CLINICAL CASES IN CARDIOVASCULAR MEDICINE: 2021

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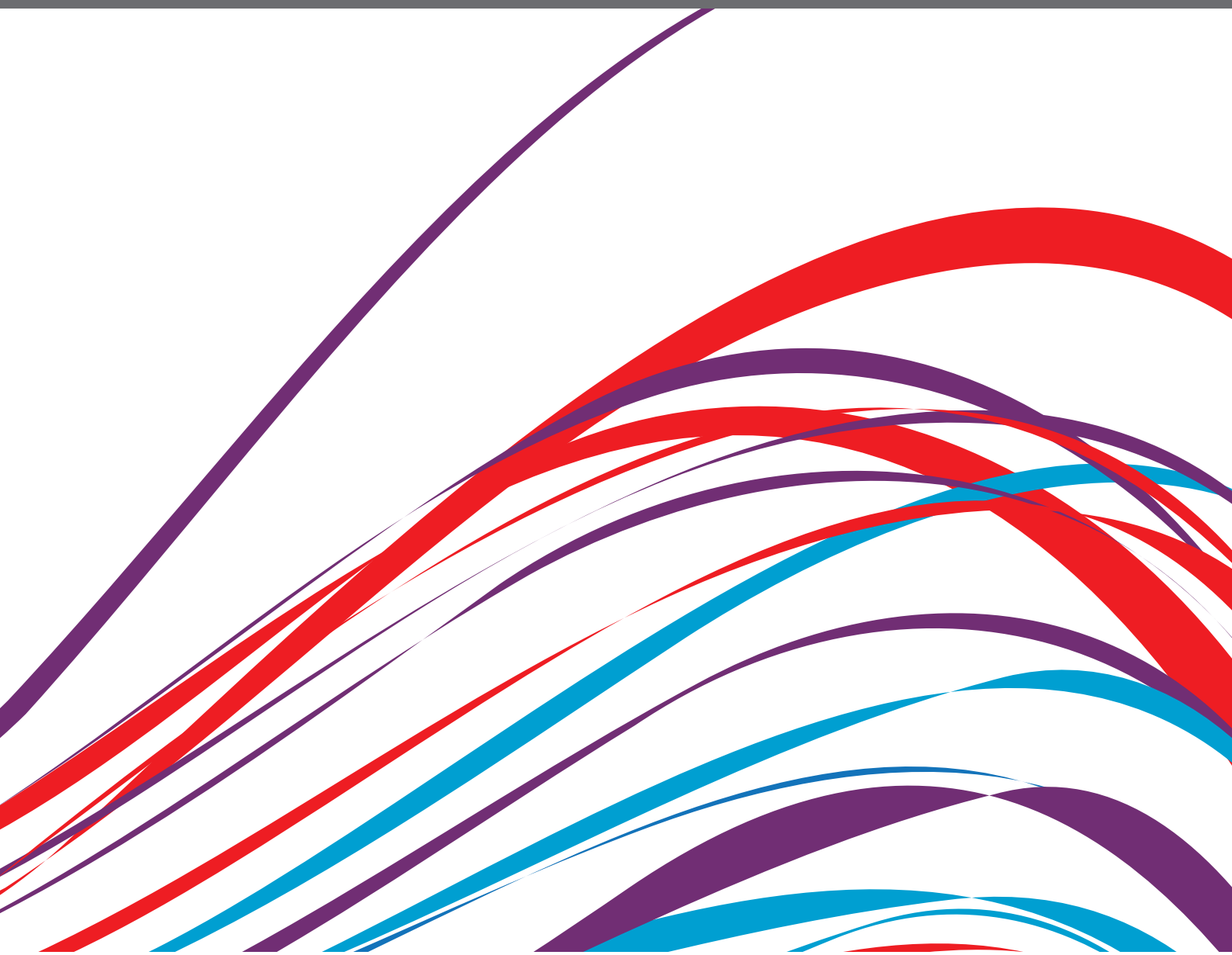

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CLINICAL CASES IN CARDIOVASCULAR MEDICINE: 2021

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EDITORIAL
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Editorial: Clinical Cases in Cardiovascular Medicine: 2021

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Keywords: myocardial infarction, systemic inflammation, pheocromocytoma, myocardial bridging, extracorporeal shockwave myocardial revascularization, multisystem inflammatory syndrome, Wolff-Parkinson-White syndrome, eosinophilic granulomatosis

Editorial on the Research Topic

Clinical Cases in Cardiovascular Medicine: 2021

In the present Frontiers Research Topic, an international selection of high-quality case reports contributed to advance our understanding of personalized approaches to cardiovascular diagnosis and treatment, beginning with the patient physician communication, to bedside clinical assessment, advanced diagnostic and imaging technologies.

Indeed, these case reports provided insight into the differential diagnosis, decision making, and clinical management of unusual cases, also representing a valuable educational tool.

Several contributions (Li and Liu; Wu et al.; Ye et al.) focused on rare symptoms that can be occur in specific cardiac diseases, suggesting the presence of multiple and complex pathogenic mechanisms (1, 2).

In this view, Ye et al. presented a case of acute myocardial infarction as a rare complication of acute chlorpyrifos poisoning. The complex relationships between poisoning and myocardial infarction are not only represented by the great variety of symptoms, but also by the conflicts of treatments for both conditions. Indeed, atropinization contributes to the control of muscarinic symptoms of chlorpyrifos poisoning, but can also increase the heart rate and myocardial oxygen consumption, which can worse myocardial ischemia.

Wu et al. showed that some pathological conditions can be diagnosed at the onset of rare symptoms, apparently unrelated with the disease as in the case of a hypertensive 59-older patient with covert pheochromocytoma who had a sudden hypotension and shock. These symptoms are rare and apparently inconsistent with pheocromocytoma, but a possible pathogenic explanation can be related to tumor necrosis that leads to a sudden decrease in continuous catecholamine secretion, with subsequent hypotension.

Furthermore, Li and Liu described another atypical case characterized by a usually benign cardiac congenital anatomical variation, the myocardial bridging (MB) of the coronary artery. However, in the case of a 41-year-old man, the association between MB and hypothyroidism contributed to the occurrence of myocardial infarction. In fact, MB initiated the development of coronary atherosclerotic lesions, but hypothyroidism further contributed to the occurrence of myocardial infarction by multiple mechanisms including endothelial dysfunction, increased platelet activation, hypercholesterolemia, increased levels of low-density lipoprotein cholesterol, and hypertriglyceridemia.

Another study by Akbar et al. focused on the efficacy of specific therapies, such as extracorporeal shockwave myocardial revascularization. Akbar et al. presented a case series of four patients with coronary artery bypass grafting-stable angina pectoris who refused surgery and who underwent

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extracorporeal shockwave myocardial revascularization obtaining an improvement of the ischemic response, functional capacity, and physical component of quality of life.

Systemic inflammation is another pathogenic factor that can interact at multiple levels on the cardiovascular system and many case reports in the present Research Topic pointed out its relevant role. Immuno-inflammatory mechanisms may play a relevant pathogenic role in some cardiac diseases, contributing to development of coronary artery disease (3) and cardiac arrhythmias, modulating both atrial (4, 5) and ventricular substrates (6). The role of inflammatory cytokines has recently become more clear with COVID-19, a systemic inflammatory disease, that can cause myocardial injury (7, 8), with an unexpectedly high prevalence of arrhythmic events (9).

In this respect, Bemtgen et al. described a case of an 18-year-old male patient affected by a multisystem inflammatory syndrome, a novel hyperinflammatory syndrome associated with SARS-CoV-2 infection, where a myocardial biopsy revealed small vessel-associated immune cell infiltrates, without myocardial necrosis, with fast and favorable response to immunomodulatory therapy.

Inflammation can also play an important role in other inflammatory diseases: Cui et al. described an interesting case of eosinophilic granulomatosis with polyangiitis that was manifested as myocardial infarction with non-obstructed coronary arteries. Also in this case, the immunosuppressive therapy led to regression of symptoms with significant clinical resolution.

Alania-Torres et al. described a rare case of patient affected by arrhythmogenic left ventricular cardiomyopathy who developed a myocarditis induced by coronavirus disease 2019 (COVID-19) mRNA vaccine. This case report is particularly interesting from a diagnostic and pathogenic point of view, because both conditions myocarditis and a hot phase of the arrhythmogenic left ventricular cardiomyopathy can have similar ECG, echocardiographic and MRI findings and, moreover, both might be pathophysiologically related.

Yang et al. suggested the further complexity of the relationships between immune modulation and cardiac disease presenting a case of a 33-year-old man with a history of metastatic thymoma treated with sintilimab, who developed grade 3 immune checkpoint inhibitor (ICI)-related myocarditis, complicated with myositis/myasthenia gravis.

Wang et al. described a case of a patient with pneumonia and myocarditis, characterized by the coexistence of Wolff-Parkinson-White (WPW) syndrome and Brugada electrocardiogram (ECG) patterns. Even if this association has already been reported in previous papers, the peculiarity of this case is due to the particular dynamic changes of QRS complex, relating to fever, suggesting the possible modulating role of inflammation on cardiac electrical activity.

In conclusion, the high-quality contributions presented in this Research Topic significantly enriched our knowledge about the field of cardiovascular diseases, shedding light on rare symptoms, complex physiologic and pathogenic mechanisms, that can have relevant implications also for the choice of appropriate treatments in these patients. These studies also provide important suggestions for further investigation in this area.

AUTHOR CONTRIBUTIONS

MA and LR contributed to the conception, design, and drafting of the work. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Pheochromocytoma in a 59-Year-Old Woman Presenting With Hypotension

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Background: Pheochromocytoma patients who present with shock are extremely rare. Here, we report a patient who presented with shock and was diagnosed with pheochromocytoma.

