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CME ARTICLE

Diabetes mellitus and heart disease

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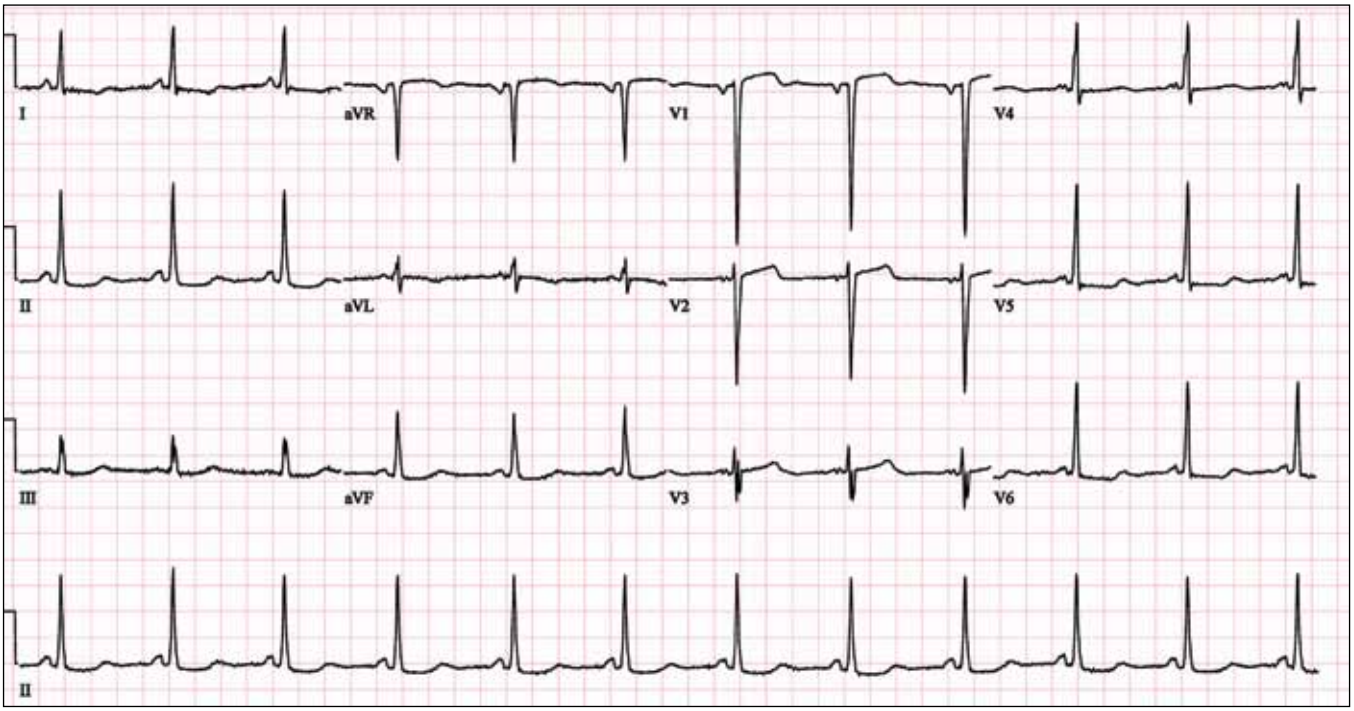

Fig. 1 ECG shows ST-T segment changes in the inferolateral leads.

CASE 1
CLINICAL PRESENTATION

A 62-year-old Chinese man was admitted with central, nonradiating chest pain associated with breathlessness and palpitation, which lasted 10 minutes while at rest. He had been having intermittent exertional central chest discomfort over the past few months. He suffered from hypertension, type 2 diabetes mellitus and dyslipidaemia, and had a past history of eczema. He neither smoked nor consumed alcohol. On examination, his blood pressure (BP) was 188/105 mmHg and his heart rate was 107 beats per minute (bpm). Cardiovascular and other systemic examinations were unremarkable. What does the electrocardiogram (ECG) in Fig. 1 show?

