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Case Report

A silent myocardial infarction with normal coronary arteries associated with Graves' disease

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ABSTRACT

Acute myocardial infarction (AMI) is a scarce but fatal complication in Graves' disease (GD). Silent myocardial infarction (MI) associated with GD has never been reported. A 37-year-old male patient was admitted due to poorly controlled hyperthyroidism and persistent fever. But the patient did not complain of chest pain on admission. The electrocardiogram (ECG) showed Q waves and ST-segment elevations. Cardiac troponin I (cTnI) was sharply increased. He was qualified to an emergency coronary angiography which showed normal coronary arteries without any stenosis. The potential mechanisms for AMI with angiographically normal coronary arteries in the setting of hyperthyroidism may be attributed to the hyper-metabolic state due to thyrotoxicosis, severe vasospasm in coronary artery, coagulation abnormalities, and the inflammatory/autoimmune milieu. In conclusion, patients with GD-associated silent MI are unusual. Early recognition and diagnosis by clinicians provide a better prognosis. This case demonstrates the importance of ECG and cTnI screening among GD patients.

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in adults. The clinical manifestations of GD are diversified and it may involve multiple organ systems, including neuromuscular, cardiovascular, gastrointestinal, reproductive, and ocular systems.[1] Amongst, systolic hypertension and arhythmia are two common cardiovascular complications.[1] Acute myocardial infarction (AMI) induced by hyperthyroidism is unusual.[2–4]

AMI with few or no symptoms is called silent myocardial infarction (MI). To our knowledge, silent MI associated with GD has never been reported. The purpose of this report is to describe the case of a 37-year-old man who presented GD-associated silent MI with normal coronary angiography.

Case report

A 37-year-old Chinese man was admitted to our hospital with chief complaint of palpitation, poor appetite and persistent fever. Notably, he did not show symptoms of chest tightness, chest pain or dyspnea. He was diagnosed as GD for 6 years, but refused the treatment with anti-thyroid medications. He suffered from palpitation for the past year. Twenty days ago, he developed symptoms of poor appetite and nausea, followed by a persistent fever a week prior to admission. The temperature ranged from 37.5 °C to 38 °C, without noticeable infective triggers (e.g., cold, respiratory tract infection, etc).

The patients did not exposed to emotional stress, extreme cold, or intense physical exercise recently. And he did not have diabetes, connective tissue disorders, migraine headache, or numbness/cold in the extremities based on medical history. The patient had smoked for 18 years (approximately 10 cigarettes per day) but did not addicted to alcohol or cocaine. The subject's family history was unremarkable.

On physical examination, he appeared acutely ill, but his consciousness was fairly clear. The patient's heart rate was 124 beats per minutes, respiration rate was 20/min, blood pressure was 110/73 mmHg, and body temperature was 37.4 °C. There was no discoloration in the extremities. His thyroid could be touched, grade-II enlargement without palpable thyroid nodule. His neurologic and muscular examinations were unremarkable.

The electrocardiogram (ECG) (Fig. 1A) on admission revealed Q waves in leads II, III, aVF and 1.5–4 mm of ST-segment elevations in

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CMRI, cardiac magnetic resonance imaging; cTnI, cardiac troponin I; CT, computed tomography; CRP, C reactive protein; CK-MB, creatine kinase-muscle/brain; ECG, electrocardiogram; GD, Graves' disease; IL-6, interleukin-6; LDH, lactate dehydrogenase; MI, myocardial infarction; OCT, optical coherence tomography; SCAD, spontaneous coronary artery dissection; TSH, suppressed thyroid-stimulating hormone; T4, thyroxine; TRAb, thyroid-stimulating hormone receptor antibodies; T3, triiodothyronine