Case Summary: A 59-year-old woman with a history of hypertension without any treatment for 5 years presented with chest tightness. Vital signs on arrival indicated blood pressure of 78/50 mmHg. Twelve-lead electrocardiogram indicated ST-segment depression in leads II, III, aVF, and V3–V6 and QT prolongation. Coronary angiogram revealed no evidence of coronary artery disease. Contrast-enhanced computed tomography demonstrated an inhomogeneous right adrenal mass (2.5 × 3.0 cm). Her 24-h urinary norepinephrine and catecholamine levels were elevated. The patient underwent laparoscopic right adrenalectomy. Histopathology confirmed adrenal pheochromocytoma with residual necrosis. The patient was diagnosed with pheochromocytoma. During the 2-year follow-up, the patient was asymptomatic, and her blood pressure remained normal without medication. ECG showed that the ST-segment depression in leads II, III, aVF, and V3–V6 and the QT prolongation had disappeared. The patient showed no signs of recurrence, with normal urine norepinephrine and catecholamine levels.

Conclusion: Patients with pheochromocytoma can present with hypotension or even shock. Clinicians should suspect pheochromocytoma when a patient with a history of hypertension has sudden hypotension or even shock.

Keywords: pheochromocytoma, hypotension, shock, electrocardiogram, cardiovascular complication

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INTRODUCTION

Pheochromocytoma is a rare neuroendocrine tumor that originates from the adrenal medulla or extra-adrenal paraganglion chromaffin tissue and secretes catecholamines (1). The clinical manifestations of patients with pheochromocytoma are diverse, ranging from asymptomatic to cardiac arrest. The typical triad, including episodic headache, palpitations and sweating, only occurs in 24% of pheochromocytoma patients (2, 3). This often misleads clinicians to make a wrong diagnosis. Hypertension is one of the most common manifestations of pheochromocytoma and can be persistent or paroxysmal.

Shock is defined as insufficient perfusion of organs and peripheral tissues, and is classified as hypovolemic, cardiogenic, or restrictive (vasodilatation/distribution) according to its etiology. However, pheochromocytoma patients who present with shock are extremely rare. The pathophysiological factors of hypotension or shock include tumor necrosis leading to a sudden decrease in continuous catecholamine secretion, adrenergic receptor desensitization, and decreased vascular volume. Here, we report a case of a patient with pheochromocytoma characterized by shock.

CASE PRESENTATION

A 59-year-old woman presented with chest tightness for 2 h. 2 h before admission, the patient experienced chest tightness accompanied by palpitations, dizziness, vomiting and sweating.

The patient had a history of hypertension for 5 years without any treatment or etiological diagnosis. The patient denied a family history of premature coronary artery disease and special personal history, such as smoking and drinking.

Vital signs on arrival indicated blood pressure 78/50 mmHg, heart rate 102 beats per min and a respiratory rate of 26 beats per minute. The patient was conscious, but her lips were cyanotic. Her face was pale, and her extremities were wet and cold. There was no obvious abnormality in the heart or lung examination. Jugular vein engorgement and peripheral edema were not found.

The troponin I level was 1.16 ng/mL (reference interval <0.04). Hemoglobin, leukocytes, electrolytes, B-type natriuretic peptide, liver function, renal function, and D-dimer were not significantly abnormal. Twelve-lead electrocardiogram (ECG) indicated a sinus rhythm with ST-segment depression in leads II, III, aVF, and V3–V6 and QT prolongation (QTc 529 ms) (**Figure 1**). Coronary angiogram revealed no evidence of coronary artery disease (**Figure 2**). Echocardiography showed a thickened ventricular septum (12 mm) and normal left ventricular function without abnormal wall motion (left ventricular ejection fraction of 55%). Chest computed tomography showed no obvious abnormality, but abdominal computed tomography showed an adrenal mass. Contrast-enhanced computed tomography demonstrated an inhomogeneous right adrenal mass (2.5 × 3.0 cm, **Figure 3**). The urinary norepinephrine level was 288.8 nmol/24 h (reference interval 80.3–164.0), and the urinary catecholamine level was 307.4 nmol/24 h (reference interval 94.5–238.3). 24 h urinary epinephrine level was normal.

Saline solution and dopamine injection were administered to maintain blood pressure. The patient's condition gradually improved, and her blood pressure gradually stabilized. 7 days later, the patient was transferred to the urology department and successfully underwent laparoscopic right adrenalectomy. Histopathology confirmed adrenal pheochromocytoma with residual necrosis. Immunohistochemistry confirmed that chromogranin A, neuron-specific enolase and synaptophysin were positive. The patient was diagnosed with pheochromocytoma.

The patient was free of complications during hospitalization. During the 2-year follow-up, the patient was asymptomatic, and her blood pressure remained normal without medication. ECG

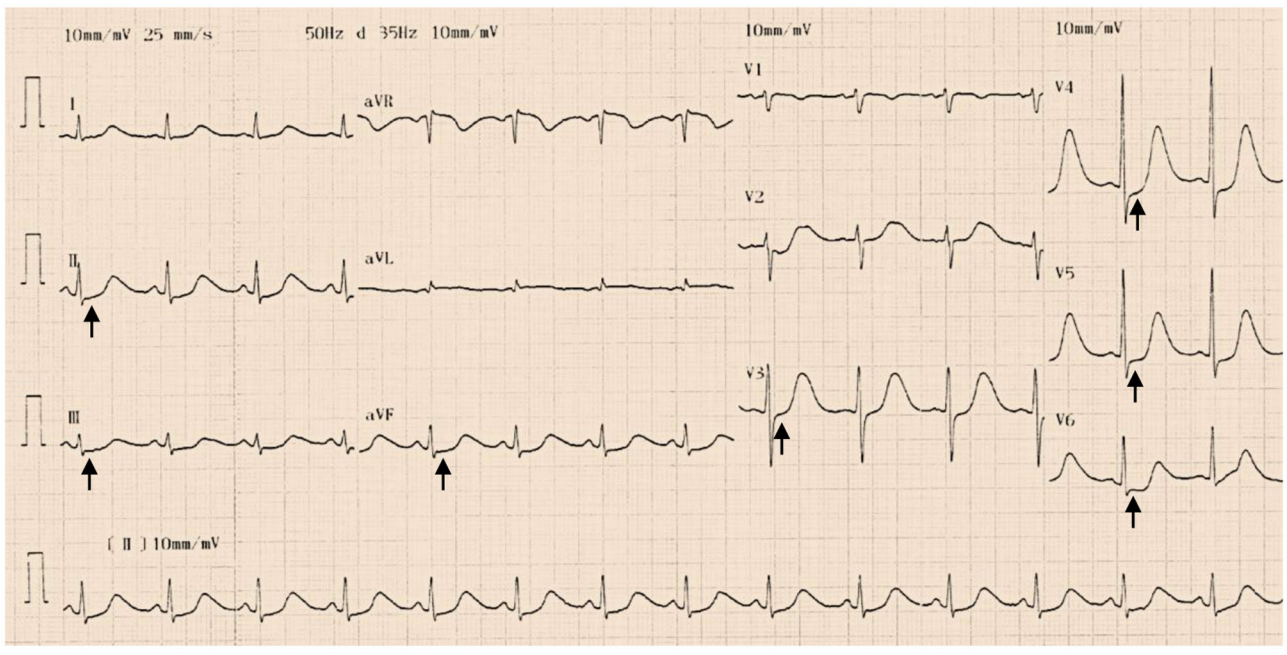

FIGURE 1 | Twelve-lead electrocardiogram indicated a sinus rhythm with ST-segment depression in leads II, III, aVF, and V3–V6 (black arrows) and QT prolongation (QTc 529 ms) at admission.

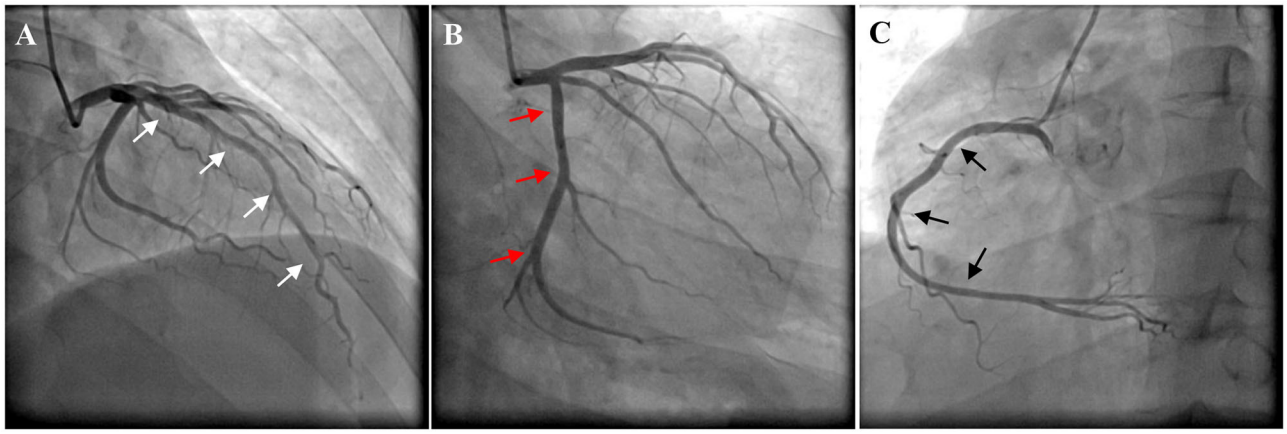

FIGURE 2 | Coronary angiogram revealed no evidence of coronary artery disease. **(A)** Left anterior descending artery (white arrows). **(B)** Left circumflex artery (red arrows). **(C)** Right coronary artery (black arrows).