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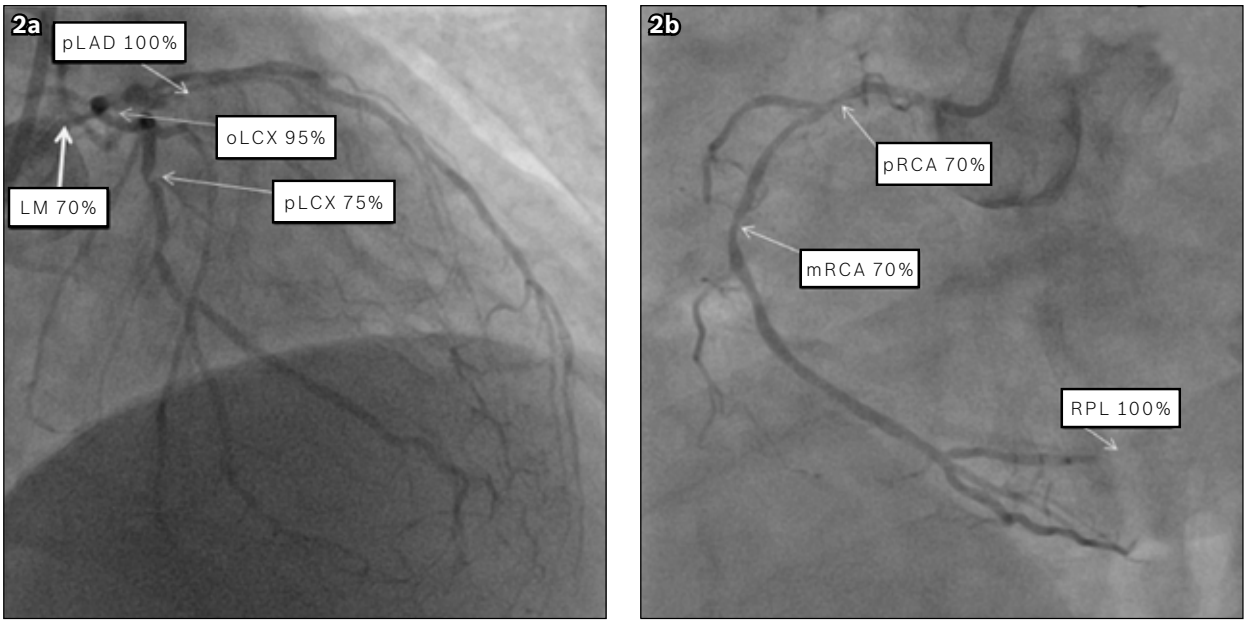

Fig. 2 (a) Coronary angiography (right anterior oblique-caudal view) shows diffuse left main and triple vessel disease. (b) Coronary angiography (left anterior oblique view) of the right coronary artery shows diffuse involvement in the proximal, mid and distal segments.
LM: left main coronary artery; mRCA: mid segment of right coronary artery; oLCX: ostial segment of left circumflex coronary artery; pLAD: proximal segment of the left anterior descending coronary artery; pLCX: proximal left circumflex coronary artery; pRCA: proximal segment of right coronary artery; RPL: right posterolateral branch of right coronary artery

ECG INTERPRETATION

ECG shows a 1-mm ST segment depression in the inferolateral leads, i.e. II, III, aVF, V5–6, with T wave inversion in leads I and aVL (Fig. 1).

CLINICAL COURSE

Cardiac enzymes showed normal creatine kinase (CK) level and myocardial fraction (CK-MB), but a mildly elevated troponin I level (0.431 µg/L; normal < 0.039 µg/L). Based on the clinical presentation of angina at rest, dynamic ST depression on ECG and elevated troponin levels, the patient was diagnosed with non-ST segment elevation myocardial infarction (NSTEMI).

Coronary angiography (Fig. 2a) showed diffuse left main and triple vessel disease (LM-TVD), with 70% stenosis of the mid left main (mLM) coronary artery, 100% stenosis of the proximal left anterior descending (pLAD) coronary artery, 95% ostial and 75% proximal stenoses of the left circumflex (LCX) coronary artery, 70% stenosis of the obtuse marginal 1 artery and 80% stenosis of the obtuse marginal 2 artery. Fig. 2b showed 70% stenoses of the proximal and mid segment of the right coronary artery (RCA), and 100% occlusion of the right posterolateral (RPL) branch of the RCA.