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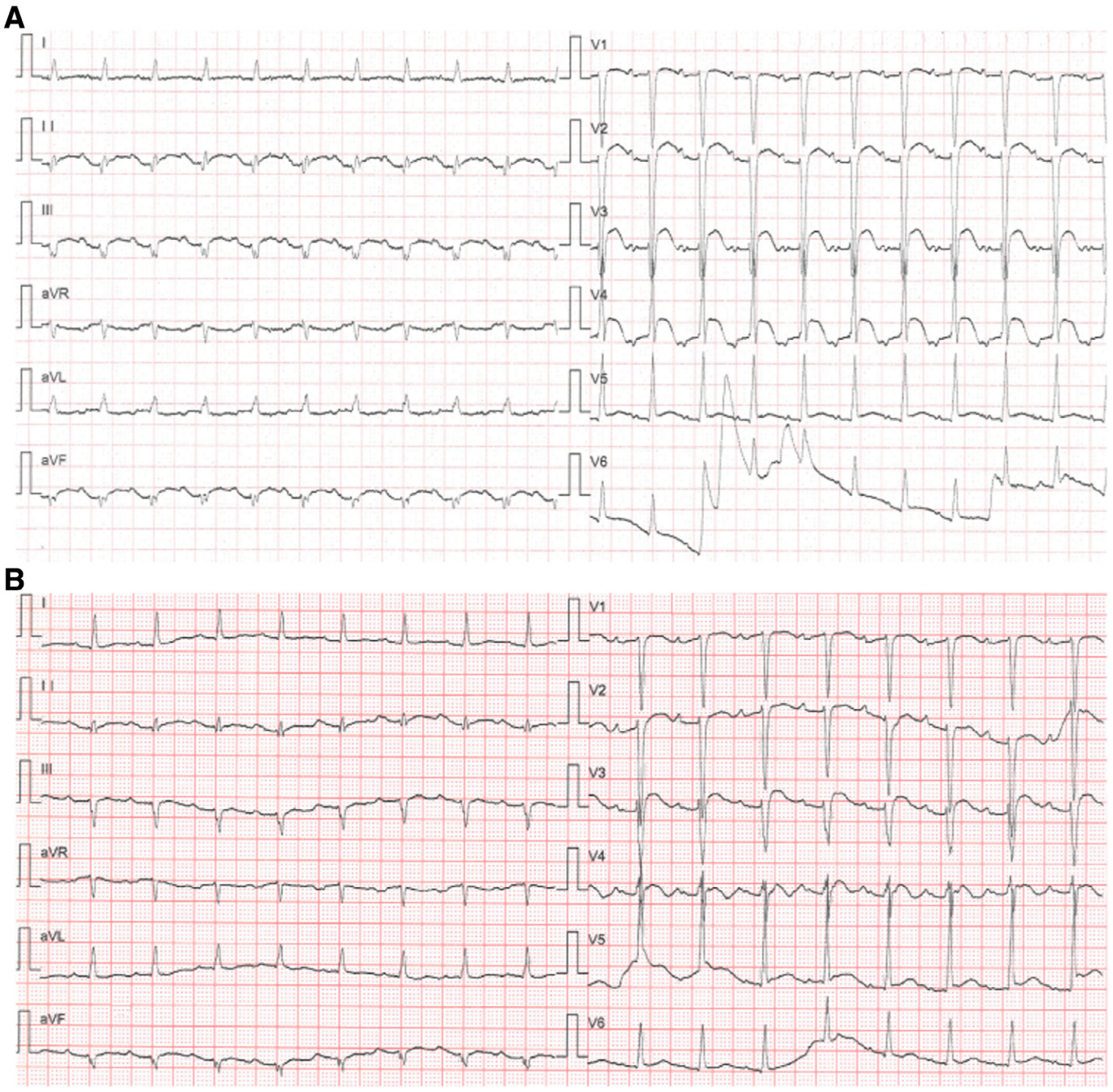

Fig. 1. (A) ECG of the presented patient with an acute myocardial infarction on admission day. (B) ECG of the presented patient at discharge.