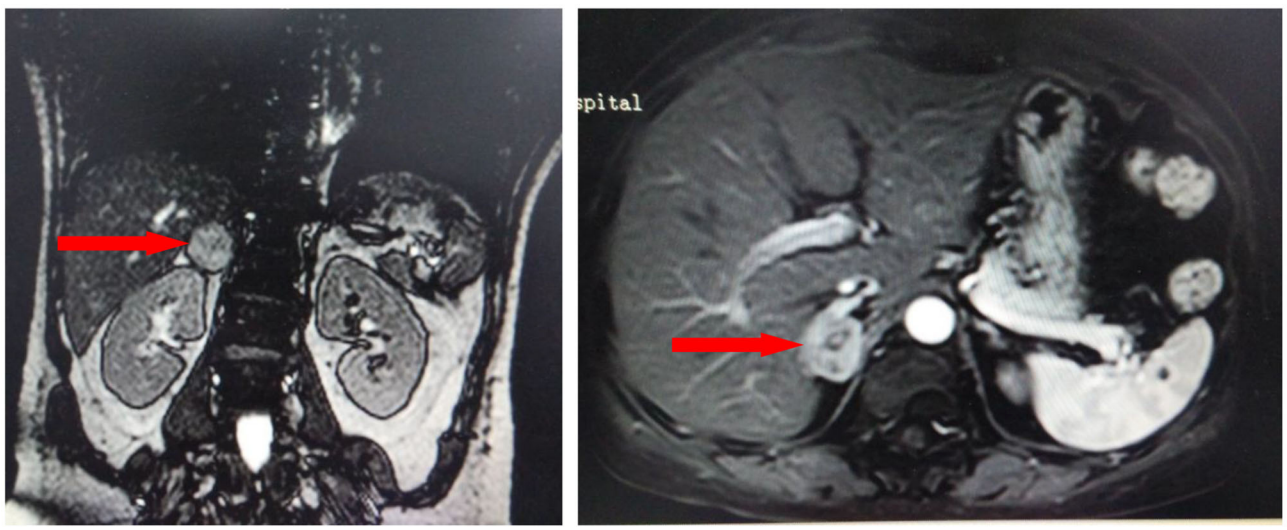

FIGURE 3 | Contrast-enhanced computed tomography demonstrated an inhomogeneous right adrenal mass (2.5 × 3.0 cm, red arrows).

showed that the ST-segment depression in leads II, III, aVF, and V3–V6 and the QT prolongation had disappeared (**Figure 4**). The patient showed no signs of recurrence, with normal urine norepinephrine and catecholamine levels (**Table 1**).

DISCUSSION

Pheochromocytoma can produce excessive amounts of catecholamines, especially epinephrine and norepinephrine, and release them continuously or intermittently (4, 5). Pheochromocytoma has various clinical manifestations. The typical triad of pheochromocytoma, including episodical headache, palpitations and sweating, lasts from a few minutes to a few hours as a direct consequence of excessive catecholamine secretion and is often accompanied by hypertension (6). Approximately 90% of patients with pheochromocytoma present with sustained or paroxysmal hypertension (7, 8). Hypertension in pheochromocytoma usually manifests as high peripheral resistance and low heart index. Norepinephrine secreted by pheochromocytoma increases peripheral vascular resistance, leading to increased systolic and diastolic blood pressure (9). Epinephrine-secreting pheochromocytoma usually causes patients to experience paroxysmal symptoms, such as headaches, palpitations, sweating and anxiety, while patients with norepinephrine-secreting tumors usually have persistent symptoms (such as persistent hypertension) related to the continuous catecholamine overdose (10). In our case, the patient's norepinephrine level was elevated, but the epinephrine level was normal. The patient did not present with the typical triad of pheochromocytoma, which may be because the tumor secreted norepinephrine rather than epinephrine. The patient had a history of hypertension for 5 years, and persistent

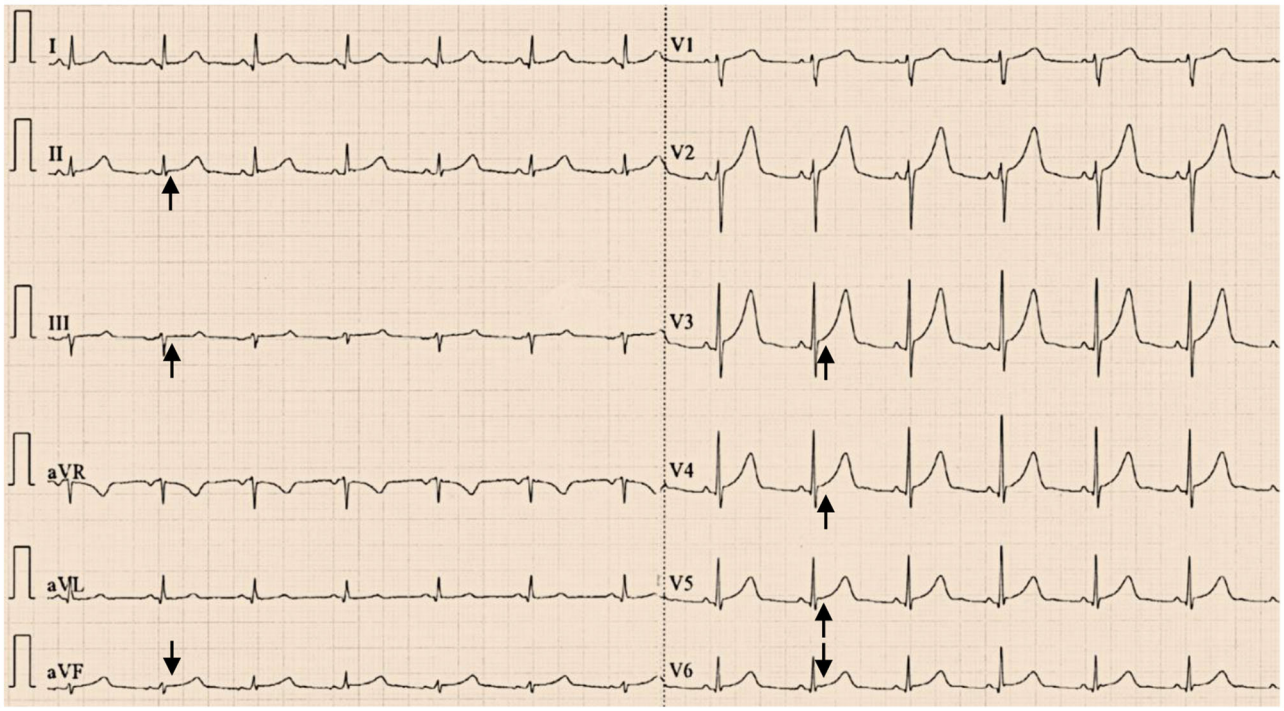

FIGURE 4 | Twelve-lead electrocardiograms showed that the ST-segment depression in leads II, III, aVF, and V3–V6 had disappeared (black arrows) with normal QT interval (QTc 424 ms) at the 2-year follow-up after resection of the pheochromocytoma.

hypertension is related to the continuous catecholamine overdose produced by norepinephrine-secreting tumors.

Occasionally, patients with pheochromocytoma experience hypotension or even shock. The pathophysiological factors of hypotension and shock include tumor necrosis leading to a sudden decrease in continuous catecholamine secretion, adrenergic receptor desensitization, and decreased vascular volume (11). Some cardiovascular events, such as myocardial infarction and arrhythmia, can also cause shock (12). In our case, the pheochromocytoma concomitant with circulatory shock may have been related to the sudden decrease in catecholamine secretion caused by tumor necrosis, and histopathology confirmed an adrenal pheochromocytoma with residual necrosis.

Pheochromocytoma can also cause other cardiovascular complications, including cardiac hypertrophy, heart failure, arrhythmias, ischemic heart disease and even acute myocardial infarction, which are due to the effects of secreted catecholamines (3, 13). Norepinephrine secreted by pheochromocytoma can cause structural and functional remodeling of the heart, such as left ventricular hypertrophy. Catecholamines, especially norepinephrine, can cause myocardial damage by increasing the oxygen consumption and apoptosis of cardiomyocytes and can further lead to left ventricular systolic dysfunction and dilated cardiomyopathy (14, 15). Some factors can lead to an imbalance of the oxygen supply and demand, such as cardiotoxicity of catecholamines, increased muscle mass and coronary artery spasm, causing myocardial ischemic necrosis (16, 17). Patients may have chest pain and tightness, and ECG may manifest as ST-segment elevation or depression. Myocardial enzymes may be elevated (18, 19). In some cases, pheochromocytoma is associated with Takotsubo cardiomyopathy, characterized by reversible left ventricular apical ballooning (20–22). The level

TABLE 1 | Timeline table with relevant laboratory data from the episode of care.