The haemoglobin and serum creatinine levels of the patient were normal. Risk factor evaluation revealed a glycated haemoglobin level of 7.5%. Lipid panel showed mixed dyslipidaemia (total cholesterol 5.76 mmol/L; low-density lipoprotein cholesterol 2.88 mmol/L; high-density lipoprotein cholesterol 1.25mmol/L; triglycerides 3.58 mmol/L). Echocardiography showed moderate left ventricular systolic dysfunction (ejection fraction 35%), with multiple regional wall motion abnormalities and increased left ventricular wall thickness. The patient was started on dual antiplatelet therapy (aspirin and clopidogrel), low-molecular-weight heparin (LMWH), beta-blockers, angiotensin-converting enzyme inhibitor, statin and nitrate. In view of the diffuse LM-TVD and presence of diabetes mellitus, coronary artery bypass grafting (CABG) was offered as a preferred choice for revascularisation. The patient initially declined CABG, and against medical advice, was discharged with medical therapy. He was readmitted with intractable angina and agreed to undergo CABG. He subsequently underwent emergency CABG with three grafts – left internal mammary artery to the left anterior descending coronary artery, and saphenous venous grafts to the right posterior descending branch of the right coronary artery and obtuse marginal branch of the LCX coronary artery.

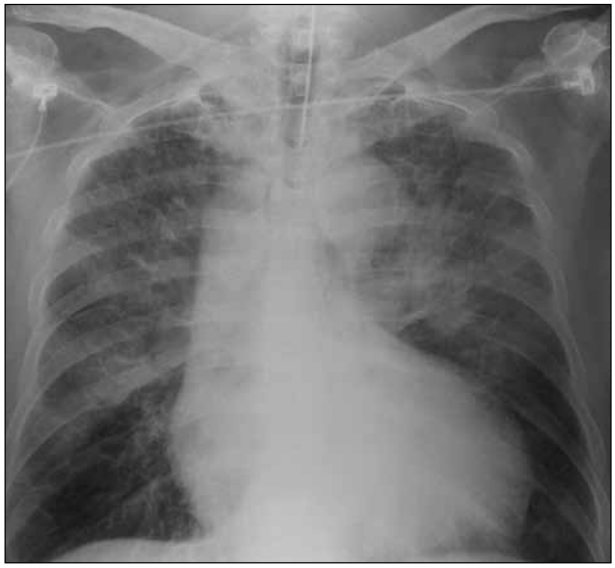

Fig. 3 Chest radiograph shows bilateral upper lobe diversion associated with acute pulmonary oedema and cardiomegaly.