leads II, III, aVF as well as V2–V4. The cardiac troponin I (cTnI) was 5995 pg/mL (normal value ≤ 34.2 pg/mL) (Fig. 2). There was no electrolyte or acid-base disturbances in this patient. The levels of fasting glucose and lipids, blood coagulation tests and D-dimer were within normal range. In addition, no abnormalities of lactate dehydrogenase (LDH), antibodies/antigens of adenovirus, influenza virus, and respiratory syncytial virus were observed in the current case. Echocardiographic evaluation revealed anterior mitral leaflet prolapse with moderate cardiac insufficiency. No pericardial effusion was observed. We diagnosed silent MI based on typical ECG findings and elevated troponin levels without chest pain. The emergency coronary angiography was performed within 1 h after his arrival at our hospital. The result revealed normal coronary arteries with no sign of any suspicious stenosis, spontaneous coronary artery dissection (SCAD), or atherosclerosis (Fig. 3). Thereafter, the concentration of troponin (Fig. 2) and the ST-segment elevation in ECG (Fig. 1B) decreased gradually.

The patient was still hyperthyroid with markedly elevated serum-free thyroxine (T4), triiodothyronine (T3), thyroid-stimulating hormone receptor antibodies (TRAb), and suppressed thyroid-stimulating hormone (TSH) (Table 1). The thyroid ultrasound scan revealed a diffusely enlarged thyroid gland with small nodules in the parenchyma of right gland. The clinical score of Burch-Wartofsky was 30, meaning a little possibility of thyrotoxic crisis. He was treated with methimazole and propanolol during hospitalization. The thyroid function of the patient was significantly improved with free T3 3.08 pg/mL and free T4 20.44 ng/L on the day of hospital discharge (Table 1).

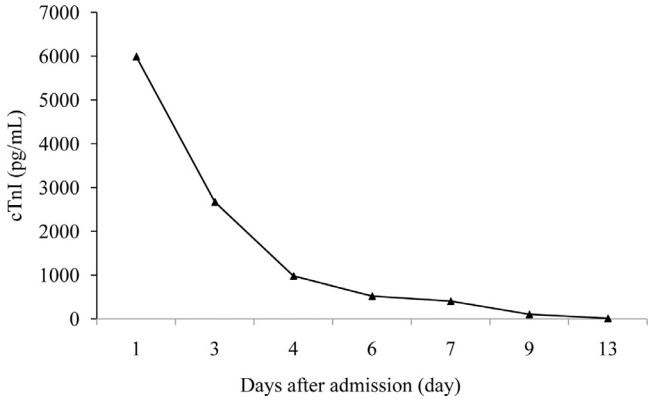

Fig. 2. The troponin concentration changes of presented patient during the period of hospitalization.

The temperature of the patient was 37.5–38 °C one week prior to admission. Full blood count showed slightly increased monocytes (1.44×10^9/L) and neutrophils (10.23×10^9/L). C reactive protein (CRP), interleukin-6 (IL-6), and ferritin concentration presented an obvious increase as well. The titers of anti-dsDNA antibodies, antinuclear antibodies, anticardiolipin antibodies and lupus anticoagulant were within normal range. There were no other clinical or biological clues of bacterial/virus infections according to physical examination and imaging tests including chest X ray and pulmonary computed tomography (CT). The patient was diagnostic treated with Moxifloxacin (0.6 g /day), cefoperazone sodium and tazobactam (2.25 g /day). However, his temperature fluctuated between 36.3 and 38 °C. Thus, it was assumed that the fever may be attributed to inflammation and autoimmune status according to the elevation of CRP, interleukin-6 and ferritin. Then, we treated the patient with methylprednisolone (40 mg/day) and the temperature could immediately return to normal range.

Two months later, the patient was admitted to our hospital for I^{131} treatment. The follow-up observation revealed that neither AMI attack nor persistent fever occurred up to now.