	Patient's value	Reference interval
Initial laboratory values on presentation		
Hemoglobin, g/L	124.0	113.0–151.0
Leukocytes, $\times 10^9$/L	5.6	3.7–9.2
Troponin I, ng/mL	1.16	<0.04
B-type natriuretic peptide, pg/ml	58.0	<76.0
D-dimer, mg/L	0.2	<0.6
Serum sodium, mmol/L	3.9	3.5–5.5
Serum potassium, mmol/L	141.0	135.0–148.0
Creatinine, μmol/L	45.4	45.0–105.0
Alanine aminotransferase, U/L	38.0	5.0–40.0
Glutamic oxaloacetic transaminase, U/L	34.0	5.0–40.0
Urinary norepinephrine, nmol/24 h	288.8	80.3–164.0
Urinary catecholamine, nmol/24 h	307.4	94.5–238.3
Urinary epinephrine, nmol/24 h	18.6	12.5–70.4
Laboratory values at the 2-year follow-up		
Urinary norepinephrine, nmol/24 h	128.2	80.3–164.0
Urinary catecholamine, nmol/24 h	196.3	94.5–238.3
Urinary epinephrine, nmol/24 h	21.4	12.5–70.4

of B-type natriuretic peptide is generally significantly elevated in these patients (23). In our case, the typical wall motion abnormalities of Takotsubo cardiomyopathy were not reflected in echocardiography, and the B-type natriuretic peptide level was normal. Therefore, the suspicion of Takotsubo cardiomyopathy caused by pheochromocytoma was not confirmed. The ECG of patients with pheochromocytoma may also show a variety of abnormalities in the heart rhythm, conduction, and repolarization, including a significantly prolonged QT interval and deep and wide, symmetrical, inverted T waves. A prolonged QT interval may induce the risk of torsade de pointes ventricular tachycardia (24). In our case, preoperative ECG showed ST-segment depression in leads II, III, aVF and V3–V6 and QT prolongation, and follow-up ECG showed that these changes had disappeared after laparoscopic adrenalectomy.

LIMITATIONS

The patient did not undergo echocardiography again to determine whether the ventricular septum returned to normal thickness during the 2-year follow-up.

CONCLUSION

Occasionally, patients with pheochromocytoma can present with hypotension or even shock. Pheochromocytoma should be suspected when a patient with a history of hypertension has sudden hypotension or even shock.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors contributed in this patient care, diagnosis and treatment, and in writing this article, contributed to the article, and approved the submitted version.

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CASE REPORT
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Case Report: Effective Treatment for Acute Chlorpyrifos Poisoning Complicated by a Non-ST-Segment Elevation Myocardial Infarction

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Background: Acute myocardial infarction (AMI) is a rare complication of acute organophosphorus pesticide poisoning. Although chlorpyrifos has been widely used as an organophosphate insecticide, a few cases of AMI complicated by chlorpyrifos poisoning have been reported thus far. Hence, a suitable treatment strategy remains to be explored.

Case Presentation: Based on the clinical manifestations, medical history, results of an auxiliary examination, and serum biomarkers, a 65-year-old male farmer with complaints of nausea, vomiting, chest tightness, and pain was clearly diagnosed as having a severe chlorpyrifos self-poisoning with acute non-ST-segment elevation MI. Because the patient and his family confirmedly refused a coronary intervention, conservative treatment was used instead. It should be noted that there were some conflicts of the management for chlorpyrifos poisoning and AMI. Although rapid atropinization would contribute to the relief of muscarinic symptoms, it would also lead to an increased heart rate and myocardial oxygen consumption in AMI. Furthermore, the reduction of platelet aggregation, which is necessary for coronary recanalization of an AMI patient, is known to aggravate the gastrointestinal injury caused by poisoning. In this case, these conflicts were properly addressed, which led to an excellent effect and prognosis of the patient.

Conclusions: To our knowledge, this is the first case report of acute chlorpyrifos poisoning with AMI. It is emphasized that patients with chest pain or coronary heart disease should be treated with atropine more cautiously because of the possible AMI. Moreover, proper resolution of conflicts in the management for chlorpyrifos poisoning and AMI played contributing roles in patient improvement.

Keywords: acute myocardial infarction, chlorpyrifos poisoning, treatment strategy, atropine, antiplatelet agents

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INTRODUCTION

Chlorpyrifos is a highly efficient, broad-spectrum, organophosphate insecticide that is widely used in agricultural production (1). Compared with traditional organophosphate insecticides, cholinesterase is inhibited more strongly and lastingly by chlorpyrifos. Besides, atropine poisoning is prone to occur during the treatment of chlorpyrifos poisoning (2). Acute myocardial infarction

(AMI) is a rare complication of acute organophosphorus pesticide poisoning that has a high risk of mortality. To our knowledge, this is the first report of chlorpyrifos poisoning combined with AMI. In this report, the disease course and clinical manifestations are introduced in detail. Moreover, conflicts of treatment in chlorpyrifos poisoning and AMI are highlighted. Eventually, the patient showed a dramatic improvement after appropriate medical management.

CASE DESCRIPTION

A 65-year-old male farmer presented to our hospital with complaints of nausea, vomiting, chest tightness, and chest pain in March 2020. Three hours prior to presentation, the patient consumed 400 mL of chlorpyrifos in an attempt to commit suicide. Then, he presented with nausea, vomiting, sweating, and muscle tremors accompanied by slight chest tightness and pain. After he was found by his family, the patient was immediately sent to a local community hospital where gastric lavage was carried out and 10 mg of atropine was intravenously injected. However, the symptoms were not resolved, and his chest pain worsened. For further treatment, he was transferred to our hospital. His medical history included hypertension for 20 years and coronary heart disease for half a year. Six months ago, the patient underwent percutaneous coronary intervention (PCI), during which, a stent was implanted in the left anterior descending coronary artery. He consumed alcohol occasionally and had a 20-year history of smoking and smoked 40 cigarettes per day.

On physical examination, the patient was restless. His axillary temperature was 36.9°C, blood pressure was 145/100 mmHg, heart rate was 105 beats/min (bpm), and respiratory rate was 20 breaths/min. The diameters of both pupils were 4 mm. His heartbeat was fast and regular, without a murmur, and his upper abdomen was mildly tender. The skeletal muscle of the extremities went into spasm, with an increased muscle tone. The lungs were clear, and the neurologic examination was unremarkable.

In the coagulation analysis, the international normalized ratio was 1.52, and the D-dimer level was 1.044 μg/mL. Cholinesterase level was 498 U/L, NT-pro BNP was 3,667.4 pg/mL, cardiac troponin I was 1.005 ng/mL, creatine kinase was 526 U/L, creatine kinase isoenzyme-MB was 34 U/L, alpha-hydroxybutyric dehydrogenase was 220 U/L, and lactate dehydrogenase was 282 U/L. Levels of electrolytes, as well as tests for liver and renal function, were within normal limits. As shown in **Figure 1A**, an electrocardiogram taken at the local community hospital showed a symmetrical negative T wave in leads V1–V6 and an upsloping ST-segment at the J point continuing into positive symmetrical T waves in leads II, III, and aVF. Chest radiography and abdominal ultrasound revealed no obvious abnormalities.

Based on the above clinical manifestations, medical history, result of auxiliary examinations, and level of serum biomarkers, the patient was conclusively diagnosed with an acute non-ST-segment elevation MI, severe chlorpyrifos poisoning, and grade 1 hypertension (very-high-risk group).

After admission to the cardiac care unit, the patient received oxygen by nasal cannula. Because the patient and his family refused coronary intervention, pharmacologic treatment was provided instead. For AMI, the patient was orally administered with 180 mg of ticagrelor, 0.3 g of aspirin, 10 mg of rosuvastatin calcium, and 25 mg of metoprolol tartrate. For hypertension, oral

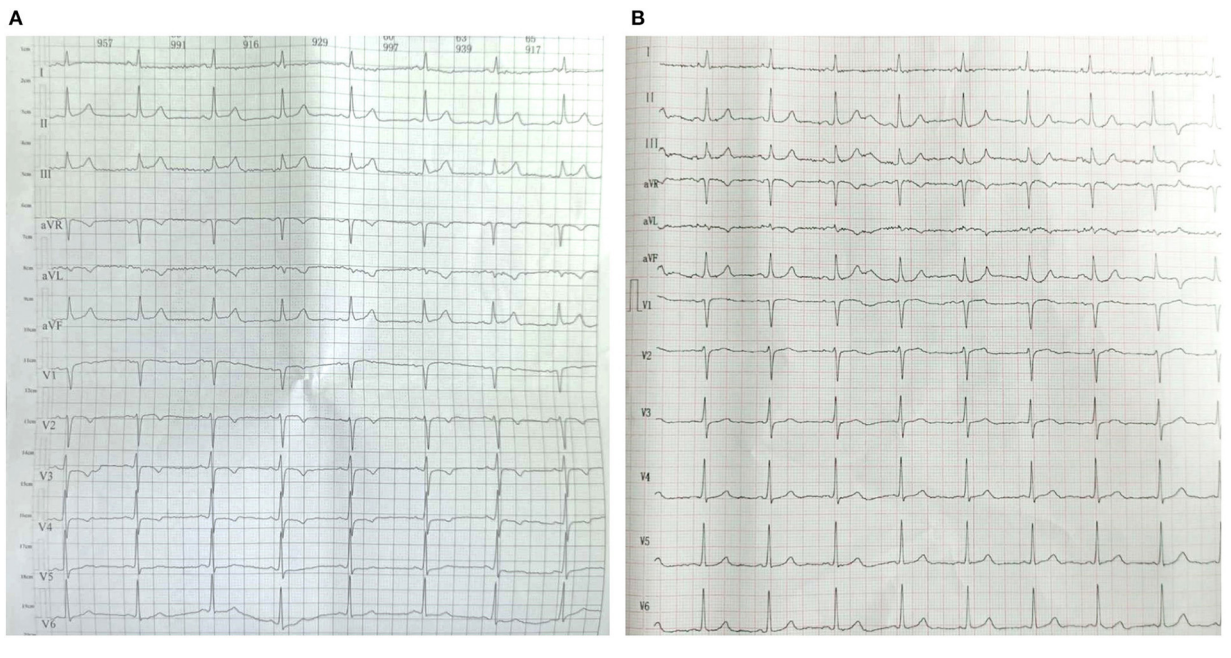

FIGURE 1 | Electrocardiogram of the patient before admission **(A)** and at discharge **(B)**.