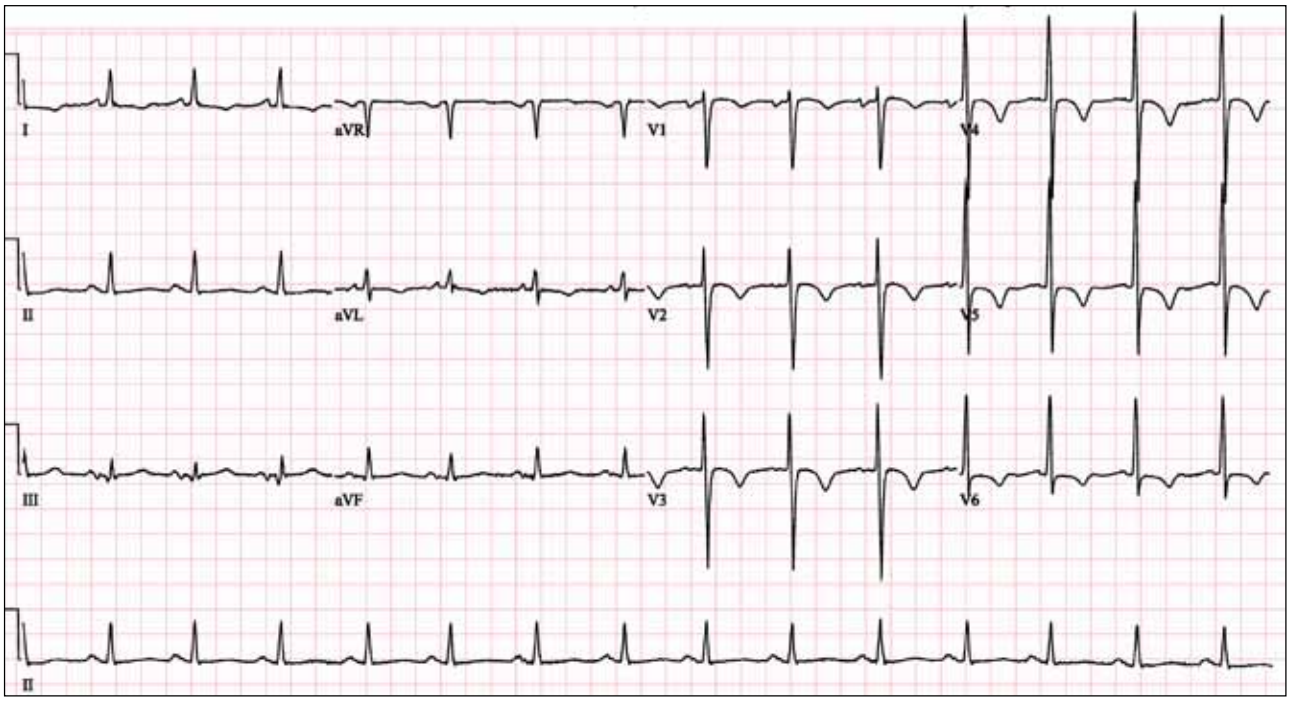

Fig. 4 ECG shows sinus rhythm with deep T wave inversion and prolonged QTc interval.

CASE 2
CLINICAL PRESENTATION

A 65-year-old man, who was a former chronic smoker and social drinker, was admitted with acute onset of breathlessness associated with wheezing and diaphoresis, without chest pain or palpitations. He denied any history of fever or cough, and had a longstanding history of diabetes mellitus, hypertension, dyslipidaemia, chronic obstructive pulmonary disease and microcytic hypochromic anaemia. The patient had tried nebulisation at home without relief. When the patient first presented to the emergency department, he was feeling drowsy and gasping for breath, and needed to be intubated.

In the intensive care unit, the patient's heart rate was 92 bpm and his BP was 103/67 mmHg. Cardiovascular examination revealed dual heart sounds with a soft, nonradiating ejection systolic murmur at the aortic area. Respiratory examination revealed extensive bilateral wheezes with crepitation and reduced air entry at the lung bases. Post intubation, chest radiograph showed diffuse air space and interstitial opacities in both lungs, with upper lobe diversion and evidence of cardiomegaly (Fig. 3). The findings were suggestive of acute pulmonary oedema. Describe the ECG in Fig. 4.

ECG INTERPRETATION

ECG showed sinus rhythm, normal axis and deep T wave inversion in leads V2–V6, and prolonged QTc interval (491 msec).

CLINICAL COURSE

Soon after the patient was intubated and admitted to the cardiac intensive care unit, arterial blood gas analysis showed hypoxia with severe respiratory acidosis (pH 7.0, pCO_2 118.5 mmHg with pO_2 at 67 mmHg, SaO_2 79%). Other laboratory investigations revealed raised white blood cells with neutrophilic predominance and raised inflammatory markers, including C-reactive protein and procalcitonin. Serum creatinine and urea levels were 127 mmol/L and 6.0 mmol/L, respectively. Blood and sputum cultures were negative. N-terminal pro-brain natriuretic peptide was elevated at 7,370 pg/mL, while serial cardiac enzymes showed normal CK level and CK-MB, with borderline raised troponin I at 0.180 µg/L.

The patient was diagnosed with acute pulmonary oedema with severe type II respiratory failure. He was treated with mechanical ventilation, intravenous diuretic, antibiotics and bronchodilators with systemic steroids, and extubated on the third day of admission. His medical management was adjusted and optimised. Echocardiogram showed dilated left heart chambers, left ventricular hypertrophy (LVH) and moderate left ventricular systolic dysfunction. The left ventricular ejection fraction was quantitated to be 40%. Coronary angiography revealed normal coronaries, while renal ultrasonography showed evidence of renal parenchymal disease, although renal Doppler was negative for renal artery stenosis. The nonischaemic cardiomyopathy was likely due to diabetic cardiomyopathy.

