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Case Report
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A Chest Pain Patient Quadruples Possible Cardiac Syndromes-Acute Coronary Syndrome, Takotsubo Syndrome, Cardiac Anxiety Syndrome and Kounis Syndrome: A Challenging Case Report and Review of the Differentiation

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Abstract

This case report illustrates the clinical course and differentiation of severe cardiac syndromes in a female patient in her 50s presenting with acute chest pain, meanwhile in allergic state and stress condition. The patient was totally relieved from chest pain by oral anti-histamine and further stay was uneventful. The first impression was cardiac anxiety syndrome. As the troponin elevated with typical ECG changes, coronary angiography and left ventriculography was performed. The negative findings indicated the diagnosis as MINOCA, possible Kounis syndrome. The cardiac MR imaging of the patient classified the final diagnosis as TTS. Cardiologists should be aware of the possible cardiac syndromes in one patient, which may have important clinical implications particularly in the presence of concomitant non-atherosclerotic disease, allergic state and stress condition. This discreet differentiation helps to avoid unnecessary therapy or even coronary intervention.

Keywords: Chest pain; Acute coronary syndrome; Takotsubo syndrome; Cardiac anxiety syndrome; Kounis syndrome

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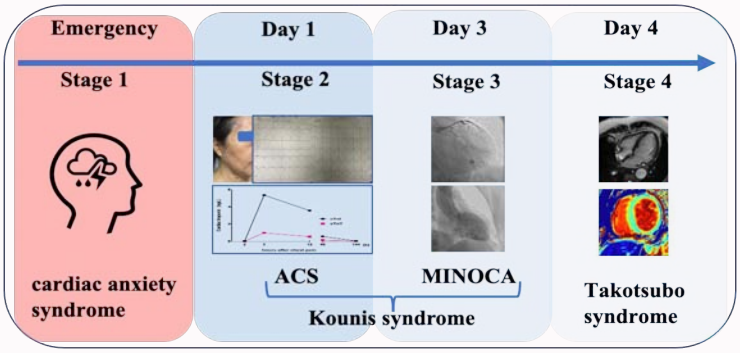

Graphical Abstract:

Introduction

Acute Chest Pain (ACP) accounts for a significant number of reasons that people seek medical care [1]. Differentiation and triage of emergency department patients with ACP, especially suspected Acute Coronary Syndrome (ACS), consume a large and increasing amount of healthcare resources. It has been estimated that over 9 million ED patients with ACP are seen annually in the United States alone, with related healthcare costs of $13–15 billion [2].

Women who present with chest pain are at risk for underdiagnosis, and potential cardiac causes should always be considered. When an anxious woman presents to ED with chest pain after sudden extreme stress, the differentiation of three syndromes-acute coronary syndrome, heartbroken

syndrome and cardiac anxiety syndrome-might be the priority [3]. Immediately related screening tests are followed as: Electrocardiogram (ECG), myocardial injury markers, and even coronary angiography. That can help identify relevant diagnoses and triage. Dynamic or typical ECG for cardiac ischemia, or myocardial injury markers such as troponins, elevation can differentiate cardiac anxiety syndrome from acute coronary syndrome and effort syndrome [4].

Coronary angiography and left ventriculography partially contribute to identify the diagnosis of acute coronary syndrome and Takotsubo Syndrome (TTS) [5]. If a chest pain patient with allergic reaction presents to ED, Kounis syndrome is also included to the differentiation. Kounis syndrome (KS) is defined by the occurrence of an Acute Coronary Syndrome (ACS) in the setting of an allergic, hypersensitivity or anaphylactic condition [6]. The syndromes may overlap together, when an anxious woman with allergic condition presented with chest pain in the ED. In this case, we describe a case of anxious woman presenting with chest pian associated with urticaria. The differentiation and management of this kind of patients will be briefly discussed.

Our case report illustrates that the presence of allergic condition and anxiety state makes the differentiation of acute chest pain more challenging and requires careful discrimination and management in order to reduce the risk of cardiovascular complications, as well as unnecessary coronary intervention.

Almost no previously published articles have focused on four possible cardiac syndromes in one patient along state of the disease progress, particularly with normal coronary angiography results, typical cardiac injury marker elevation and no typical apical ballooning. This was a secondary aim of the present case study.

Case Presentation

Stage 1 at ED

A 58-year-old female patient presented with a five-hour history of retrosternal chest pain, associated with suffocation and sweating. Ten minutes later, the symptom of chest pain slightly relief after taking "loratadine". Then the patient came to the ED of Peking University of Shenzhen Hospital for further treatment. On arrival at the ED, the patient reported the chest pain already totally resolved.