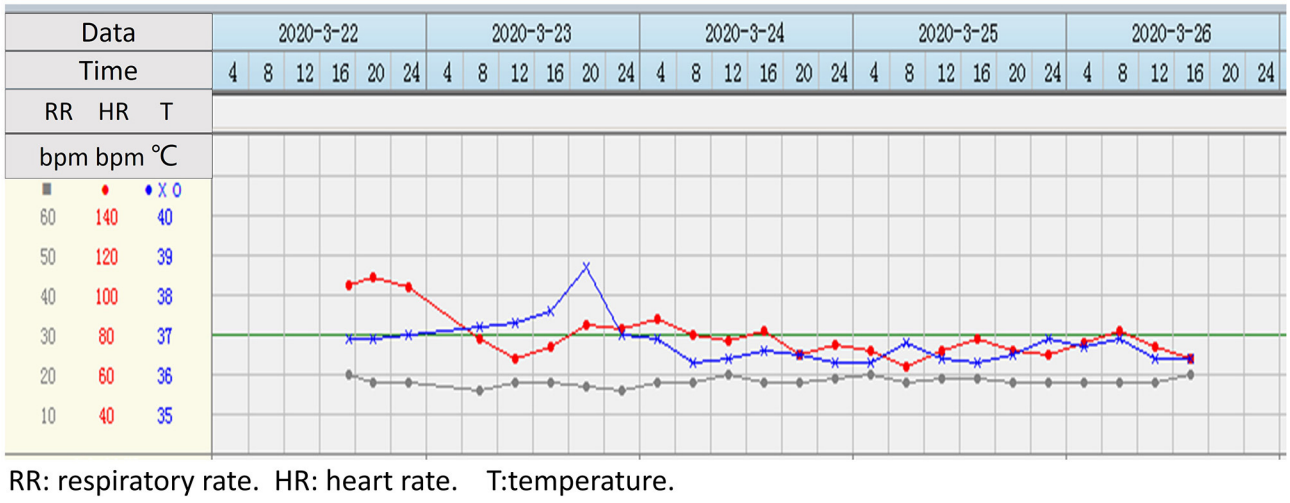

FIGURE 2 | Real-time monitoring of the patient's vital signs during hospitalization.

valsartan (40 mg) in the form of dispersible tablets was given. For chlorpyrifos poisoning, he was treated using an intravenous injection of 2 g of pralidoxime iodide for the revitalization of cholinesterase. Additionally, parenteral nutrition support and 40 mg of pantoprazole sodium injection for rehydration, maintenance of nutrition, and protection of gastric mucosa were provided. On the following day, his chest pain diminished. However, he reported an obvious upper abdominal pain, accompanied by tarry stools. Considering that the bedside abdominal ultrasound revealed none of the clinically significant findings, he was treated with 8 mg of norepinephrine tartrate injection and 2 g of oral sucralfate tablets to control the gastrointestinal bleeding and protect the gastric mucosa. As shown in **Figure 2**, his heart rate dropped to 79 bpm after taking metoprolol tartrate tablets. A low dose of atropine and metoprolol tartrate was simultaneously adjusted to maintain the heart rate to <90 bpm. At night, he developed a fever of 38.6°C. A routine blood test revealed that his WBC count was 6,200 per cubic millimeter, with 73.9% of neutrophils, 14.1% of lymphocytes, and 12.0% of monocytes. His hemoglobin level was 12.8 g/dL. The patient was treated with an injection of 0.9 g of lysine acetylsalicylate and 3 g of cefoperazone sodium.

On day 4 of admission, his abdominal pain eased. Re-examination of the electrocardiogram revealed a normal sinus rhythm and the T-wave inversion in leads V1–V4 disappeared, without a pathological Q wave (**Figure 1B**). The patient was allowed to consume some liquid food, and the infusion volume was reduced. On day 5 of admission, cholinesterase levels rose from 498 to 4,476 U/L (**Figure 3A**), and cardiac troponin I decreased from 1.005 to 0.134 ng/mL (**Figure 3B**). Due to economic reasons, the patient and his family expressed a strong desire to be sent home for further rehabilitation. He continued taking aspirin, ticagrelor, and rosuvastatin after discharge. When followed-up on August 26, 2020, his condition was stable, and delayed encephalopathy was not observed.

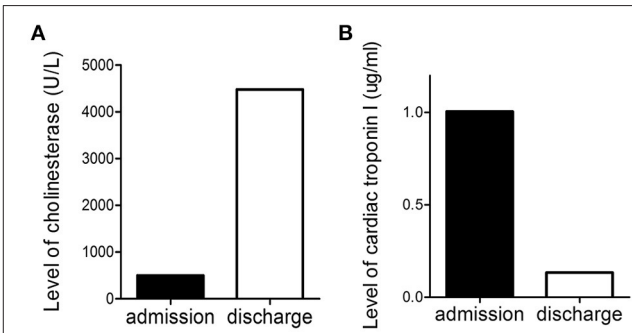

FIGURE 3 | Level of cholinesterase **(A)** and cardiac troponin I **(B)** before admission and at discharge.

DISCUSSION

Among patients with organophosphate poisoning, cardiac complications represented by myocardial injury (3), cardiac arrhythmias (4), and cardiac arrest (5) might be serious and fatal. AMI is a rarely reported complication of organophosphate poisoning. Two previous studies on 22,425 female and 55,748 male subjects explored the relationship between pesticide use and risk or mortality from AMI (6, 7). However, no case of AMI simultaneously accompanying organophosphate poisoning, especially chlorpyrifos, had been reported. In this case, AMI was clearly defined by increased levels of cardiac biomarkers together with either compatible symptoms or ECG changes. In a previous study, STEMI was diagnosed when the ST-segment elevation at the J point ≥1 mm was seen in at least two contiguous leads in any location on the ECG, new left bundle-branch block occurred, or documented new Q waves were observed. In the absence of these observation on the ECGs before admission and at discharge, the patient was considered to have a NSTEMI. The patient with AMI and poisoning was demonstrated for the first time. This is

especially important for the field of this case provides valuable experience for the treatment of acute chlorpyrifos poisoning with AMI.

In this case, chest tightness and pain occurred after chlorpyrifos self-poisoning and worsened after gastric lavage and atropine injection. Some of the possible mechanisms for AMI are listed as follows. First, direct cardiotoxicity, sympathetic and parasympathetic overactivity, and hypoxemia resulting from chlorpyrifos poisoning played critical roles in the formation of AMI. Second, coronary artery spasm caused by pain and tension during gastric lavage could aggravate myocardial ischemia. Moreover, rescue atropine can increase the heart rate and myocardial oxygen consumption; hence, it is important to note that patients with chest pain or coronary heart disease should be treated with atropine more cautiously because of the possibility of an AMI.

Another highlight of this case is that we noted and addressed the conflicts of treatment for chlorpyrifos poisoning and AMI. First, there was no delay in atropinization, which contributed to the control of muscarinic symptoms. However, atropinization can increase the heart rate and myocardial oxygen consumption, which are harmful to patients with myocardial infarctions. To address this issue, beta-blockers and atropine were simultaneously administered to maintain the patient's heart rate to <90 bpm. Moreover, the reduction of platelet aggregation, which is necessary for coronary recanalization of AMI patients, would aggravate the gastrointestinal injury caused by poisoning. Synchronous use of an oral hemostatic agent and gastric mucosa protector proved to be an effective strategy. Although massive infusion would be necessary for fasting patients, it might also increase the risk of heart failure for AMI patients. Therefore, the volume of infusion should be decreased if the patient is able to ingest water and liquid food.

A limitation of the medical management reported herein was that, although we planned to perform PCI when the patient's condition stabilized, both he and his family resolutely refused the intervention citing economic reasons. Besides, cardiovascular magnetic resonance imaging failed to be performed due to the lack of a cardiac MRI machine in our hospital. Data of ejection fraction were unavailable.

In conclusion, this report provides insights into the characteristics and effective medical treatment strategy of chlorpyrifos poisoning with AMI.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

QZ and YC analyzed and interpreted the patient data regarding the disease. CYe and CYi were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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CASE REPORT
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Case Report: Lymphohistiocytic Myocarditis With Severe Cardiogenic Shock Requiring Mechanical Cardiocirculatory Support in Multisystem Inflammatory Syndrome Following SARS-CoV-2 Infection

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Multisystem Inflammatory Syndrome (MIS) is a novel hyperinflammatory syndrome associated with SARS-CoV-2 infection. It predominantly affects children (MIS-C) a few weeks after a usually asymptomatic SARS-CoV-2 infection and is only rarely seen in adults above 21 years (MIS-A). Only scarce data on histological findings in both pediatric and adult patients has been published so far. An 18-year-old male patient was admitted to hospital in a febrile state, which progressed to severe cardiogenic shock and multi-organ failure requiring extracorporeal life support. Myocardial biopsy revealed small vessel-associated immune cell infiltrates. Diagnosis of MIS-C was made after ruling out all potential differential diagnosis. Use of immunosuppressive treatment with steroids, interleukin-1 blockade and high-dose intravenous immunoglobulins resulted in the patient's full recovery. Multisystem Inflammatory Syndrome (MIS) is a new differential diagnosis of cardiac dysfunction in pediatric and adult patients. The lack of myocardial necrosis differentiates the disease from other viral myocarditis and offers an explanation for the fast response to immunomodulatory therapy and the favorable prognosis. The preceding SARS-CoV-2 infection might only have been mildly symptomatic or even asymptomatic.