Discussion

We present the case of silent MI with normal coronary arteries associated with GD in a young man according to the clinical evidences of cTnI and ECG. Notably, there are some diseases that should be considered for the differential diagnosis. Although myocarditis may result in the similar changes in cTnI and ECG, no typical clinic symptoms were observed. In addition, there was no significant history of viral infections and the screen for myocardial enzyme spectrum and respirovirus was negative, indicating that it is not likely for the patient to have myocarditis. Moreover, there were no clinical signs suggestive of coronary vasculitis caused by autoimmune disorders, such as Behçet's disease, systemic lupus erythematosus, antiphospholipid syndrome, and Takayasu disease, according to the negative autoimmune antibodies and the normal coronary angiography.

Kim et al. had reviewed all cases of AMI induced by thyrotoxicosis and found 10 cases have been described in the English literature since 1990.[3] Of note, silent MI as the initial presentation in the setting of hyperthyroidism has never been reported. Interestingly, the coronary angiography of these patients indicated either coronary spasm or normal coronary arteries.[3] Howbeit, the specific mechanism in hyperthyroidism-associated MI without coronary artery stenosis is still not thoroughly understood. To date, there are several hypothetical pathogenic mechanisms for this issue. First, it is assumed that the hypermetabolic state in the condition of hyperthyroidism augments cardiac oxygen consumption, resulting in the relative inadequacy of oxygen supply in the myocardium.[3]

Second, severe spasm in coronary artery, which may be partly attributed to hyper-reactivity of vascular smooth muscle to norepinephrine,[5] could trigger the onset of AMI as well. It is known that there are various causes which could induce the attack of coronary

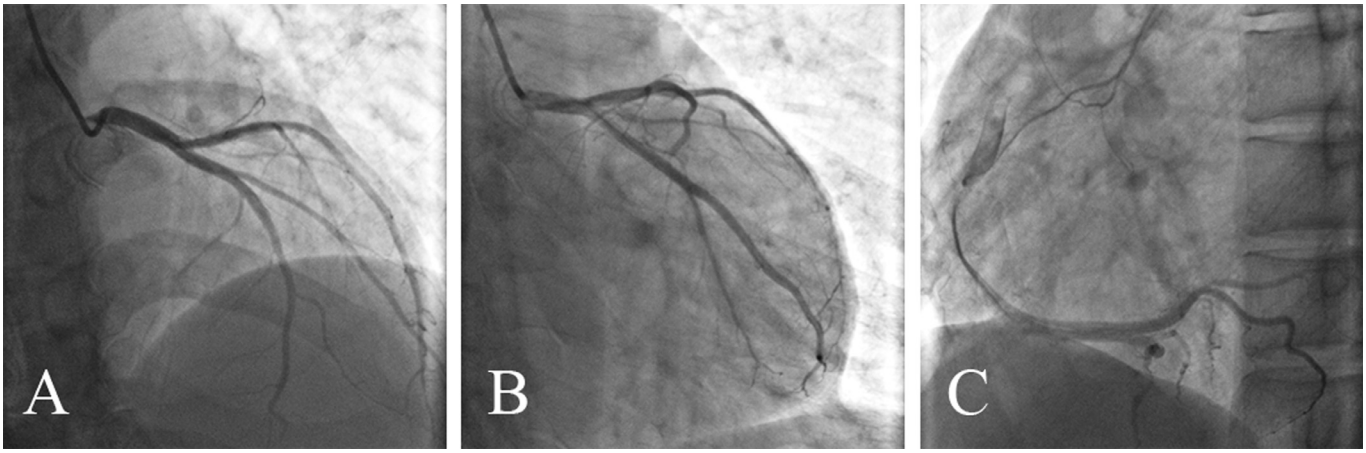

Fig. 3. Coronary angiography for left circumflex artery (A), left anterior descending artery (B), and right coronary artery (C).