The patient had a history of hypertension and anxiety. Although the patient denied any allergic history, yet his face has some urticaria as shown in Figure 1A. She was a non-smoker and had no history of drug abuse. The vital signs were unremarkable (temperature was 36.3°C, the pulse 76 beats per minute, the blood pressure 126/78 mmHg, the respiratory rate 20 breaths per minute, and the oxygen saturation 98% while he was receiving ambient air). The weight was 60 kg and the body-mass index (the weight in kilograms divided by the square of the height in meters) 24. The emergency ECG showed ST segment depression in inferior leads and V4-V6 leads (Figure 1B). At the ED, blood level of troponin T and I were negative, as high sensitivity-cTnT 0.007 ng/ml (reference range: >0.1 ng/ml) and cTnI <0.012 ng/ml (reference range: 0-0.034 ng/ml).

Stage 1: The current diagnosis impression was "cardiac anxiety syndrome", also named cardiac neurosis. It is estimated based on negative troponin, no typical ECG manifestation and anxiety history.

Stage 2: One day after admission

Given the allergic state, hypertension and further investigate the potentially atypical reason for the chest pain, the patient admitted in the cardiovascular department. As shown in Figure 1B and 2, the ECG and cardiac troponin were tested again. The T waves inversion in precordial leads were presented compared with the admission relative normal ECG. Furthermore, the blood troponins also elevated significantly compared with that of the first time at ED as shown in Figure 2.

Stage 2: The correction diagnosis for the patient was non-ST elevated myocardial infarction based on dynamic ECG changes and elevated myocardial injury markers. Given the allergic state, combined with, Kounis syndrome might be the potential reason for the coronary injury. Therefore, the physician considered the woman should immediately perform coronary angiography to revascularize the culprit coronary to save the risk cardiomyocytes. The patient was anxious with adverse outcome of the intervention and rejected the operation. So, the patients only received drugs management (aspirin, ticagrelor, fondaparinux, rosuvastatin, sacubitril valsartan and metoprolol succinate). On the second days after admission, the patient's ECG changes were presented as more deep T inversion (data not shown) and more elevated in cardiac troponin compared with the first day after admission as shown in Figure 2.

Stage 3: 3 days later

On the third day after admission, the patient accepted the intervention through the doctor's effective communication. The CAG results were shown in Figure 3. The left main and three branches (LAD, LCX and RCA) were normal. Thereafter, left ventriculography was performed to identify the potential apical ballooning for takotsubo syndrome. The result was also negative.

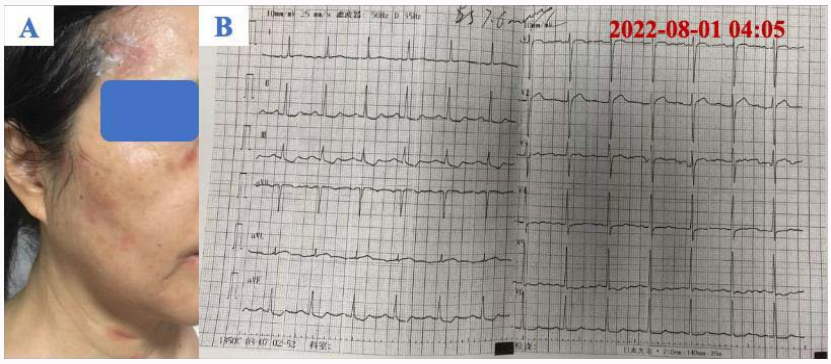

Figure 1: An acute chest patient present with urticaria on her face and atypical ischemia ECG. (A) urticaria on the patient's face; (B) the ECG shown ST slightly depression on the Inferior wall lead.

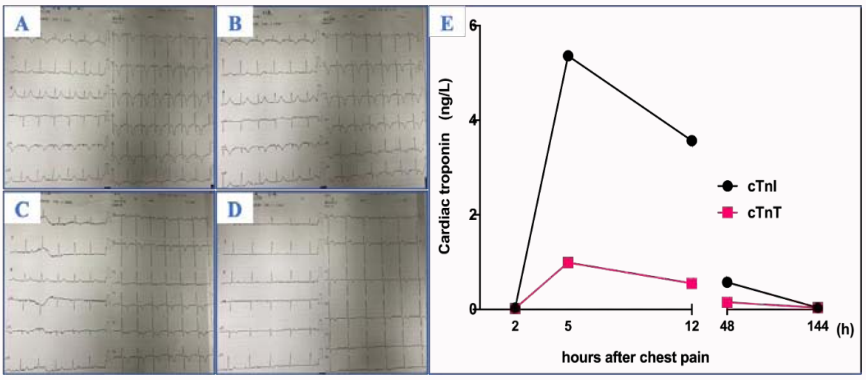

Figure 2: ECG and the troponin dynamics of the patients. (A-D), ECG changes with precordial T inversion. (E), troponin changes of the patients with rapid increased at five hours after chest pain and immediately decreased.