Keywords: COVID-19, V-A ECMO, Impella®, MIS-C, Multisystem Inflammatory Syndrome in children, myocardial biopsy

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) with respiratory failure is the primary complication of an infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in adults. Here, diagnosis and treatment is progressively better understood (1). In pediatric patients however, a novel hyperinflammation syndrome called Multisystem Inflammatory Syndrome in Children (MIS-C) is a serious pathology caused by a SARS-CoV-2 infection (2). The awareness and knowledge on this hyperinflammation syndrome are steadily growing among pediatricians, but the more uncommon adult variant of this syndrome, Multisystem Inflammatory Syndrome in Adults (MIS-A), is widely unknown in adult medicine. The threshold between the pediatric and the adult variant is 21 years as defined by the CDC (3). Only scarce data on histological findings in both pediatric and adult patients has been published so far.

Here, we report the case of a young adult with severe cardiogenic shock diagnosed with severe MIS-C backed by myocardial biopsy and rapid recovery following initiation of immunosuppressive treatment.

CASE DESCRIPTION

An 18-year-old male patient presented to the emergency department with hyperpyrexia (42°C), chills and tachycardia. Physical examination and chest X-ray revealed no pathological findings. Laboratory tests showed elevated C-reactive protein (CRP; 105.9 mg/l, reference range <5 mg/l) as well as interleukin 6 serum levels (IL-6; 128 pg/ml, reference range <7 pg/ml), but only modestly elevated procalcitonin (PCT; 0.12 ng/ml, reference range <0.05 ng/ml) (**Figure 1**). The patient was admitted to a standard care ward and an empiric antibiotic therapy was initiated.

The patient's medical history was unremarkable. Approximately 2 months prior to admission, the patient was exposed to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and went into quarantine. A few days after this exposure, he complained he had lost his sense of smell, but he experienced no other symptoms. Neither during his quarantine nor after his initial admission to the hospital was an active SARS-CoV-2 infection ever proven, despite repeated nasopharyngeal swabs.

Following admission, the patient's condition steadily deteriorated. After 3 days he was transferred to the intensive care unit (ICU) due to arterial hypotension with suspected septic shock. Initially, intravenous fluid resuscitation and a low rate of noradrenaline (0.01 μg/kg/min) were sufficient to stabilize the patient's blood pressure. A generalized rash affecting the abdomen and all limbs occurred. On day 4 following hospital admission, transthoracic echocardiography revealed a severely impaired left ventricular cardiac function (left ventricular ejection fraction, LVEF, 25%, **Supplementary Video 1**). No relevant ECG pathologies were seen beside sinustachycardia. At that time, Pulse Contour Cardiac Output (PiCCO; Getinge, Rastatt, Germany) measurement confirmed marginal cardiac output of 4.4 l/min (reference range: 4–8 l/min). Computed tomography showed enlarged abdominal lymph nodes, wall thickening of the colon and polyserositis with pericardial and pleural effusions and ascites. Respiratory failure due to pulmonary edema required non-invasive ventilation (NIV).

Subsequently, on day 4 after hospital admission, liver and renal failure and massive systemic inflammatory response became evident (**Figure 1**). The rheumatology workup (anti-nuclear antibodies (ANA), extractable nuclear antigen (ENA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-phospholipid antibodies, complement) were unremarkable. Microbiological investigation only revealed positive SARS-CoV-2 serology (anti-S1 and anti-N antibodies).

Four days after initial hospital admission, the patient was transferred to our hospital, a tertiary care center in Freiburg, Germany. Upon admission, levosimendan infusion was started. The following day, endomyocardial biopsy (EMB) was performed. Signs of hypoperfusion end organ failure persisted (elevated lactate, renal function, **Figure 1**). For this reason, a percutaneous ventricular assist device (Impella®, Abiomed, Danvers, NJ, United States of America) was implanted. Subsequently, cardiac output improved from 3.6 to 4.9 l/min and pulmonary capillary wedge pressure decreased from 26 to 21 mmHg.

However, due to both progressive hypoxemia under NIV with a required fraction of inspired oxygen (FiO_2) of up to 100% and to worsening neurological symptoms (sopor), invasive mechanical ventilation was indicated. Within just a few hours after endotracheal intubation, additional venoarterial extracorporeal membrane oxygenation (V-A ECMO) support was required, because of worsening hypoperfusion and severe end-organ failure (**Figure 1**).

EMB showed a significant infiltration of immune cells into the heart. Especially CD68+ macrophages but also CD3+ T cells were found to be located primarily around small vessels within the myocardium, as shown by immunohistochemical stainings (see circle). Masson Trichrome and HE stainings further demonstrated the presence of perivascular fibrosis in serial tissue sections, but no myocyte necrosis (**Figures 2A–D**, see circle). Nested (RT-) PCR for the detection of enteroviruses (including coxsackieviruses of group A and B, echoviruses), parvovirus B19, human herpesvirus 6, Epstein Barr Virus, adenoviruses, human cytomegalovirus, herpes simplex virus type 1 and 2, human herpesvirus 7 (HHV7), varizella zoster virus, influenza A and B viruses, Toxoplasma gondii or borrelia spp. was negative in the myocardium and EDTA blood.

Abbreviations: ACR, American College of Rheumatology; ANA, Anti-nuclear antibody; ANCA, Anti-neutrophil cytoplasmic antibodies; CD, cluster of differentiation; CDC, Centers for Disease Control and Prevention; CRP, C-reactive protein; EMB, endomyocardial biopsy; ENA, Extractable nuclear antigen; FiO_2, fraction of inspired oxygen; HE, hematoxylin-eosin; ICU, Intensive care unit; IL-1, interleukin 1; IL-6, interleukin 6; IVIG, intravenous immunoglobulin; LVEF, left ventricular ejection fraction; MIS-C, Multisystem Inflammatory Syndrome in Children; MIS-A, Multisystem Inflammatory Syndrome in Adults; NIV, non-invasive ventilation; PCT, procalcitonin; PiCCO, Pulse Contour Cardiac Output; PIMS-TS, Pediatric Inflammatory Multisystem Syndrome temporarily associated with SARS-CoV-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; V-A ECMO, venoarterial extracorporeal membrane oxygenation; WHO, World Health Organization.

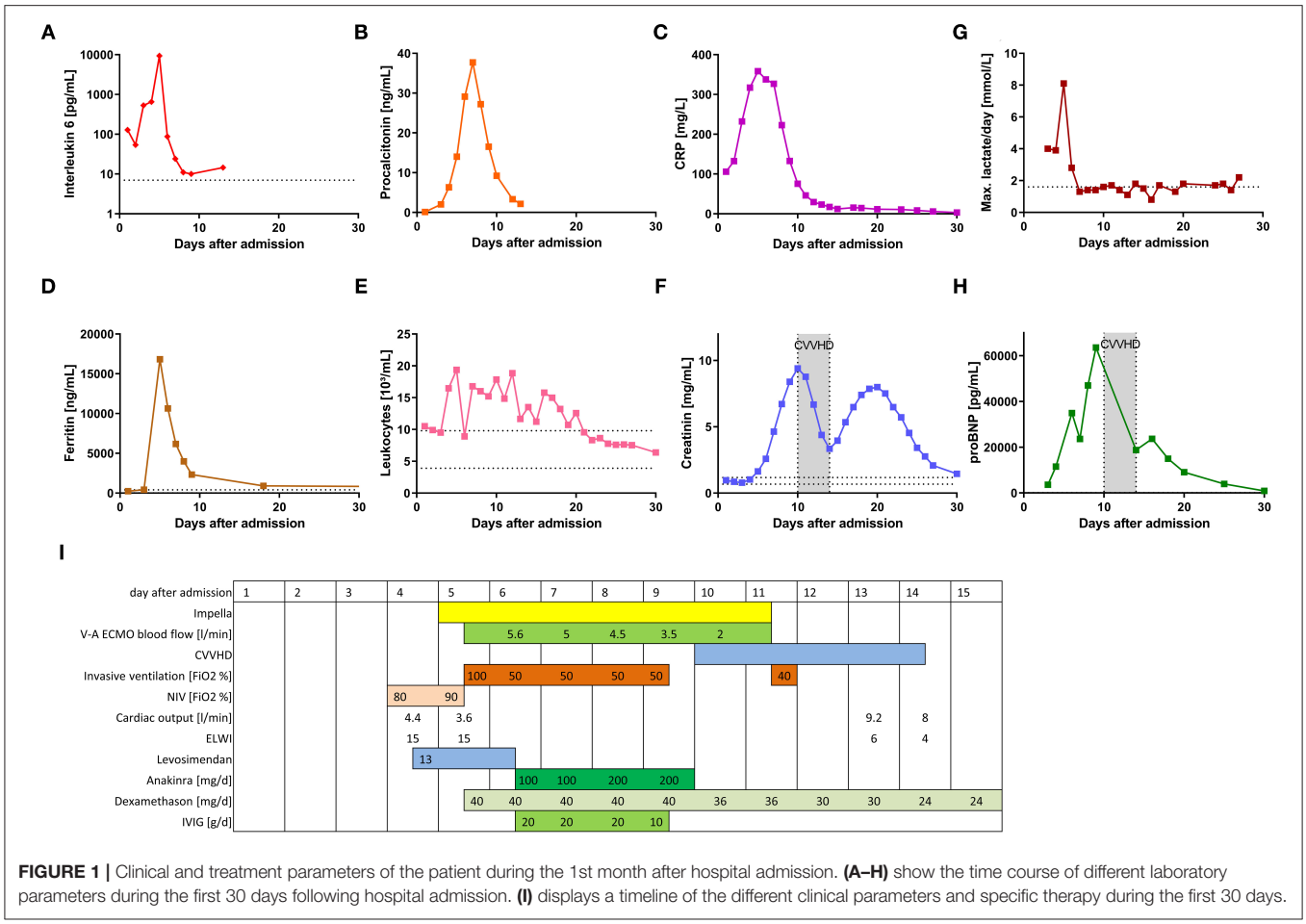

FIGURE 1 | Clinical and treatment parameters of the patient during the 1st month after hospital admission. **(A–H)** show the time course of different laboratory parameters during the first 30 days following hospital admission. **(I)** displays a timeline of the different clinical parameters and specific therapy during the first 30 days.