Table 1
Results of thyroid function and thyroid auto-antibodies

	TSH	FT3	FT4	TG	A-TG	A-TPO	TRAb
Normal range	0.27–4.2 (uIU/mL)	2–4.4 (pg/mL)	9.32–17.09 (ng/L)	3.5–77 (ug/L)	0–155 (IU/mL)	0–34 (IU/mL)	0–1.58 (IU/L)
1st Admission	0.011	11.44	71.76	48.16	855.7	193.5	21.05
1st Discharge	0.006	3.08	20.44				
2nd Admission	0.005	23.13	77.69	35.99	855.4	194.4	16.8

TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TG, thyroglobulin; A-TG, thyroglobulin autoantibodies; A-TPO, antithyroid peroxidase antibodies; TRAb, thyroid-stimulating hormone receptor antibodies

spasm including hyperventilation, raynaud phenomenon, migraine headache, catecholamine surge, low level of serum magnesium, smoking, alcohol-cocaine abuse, etc.[6] All these triggers, except smoking, were not identified in this patient. Interestingly, Lewandowski et al. also reported that a young female smoker had AMI with coronary artery spasm as the first presentation of thyrotoxicosis.[7] In addition, vasospasm in coronary artery was identified to be more prominent in smokers.[8] We assumed that hyperthyroidism combined with cigarette smoking may be adequate to drive the balance towards development of coronary artery spasm. Accordingly, it is worthwhile to identify whether smoking and thyrotoxicosis state act synergistically that contribute to the vasospasm and the subsequent onset of AMI.

Third, hyperthyroidism is often accompanied by coagulation abnormalities. The increased prothrombotic substances (e.g., von Willebrandt factor) and reduction of anticoagulative factors such as protein C and plasmin-antiplasmin complexes add the likelihood of thrombus formation.[3,8] Such abnormality might be another factor that result in the hyperthyroidism associated AMI.

Fourth, GD related autoimmune milieu may also be involved in the onset of AMI. An elevation of IL-6 has been found in the condition of acute coronary syndrome (ACS).[9] Meanwhile, IL-6 is an important pathogenic cytokine for GD development.[10] One could postulate the potential role of IL-6 in the development of AMI in the setting of GD. It would be significant to investigate the correlation between the AMI risk in GD and the titer of IL-6. Interestingly, titers of IL-6, ferritin, and CRP were markedly increased in this young man who had no typical cardiovascular risk factors except the smoking habit. Moreover, persistent fever could be efficiently controlled by methylprednisolone. Collectively, these evidences indicated inflammatory and immune responses in the subject, which may be one of the main pathogenic mechanisms of GD-associated AMI.

Furthermore, silent MI presenting in the current case has parallel lethality and recurrence rate compared with recognized MI.[11] So far as we know, this is the first case report of silent MI in a patient with GD and no previous study has investigated the relationship between these two clinic conditions. It would be significant to identify the underlying molecular mechanisms. More importantly, due to the occult characteristics of silent MI, awareness of the possibility of such serious complication in GD patients would provide a better prognosis. This case demonstrates the potential clinical value of ECG and cTnI as routine screening among GD patients, especially in subjects with smoking habit and high levels of inflammatory mediators.

Howbeit, the current case has some limitations. Firstly, cardiac magnetic resonance imaging (CMRI) has been considered as a sensitive and specific tool in assessing myocardial viability.[12] We lacked the data of CMRI due to the financial pressures the patient faced. Secondly, SCAD could be provoked by various pathological situations or emotional/physical stress, such as severe hypertension, atherosclerosis, collagen diseases, cocaine abuse, intense emotional trauma, peripartum episode, etc.[13] Although we did not recognize any possible triggers in the current case and the angiography failed to identify any clues for SCAD, optical coherence tomography (OCT) should be performed to rule out the possibility of this disease. Thirdly, we did not monitor the dynamic changes of inflammatory mediators (such as IL-6, CRP, ferritin, etc.), which would be significant to uncover the pathogenic mechanism of inflammation and autoimmunity in GD associated silent MI.

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S Shao and S Hu conceived paper and approved final version. S Shao and C Li wrote the manuscript. C Li and F Chen collected the patient information. X Yu revised manuscript and data interpretation.

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