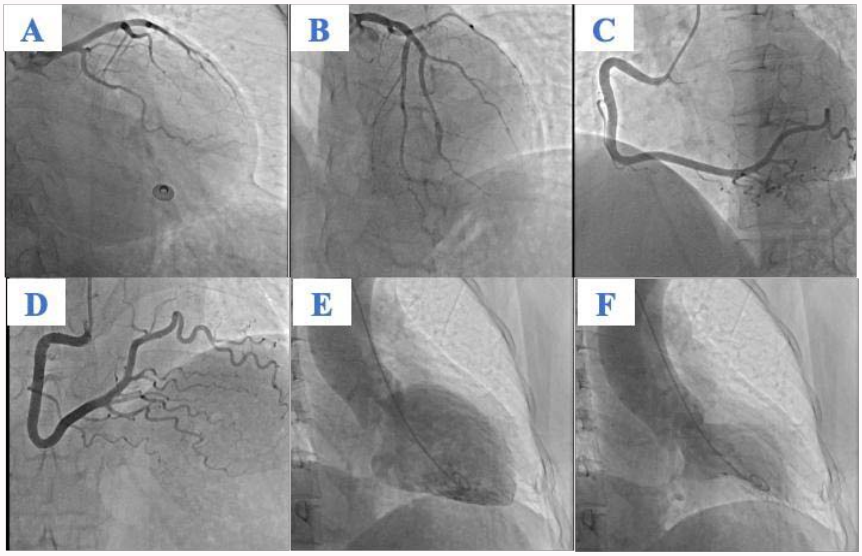

Figure 3: Coronary angiography and left ventriculography of the patients. (A-D), coronary angiography showed normal coronary artery. (E-F), left ventriculography showed normal ventricular function and contour in diastolic and systolic phrase.

Stage 3: The current correction diagnosis for the patient was Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA), and potential reason were type I Kounis syndrome (coronary spasm).

Stage 4: 4-day latter

Finally, cardiac Magnetic Resonance (cMR) was performed to evaluate the possible myocardial injury reason. Late gadolinium enhancement cardiac magnetic resonance imaging was used to diagnose a broad range of ischemic, non-ischemic or scar cardiomyopathies. As shown in Figure 4 no significant changes were found on the cMR. Tracing back the medical history, she had a fierce dispute with his family before the onset of chest pain.

Stage 4: Final diagnosis was TTS based on CAG (normal coronary), cMR results (no clue of cardiac injury) combined with completed recovery of cardiac function. Unfortunately, the apical ballooning on the left ventriculography or any cardiac dysfunction disappeared without any evidence.

At 6-month follow-up, the patient did not report recurrent angina or any other cardiovascular events.

Discussion

There are several interesting and confusing points to this case study due to the possible overlap cardiac syndrome in the patients. The patient was atypically acute chest pain relieved by oral loratadine, anti-histamine drug. Confused by her anxiety history, totally relieved symptom and negative cardiac troponin, the first depression was cardiac anxiety syndrome. With further in-depth inspection, the diagnosis wavered between TTS and MINOCA.

Due to the overlap in typical clinical presentation with Acute Coronary Syndrome (ACS), it is difficult to distinguish TTS from ACS at its initial clinical presentation, practically mixed several confounding factors. For the present case, rapid relief of chest pain, allergic state, delay of invasive inspection, no cardiac dysfunction and no typical TTS manifestation were the potential reason to increase the difficulty of differentiation.

ACS-MINOCA *vs.* TTS

Myocardial infarction in the absence of obstructive coronary artery disease is found in ≈5% to 6% of all patients with acute infarction who are referred for coronary angiography [7]. The term

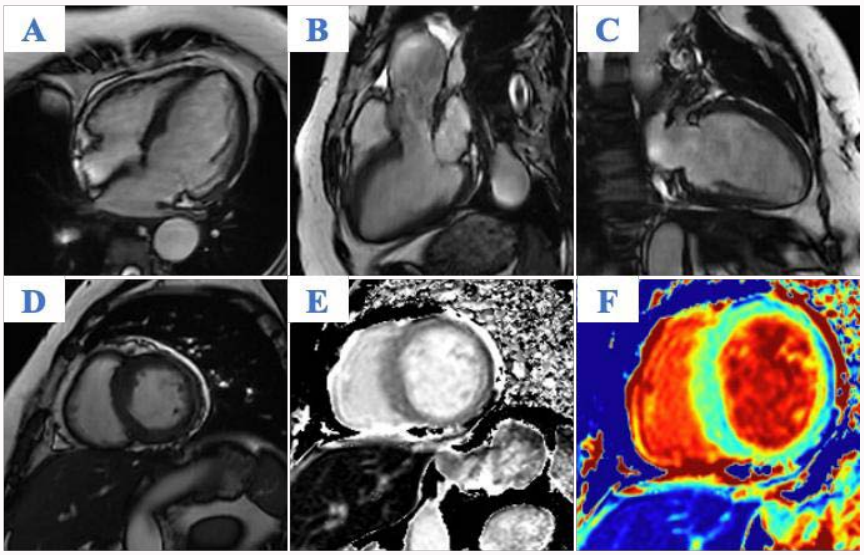

Figure 4: Cardiac MRI showed that no evidence of myocardial infarction by Late Gadolinium Enhancement (LGE). (A-D), 4 lumens, 3 lumens, 2 lumens and short axis; (E-F), T1 and T2 mapping of the myocardial evidence.