In addition, qRT-PCR did not detect SARS-CoV-2 RNA in the myocardium.

Following interdisciplinary discussion (pediatrics, rheumatology, cardiology, and infectious disease), Multisystem Inflammatory Syndrome in children (MIS-C) following preceding SARS-CoV-2 infection was diagnosed and immunosuppressive therapy including high-dose intravenous immunoglobulin (IVIG), dexamethasone and IL-1-blockade (anakinra) was initiated (**Figure 1**). Clinical and laboratory parameters improved within 3 days and 1 day, respectively (**Figure 1**). As cardiac function recovered, this enabled discontinuation of extracorporeal cardiocirculatory support (V-A ECMO, Impella®) on day seven after initiation. Cardiac necrosis parameters were only moderately elevated during the shock phase (max. TroponinT 341 ng/L, ref <14 ng/L; CK-MB max 54 U/L, ref < 24 U/L) indicating only a minor myocardial damage has occurred. Cardiac function did indeed fully recover (**Supplementary Video 2**). Renal function only was able to fully recover after 30 days to full recovery. The patient was able to be discharged 32 days after initial hospital admission.

DISCUSSION

Early during the SARS-CoV-2 pandemic, a novel hyperinflammatory syndrome was described. Initially, only pediatric cases were identified with symptoms and clinical findings, which in many respects resembled features of Kawasaki disease and Toxic Shock Syndrome (4, 5). Two synonymic terms—Multisystem Inflammatory Syndrome in Children (MIS-C) and Pediatric Inflammatory Multisystem Syndrome temporarily associated with SARS-CoV-2 (PIMS-TS)—were established (3, 6, 7). Later, a similar syndrome was reported in adults (MIS-A) (8, 9).

Our patient fulfilled the diagnostic criteria of MIS-C with fever, rash, lymphadenopathy, shock, myocardial injury, colitis, and positive SARS-CoV-2 serology, as well as severe inflammatory response. For this reason, immunomodulatory therapy based on clinical recommendations of the American College of Rheumatology (ACR) was initiated (3).

ACR recommends steroid treatment with methylprednisolone (20–30 mg/kg a day, for 1–3 days up to 1 g per day followed by tapering doses−2 mg/kg a day, maximum 60 mg a day);

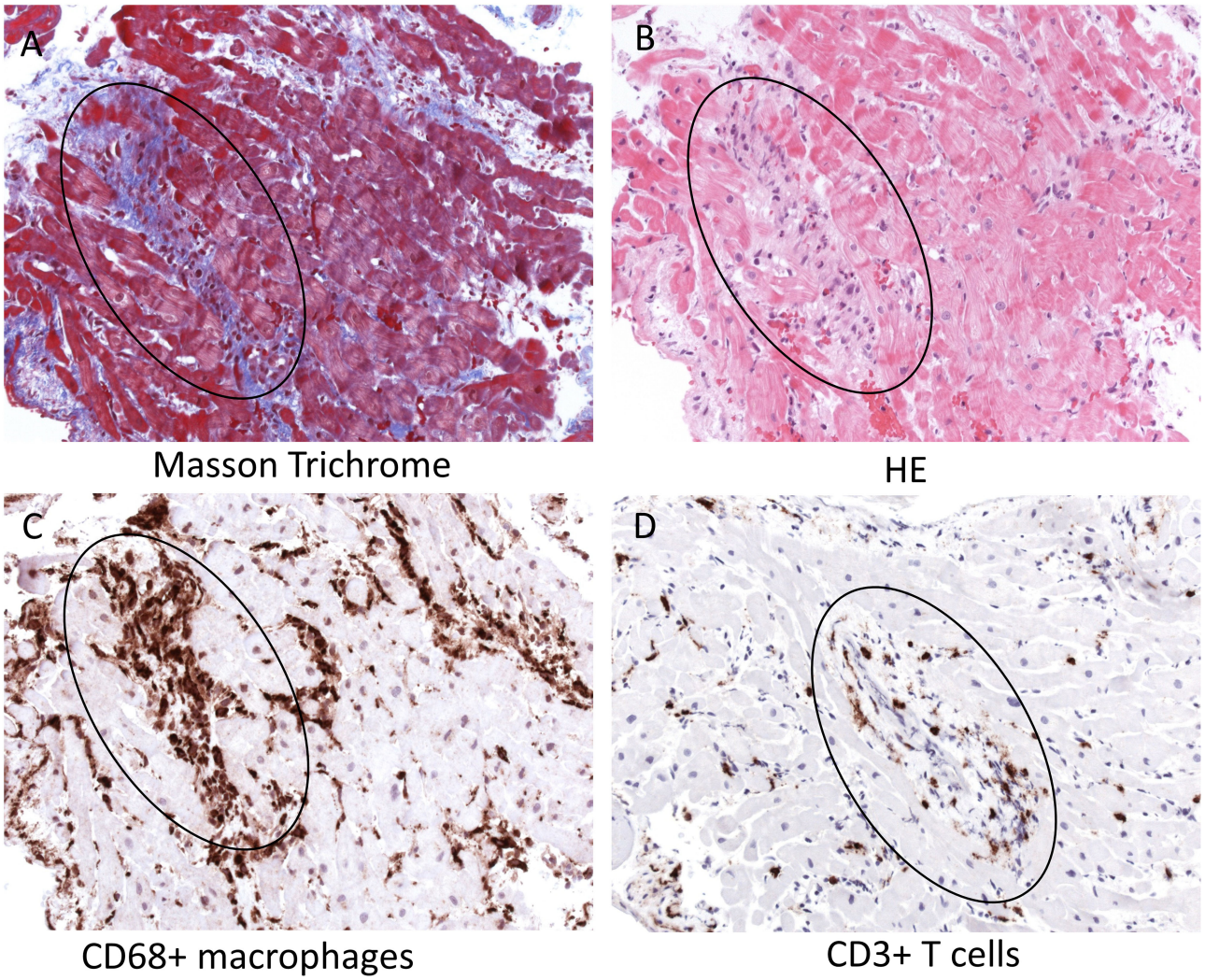

FIGURE 2 | Histopathology and immunohistochemistry of the patient's endomyocardial biopsy. Serial tissue sections of paraffin-embedded endomyocardial biopsies reveal perivascular fibrosis in absence of myocyte necrosis [Masson Trichrome **(A)** and HE **(B)** stainings, see circle] and severe infiltration of CD68+ macrophages **(C)** and CD3+ T cells **(D)** primarily around intracardiac small vessels (see circle, magnification x200). HE, hematoxylin-eosin; CD, cluster of differentiation.

high-dose intravenous immune globulin therapy (2 g/kg a dose) in moderate to severe cases; and cytokine receptor (IL-1 or IL-6) blockade (3).

As with myocardial involvement following other viral infections, cardiac injury in MIS-C may occur either due to direct cardiac invasion by the virus (10–13) or else following accompanying cytokine storm (2). Since EMB is only rarely performed, the reported cases of myocardial injury in the context of the SARS-CoV-2 infection are largely based upon clinical symptoms, laboratory results and imaging findings (e.g., electro- and echocardiography, magnetic resonance). Arrhythmias, decreased LVEF and high prevalence of cardiogenic shock were reported (14). Histopathological investigations of EMB in patients with COVID-19 revealed multi-focal lymphocytic and interstitial macrophage infiltrates (15) without substantial myocyte necrosis. Despite the fact that SARS-CoV-2 can infect macrophages but also myocytes (16), this virus is obviously not cytolytic as e.g., coxsackievirus B3 (17). So far, the exact molecular mechanisms by which the infiltration of many macrophages and less T cells are induced in MIS patients are not known. It is likely that SARS-CoV-2 rather induces an inflammatory response by cytokine release, thus resulting in a kind of indirect myocardial injury (18). Further investigations are required to investigate why in MIS patients but not in other patients with myocardial SARS-CoV-2 infections the inflammation is associated with the vessels (19). It has to be discussed whether the presence of extensive perivascular lympho-histiocytic infiltrates without myocyte necrosis may explain the rapid response to immunosuppressive therapy in our patient. This is similar to other reported cases (9, 14, 20).

CONCLUSION

Even following asymptomatic SARS-CoV-2 infection, children and young adults may develop severe Multisystem Inflammatory Syndrome in Children or Adults (MIS-C/A). In our case report, myocardial involvement (verified by endomyocardial biopsy) caused severe cardiogenic shock requiring medical as well as mechanical cardiocirculatory support. Early immunomodulatory treatment with glucocorticoids, intravenous immunoglobulin and cytokine receptor blockade helped control symptoms and interrupt uncontrolled inflammatory response. The patient's cardiac function recovered after 7 days on mechanical cardiocirculatory support with Impella® and V-A ECMO. Prompt diagnosis of MIS-C is critical, as swift use of intense immunosuppressive therapy may lead to a better prognosis for the patient. Therefore, we advise critical care clinicians to consider this differential diagnosis early on when confronted with patients suffering from severe inflammatory response and impaired cardiac function.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XB, AS, and IJ conceived and designed the case report, collected the data, and wrote the manuscript. KK contributed to the pathology diagnosis. IJ, MH, DS, and AJ contributed to the clinical diagnosis. CB supervised the conception, analysis, design of the work, and manuscript drafting. All authors critically revised the manuscript for important intellectual content and provided approval of the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.716198/full#supplementary-material

Supplementary Video 1 | Apical 4 chamber view at admission. Severely impaired left ventricular function seen directly after admission to our hospital.