DISCUSSION

Diabetes mellitus is among the most common chronic diseases in the world, affecting an estimated 180 million people in 2008.[1] It is one of the major risk factors for atherosclerotic vascular disease, including coronary artery disease (CAD). The estimated prevalence of diabetes mellitus among adults in the United States ranges from 4.4% to 17.9%. The disease is associated with a number of micro- and macrovascular complications,

including myocardial infarction, stroke, end-stage renal disease, retinopathy and foot ulcers.[2]

The National Cholesterol Education Program report from the United States, and the guidelines from Europe consider type 2 diabetes mellitus as an equivalent of CAD, thereby elevating it to the highest risk category.[3] Diabetes mellitus remains a major independent cardiovascular risk factor, even after adjusting for advancing age, hypertension, smoking, hypercholesterolaemia and LVH. Multiple earlier studies have observed that diabetes mellitus is associated with more aggressive CAD – with features including greater plaque burden, longer lesion length, different restenotic cascade and impaired event-free survival rates after revascularisation – as compared to the nondiabetic population.[4-7] Multivessel coronary heart disease is also common in asymptomatic patients with type 2 diabetes mellitus, particularly those with two or more coronary risk factors other than diabetes mellitus.[8]

Almost half of all myocardial infarctions are clinically silent or unrecognised, and one-third present with symptoms other than chest discomfort.[9] Silent ischaemia, which is the presence of objective evidence of myocardial ischaemia in the absence of chest discomfort or angina equivalent, is also commonly seen in the diabetic population, with a prevalence of 10%–20% vs. 1%–4% in the general population.[10,11] Acute coronary syndrome (ACS) has evolved as a useful operational term to refer to any constellation of clinical symptoms that are compatible with acute myocardial ischaemia. ACS represents a life-threatening manifestation of atherosclerosis, and encompasses myocardial infarction (STEMI and NSTEMI) and unstable angina (UA). The difference between UA and NSTEMI is prolonged chest pain and a rise in cardiac enzymes in the latter.[12] ACS is usually precipitated by acute thrombosis induced by rupture or erosion of atherosclerotic coronary plaques due to inflammation and plaque disruption, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow.[13] NSTEMI can present with a wide variety of symptoms, including prolonged (> 20 mins) anginal pain at rest or new onset angina, recent destabilisation of previously stable angina (crescendo angina), or post-myocardial infarction angina.

ECG changes in NSTEMI

Patients with NSTEMI typically present with ST segment depression (60%–70%), T wave inversion (10%–20%), or both, in two or more leads. According to the 2012 Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation (ESC/ACCF/AHA/WHF) Task Force, the ECG manifestation of acute myocardial ischaemia include new horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads, and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave, or R/S ratio > 1.[14] The characteristic ECG abnormalities of NSTEMI are ST-segment depression or transient elevation and/or T wave changes. ECG at rest sometimes may not adequately reflect the dynamic nature of coronary thrombosis and myocardial ischaemia.

Implications of ECG changes

In patients with NSTEMI, ST-segment depression portends a worse prognosis than those without, and this is dependent on the severity and extent of ECG changes.[15] The number of leads showing ST depression and the magnitude of ST depression indicates the extent and severity of ischaemia, and correlates with the prognosis.[15]

Some studies have cast doubt on the prognostic value of isolated T wave inversion. However, deep symmetrical inversion of the T waves in the anterior chest leads is often related to significant stenosis of the pLAD coronary artery or main stem. Other features such as an elevation (> 0.1 mV) in lead aVR have been associated with a high probability of left main or triple-vessel CAD and a worse clinical prognosis.[15]

Management of NSTEMI

In the first case, the patient had multiple cardiovascular risk factors with longstanding diabetes mellitus. He presented with typical anginal pain, ECG findings and elevated cardiac enzymes, supporting a diagnosis of NSTEMI. Diagnostic coronary angiography confirmed diffuse LM-TVD, for which the patient underwent CABG.