labelled as MINOCA. The dilemma is that elevated troponin, the evidence of myocardial injury, don't coexist with coronary stenosis, which is easily confused with other diseases with myocardial injury, such as myocarditis, Takotsubo syndrome. To this end, there is also a special scientific statement from the American Heart Association to classify and summarize them [7]. Just as this case shown, the patient had increased troponin, typical ischemia ECG and totally normal coronary artery. Therefore, the first impression diagnosis is MINOCA. Follow the guideline [7], cardiac Magnetic Resonance Imaging (cMRI) is recommended as a key investigation in MINOCA because it can exclude myocarditis, takotsubo syndrome, and cardiomyopathies, as well as provide imaging confirmation of AMI. Negative results of cMRI had excluded MINOCA for the patient. Given complete and rapid recovery of myocardial injury, Takotsubo syndrome was considered the first consideration for diagnosis. In the clinical setting, Takotsubo syndrome (TTS) is one of the most important diseases that must be accurately differentiated from Acute Coronary Syndrome (ACS) to enable appropriate follow-up and medical management. Criteria for takotsubo syndrome require the wall motion abnormalities to be transient [8]. Unfortunately, due to time delay, there is no evidence of wall motion abnormalities for the patient. Takotsubo syndrome: The mechanism (ischemic *vs.* nonischemic) responsible for this intriguing disorder remains uncertain. Consideration of the rapid recovery of cardiac injury, no evidence of myocardial infarction and the history of anxiety and stress. The final diagnosis was takotsubo syndrome. Although takotsubo syndrome can clinically mimic MINOCA, it appears to be a distinctly different syndrome and therefore should be considered separately.

Allergic history and Kounis syndrome

Allergy is a very common problem in clinical work, and the clinical value and management of allergy history are easily ignored [9]. Acute anaphylaxis combined with myocardial infarction is called Kounis syndrome (KS). Three types of KS have been described [10]. Type I involves patients with normal coronary arteries in whom the acute allergic insult induces coronary artery vasospasm with or without progression to acute myocardial infarction and cardiac enzyme elevation. The present case appeared as this type of Kounis syndrome. If patients with quiescent pre-existing atheromatous disease in whom the allergic episode induces plaque erosion or rupture, manifesting as an acute myocardial infarction, this kind was defined as type II. Type III of Kounis syndrome demonstrated as patients with coronary stent thrombosis (type III-a) or stent restenosis (type III-b) with histologic evidence of eosinophils and mast cells.

The present case has allergic condition, some urticaria on his face. Coincidently the acute chest pain of the patient was relieved by oral loratadine, anti-histamine drug. When the patient presented like MINOCA, type I Kounis syndrome was the first consideration. A retrospective cohort study of 235,420 people hospitalized for allergy in the United States showed that 2,616 people (1.1%) had new acute coronary syndrome, including 0.2% unstable angina, 0.2% ST segment elevation myocardial infarction and 0.7% non-ST segment elevation myocardial infarction [10]. In the clinical setting, when a chest pain patient presented with allergic condition, Kounis syndrome should include in the differential diagnosis.

Clinical Implications

Cardiologists should be aware of overlapping cardiac syndromes in one patient. Given the complex of chest pain and potential risk of this kind of patient, prudently differentiation for confused syndrome, such as ACS, Kounis syndrome, cardiac anxiety syndrome and TTS. This case is a classic and actual interpretation of the identification of the cardiac syndrome in the clinical setting step by step. It is important to note that in patients without an atherosclerotic stenosis, the correct differentiation diagnosis of MINOCA, either Kounis syndrome is of paramount importance to avoid unnecessary anti-platelet therapy or even coronary stenting. TTS should keep in mind when a patient present with stress condition or anxiety state. Given the transient abnormality of cardiac function, examinations, such as echocardiography and coronary angiography should be performed as soon as possible.

Finally, whether cardiac MRI can reveal the acute or chronic consequences of cardiac injury in terms of Late Gadolinium Enhancement (LGE) and/or scar in myocardium is fully investigated and should be on agenda for the differentiation diagnosis.

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