atherosclerotic CAD develop in these patients?

EAT, a new risk predictor

From other autopsied studies, the average heart weight of Thai men, age ranging from 35-45 years, varied from 265 ± 8 gm to 302 ± 7 gm.⁶ In our case, the heart weight was up to 425 gm. The thick epicardial adipose tissue (EAT) was found and possibly contributed to an excess weight. The inflammatory role of EAT had been addressed in 2003 by Mazurek and colleagues.⁴⁷ By studying the inflammatory markers of EAT vs subcutaneous fat in 42 CAD patients before undergoing coronary bypass surgery, they found that the EAT exhibited significantly higher levels of chemokine, MCP-1 and other inflammatory cytokines: IL-1, IL-6, IL-6sR, and TNF, than subcutaneous fat did. Subsequent clinical studies supported this observation. In 2005, Meenakshi K and colleague⁴⁸ measured epicardial fat thickness by echocardiogram in 110 patients who underwent coronary angiography. They found that epicardial fat is independently and linearly associated with CAD severity. Recently, Hwang et al.,⁴⁹ performed a serial Coronary Computerized Tomogram of coronary artery (CTA) in 122 asymptomatic cases who had no CAD at baseline study. After the mean follow up of 65.4 months, EAT and diabetes mellitus independently predicted the development of new non-calcified plaque with the odd ratio of 4.29 and 9.0 respectively. All of these studies supported the paracrine effect of EAT by creating local inflammation, from outside to inside the coronary artery, and contributed to atherosomatous plaque formation.⁴⁷⁻⁵⁰ Without studying the inflammatory marker of EAT, we could only ask the question but could not confirm this hypothesis in this reported case.

Conclusion

We report a sudden death after exercise of a relatively young man who had no other conventional coronary risk factors except for treated dyslipidemia. Thus, all risk calculators failed to predict this fatal event. With no other major risk factors, his advanced atherosclerosis and fatal event could have resulted from various factors. The thick EAT, which had been previously shown to be the site of the inflammatory marker, was found and possibly induced CAD development. The presence of MB of the mid LAD, 10 mm depth and 20 mm long (also known as pathologic anatomy), could reduce coronary flow during exertion leading to ischemia. The chronic use of COX-2 inhibitor could precipitate vascular thrombosis and an ischemic event. In retrospect, the inferior Q wave on ECG and the calcium score, if it had been done, might have been a better predictor of risk in our case. This case reminds us that prediction of sudden death in young AMI patient remains one of a challenging issues. We should keep searching for unidentified risk factors to find the better ways to predict and prevent these catastrophic events.

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