Management includes early evaluation, risk stratification with scores such as TIMI (Thrombolysis In Myocardial Infarction), GRACE (Global Registry of Acute Coronary Events) and CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines), appropriate optimal medical therapy with antiplatelets, antianginals, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and early invasive or conservative management based on the risk category of the patient.[12]

The TIMI risk score tool, consisting of seven 1-point risk indicators rated on presentation, has been developed and validated for UA/NSTEMI patients,[16,17] and is useful for the prediction of both 30-day and one-year mortality. A second model is based on the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial.[18] Risk models based on the GRACE database have also been developed and validated for in-hospital and six-month outcomes.[19] Therefore, in patients with UA/NSTEMI with high-risk scores, there is increased benefit from more aggressive therapies such as heparin, LMWH,[20,22] platelet glycoprotein IIb/IIIa inhibition,[22] and an invasive strategy.[23]

Diabetes mellitus is associated with aggressive CAD, and some investigators now believe that the treatment of CAD differs between patients with diabetes mellitus and the

nondiabetic population. The BARI (Bypass Angioplasty Revascularization Investigation) study was one of the earliest to indicate that the diabetic status of a patient could affect the mode of revascularisation.[24] A recent landmark study, FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: optimal management of Multivessel disease), found that CABG was superior to percutaneous coronary intervention with drug eluting stents in patients with diabetes mellitus and advanced (predominantly three-vessel) CAD.[25]

In spite of the recent advances in medical technologies and newer stents, revascularisation in diabetic patients with CAD continues to be challenging.[25] Current evidence suggests that revascularisation needs to be personalised based on multiple factors, such as type and severity of coronary artery involvement, myocardial viability, patient preference, financial concerns, comorbidities and the general condition of the patient.

Our second case was a longstanding diabetic patient who presented with acute pulmonary oedema that required invasive ventilation, secondary to non-ischaemic cardiomyopathy. In the absence of significant CAD, it was likely a manifestation of diabetic cardiomyopathy.

As compared to nondiabetic individuals, patients with diabetes mellitus have a two- to five-fold increased risk of heart failure and worse outcomes once heart failure has developed.[26] This increased risk of heart failure observed in diabetic patients is multifactorial and may be a result of ischaemic, metabolic and functional myocardial perturbations.[27] The term 'diabetic cardiomyopathy' was first coined in the early 1970s by Rubler, who identified four patients with diabetic nephrosclerosis and nonischaemic cardiomyopathy during an autopsy.[28] Diabetic cardiomyopathy has since been defined as ventricular dysfunction (both systolic and diastolic) that occurs in diabetic patients, and is independent of other causes such as CAD, hypertension and valvular heart disease. LVH is commonly observed even in the absence of hypertension.[29,30]

Pathogenesis of diabetic cardiomyopathy

Pathologic abnormalities that have been identified in the diabetic heart include myocardial lipid overload, altered substrate use, oxidative stress, fibrosis, inflammation and mitochondrial dysfunction. Although significant progress has been made in the understanding of the disease, the precise cause of diabetic cardiomyopathy remains controversial.[31] Some of the pathogenic factors implicated are glucotoxicity (leading to increased formation of advanced glycated end products, causing oxidative stress), lipotoxicity (causing myocardial cell steatosis, fibrosis, impaired calcium handling, abnormal protein C kinase signalling, and increased apoptosis) and inflammation (leading to myocardial cell fibrosis and death or irreversible damage).[30,31] Some features of diabetic cardiomyopathy include LVH, increased left ventricular filling pressures, diastolic dysfunction, and in later stages, systolic dysfunction.[32,33]

ECG changes in diabetic cardiomyopathy

There are no specific ECG changes seen in diabetic cardiomyopathy. These may vary from nonspecific ST-T changes to intraventricular conduction defects, low voltage in standard leads, LVH, left atrial enlargement, arrhythmias such as atrial fibrillation, or even transient ST elevation or depression in cases of stress-related cardiomyopathies.

Management of diabetic cardiomyopathy

Although tighter glycaemic control is associated with a lower risk of heart failure, a causal relationship between glycaemic control and heart failure has not been established. The treatment of heart failure in diabetic patients remains similar to that in nondiabetic patients. Evidence from a meta-analysis of beta blocker trials in heart failure, which included 1,883 diabetic and 7,042 nondiabetic subjects, showed that the survival benefit with beta blocker therapy was significant for both groups, with no significant difference between the two groups.[34]

The SOLVD (Studies of Left Ventricular Dysfunction) and SAVE (Survival and Ventricular Enlargement) trials have shown that both diabetic and nondiabetic patients benefit equally from ACE inhibitors.[34-36] In a meta-analysis of ACE inhibitor trials in heart failure, comprising 2,398 diabetics and 10,188 nondiabetics, the survival benefit with ACE inhibitor therapy was found to be similar for those with and without diabetes mellitus.[34] Hence, the mainstay of heart failure treatment for diabetic patients remains the same as that for nondiabetics. Treatment includes medical management with anti-failure measures, beta blockers, ACE inhibitors/angiotensin II receptor blockers, spironolactone, and in selected cases, device therapy with cardiac resynchronisation. Left ventricular assist devices and heart transplant may be indicated in advanced cases.

ABSTRACT Diabetes mellitus is responsible for diverse cardiovascular complications such as accelerated atherosclerosis, increased plaque burden and diffuse coronary lesions. It is also a major risk factor for myocardial infarction, stroke and peripheral vascular disease. Here, we present two cases. The first patient had subtle changes in the ECGs, with severe coronary artery disease requiring coronary artery bypass grafting, while the second had deep T wave inversion in the ECG and was found to have normal coronary arteries and nonischaemic cardiomyopathy. Although ECG failed to show the severity of the disease, it is invaluable as a simple, noninvasive test to aid in diagnosis. Our two cases stress the importance of a high index of suspicion and the low threshold for investigations in the diabetic population.

Keywords: diabetes mellitus, diabetic cardiomyopathy, diffuse coronary artery disease, management, non-ST elevation myocardial infarction

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201307A)

	True	False
Question 1. The following is true of the pathophysiology of diabetic cardiomyopathy:		
(a) Diabetic cardiomyopathy is only seen with coronary artery disease.	☐	☐
(b) Systolic dysfunction develops before diastolic dysfunction.	☐	☐
(c) Abnormal calcium handling, myocardial lipid overload, and advanced glycated end products are implicated in the pathogenesis of diabetic cardiomyopathy.	☐	☐
(d) Diabetic cardiomyopathy is only seen in type I diabetes mellitus.	☐	☐
Question 2. In the ACC/AHA guidelines, the following can be found about NSTEMI:		
(a) ST depression in two or more consecutive leads can be seen in NSTEMI.	☐	☐
(b) T wave inversion is a poor prognostic factor in NSTEMI.	☐	☐
(c) NSTEMI has replaced the term non-Q myocardial infarction.	☐	☐
(d) ECG can be normal in NSTEMI.	☐	☐
Question 3. The following is true of the treatment of NSTEMI in the diabetic population:		
(a) After percutaneous intervention, diabetic patients are more prone to repeated coronary procedure.	☐	☐
(b) The FREEDOM study proved the superiority of percutaneous coronary intervention over coronary artery bypass grafting in multivessel coronary artery disease.	☐	☐
(c) Recurrent coronary events after a myocardial infarction are more common in diabetic than in nondiabetic patients.	☐	☐
(d) Diabetic patients invariably suffer from multivessel coronary disease.	☐	☐
Question 4. The following is true of diabetic cardiomyopathy:		
(a) ACE inhibitors do not help in the treatment of diabetic cardiomyopathy.	☐	☐
(b) Beta blockers play a role in the treatment diabetic cardiomyopathy.	☐	☐
(c) Diabetic cardiomyopathy can be associated with minor but diffuse coronary artery disease.	☐	☐
(d) Without hypertension, left ventricular hypertrophy is not seen in diabetic cardiomyopathy.	☐	☐
Question 5. The following ECG changes can be seen in cardiomyopathy:		
(a) Atrial fibrillation.	☐	☐
(b) Deep inverted T waves.	☐	☐
(c) Intraventricular conduction abnormalities.	☐	☐
(d) Left atrial enlargement.	☐	☐

Doctor's particulars:

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SUBMISSION INSTRUCTIONS:
(1) Log on at the SMJ website: http://www.sma.org.sg/cme/smj and select the appropriate set of questions. (2) Select your answers and provide your name, email address and MCR number. Click on "Submit answers" to submit.

RESULTS:
(1) Answers will be published in the SMJ September 2013 issue. (2) The MCR numbers of successful candidates will be posted online at www.sma.org.sg/cme/smj by 27 August 2013. (3) All online submissions will receive an automatic email acknowledgement. (4) Passing mark is 60%. No mark will be deducted for incorrect answers. (5) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council. (6) One CME point is awarded for successful candidates.

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