Supplementary Video 2 | Apical 4 Chamber view after recovery. Fully recovered function seen 2 days after V-A ECMO and Impella® explantation.

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frontiers in Cardiovascular Medicine

CASE REPORT
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Case Report: Probable Myocarditis After Covid-19 mRNA Vaccine in a Patient With Arrhythmogenic Left Ventricular Cardiomyopathy

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Arrhythmogenic left ventricular cardiomyopathy (ALVC) is a rare heritable heart-muscle disorder characterized by a progressive loss of left ventricular myocardium and its replacement by fibrofatty tissue. Myocarditis is an inflammatory disease of the heart that may occur secondary to infections, immune system activation or exposure to drugs. Hot phases of ALVC present with chest pain and troponin rise, mimicking acute viral myocarditis and indicate a progression of the disease. Recently, myocarditis has also been described as an infrequent complication of coronavirus disease 2019 (Covid-19) mRNA vaccines. We herein report for the first time a case of probable myocarditis induced by Covid-19 vaccine in a patient with previous medical history of ALVC. We aim to highlight the common characteristics of ALVC and Covid-19 vaccine myocarditis and work through the differential diagnosis of these two entities.

Keywords: myocarditis, vaccine, COVID-19, arrhythmogenic left ventricular cardiomyopathy, myopathy

INTRODUCTION

The Covid-19 disease represents the largest worldwide health care challenge to date. Pfizer-BioNTech and Moderna Covid-19 vaccines (both mRNA) have significantly contributed to get the pandemic under control (1). The benefit-risk assessment for Covid-19 vaccination shows a favorable balance for all age and sex groups. However, there are a number of side-effects described after vaccination, including rare cases of myocarditis; according to the U.S. Centers for Disease Control (CDC), there are approximately 12.6 cases per million patients who receive a second dose among 12–39 year-olds (2).

ALVC is a variant of arrhythmogenic right ventricular cardiomyopathy in which the left ventricle is predominantly involved. The distinctive histopathological feature of ALVC is the loss of left ventricular myocardium, substituted by fibrous and fatty tissue. The natural history of ALVC may interpolate periods of clinical quiescence with hot phases, the latter being difficult to distinguish from a viral myocarditis (3).

Here, we report for the first time, to our knowledge, a case of probable myocarditis and associated myopathy induced by Covid-19 vaccine (BNT162b2 mRNA, Pfizer-BioNTech) in a young male patient previously diagnosed with ALVC.

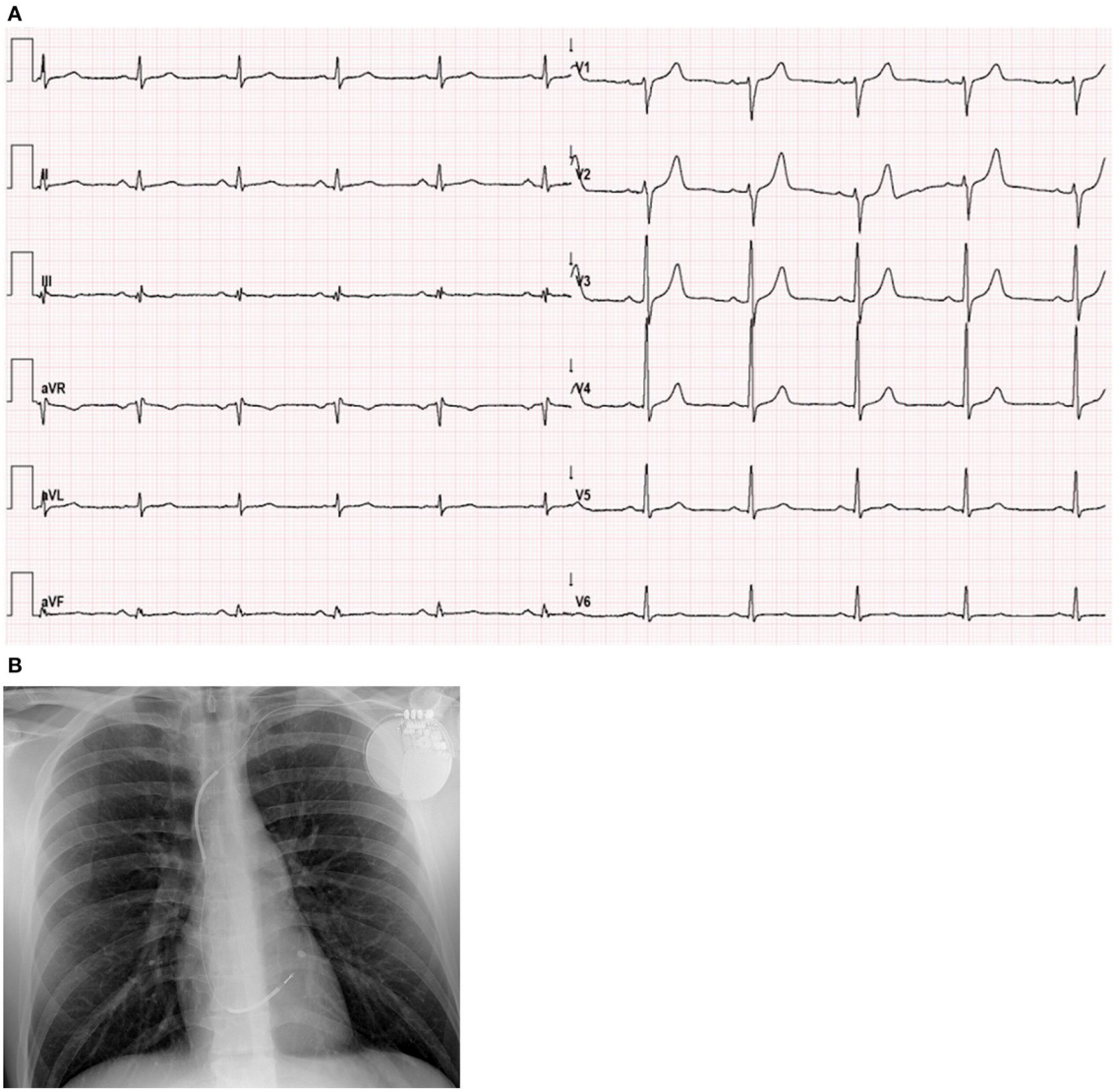

FIGURE 1 | Electrocardiogram and Chest X-ray. **(A)** ECG showed sinus rhythm, 60 bpm, normal axis, fragmented QRS in the inferior leads (III, aVF) and flat T waves in III, aVF and V6. When compared to previous ECGs, no new abnormalities were observed. **(B)** Chest X-ray with a single lead ICD, normal heart size and no signs of pulmonary congestion.

CASE DESCRIPTION

A 28-year-old male patient was diagnosed of ALVC in 2012. He carried a heterozygous radical mutation in the desmoplakin gene (p.Gln1804*), just like his father. An implantable cardiac defibrillator (ICD) was inserted in 2013 for primary prevention of sudden cardiac death.

The patient possibly suffered from a hot phase of ALVC in 2009. In fact, he had 2 myocarditis-like episodes within 6 months. A comprehensive study including viral serologies was done, with no findings. The patient had a new episode of myocarditis in September 2020. There were no red flags that suggested a secondary cause and, due to background history, no specific aetiological study was performed. He never presented concomitant neuromuscular symptoms.

The patient overall performance was good, in a New York Heart Association I class, although his left ventricular ejection fraction (LVEF) was proved to be reduced down to 40% at last examinations, so his optimized medical treatment for heart failure with depressed ejection fraction included sacubitril/valsartan 24/26 mg bid, eplerenone 25 mg od and

Abbreviations: ALVC, arrhythmogenic left ventricular cardiomyopathy; Covid-19, coronavirus disease 2019; ICD, implantable cardiac defibrillator; LVEF, left ventricular ejection fraction; SARS CoV-2, severe acute respiratory syndrome coronavirus 2; ECG, electrocardiogram; hs-cTnI, high sensitivity cardiac troponin I; CK, creatin kinase; CT, computed tomography; MRI, magnetic resonance imaging; ENG/EMG, electroneurography/electromyography.

bisoprolol 1.25 mg od. He had no prior history of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection.

In January 2021, the patient received the second dose of the Covid-19 vaccine (BNT162b2 mRNA, Pfizer-BioNTech). The next morning, he developed fever, myalgias, weakness, headache and diarrhea. Two weeks later, he was admitted to the hospital with progressive muscle weakness involving the scapular and pelvic girdles, chest pain, fatigue and dyspnea.

At admission, blood pressure was 137/74 mmHg, heart rate was 77 beats/min, temperature was 36°C and a normal blood oxygen level was confirmed. Physical examination did not show cardiac murmurs, rubs nor pulmonary crackles. The neurological assessment confirmed proximal muscle weakness, mainly localized at the lower limbs. Muscle stretch reflexes were mildly and symmetrically diminished. The patient could stand up, but presented a plodding, unstable gait and shuffling due to lack of muscle strength.

Initial evaluation at the hospital revealed a negative SARS-CoV-2 polymerase chain reaction test result. His electrocardiogram (ECG) showed sinus rhythm with fragmented QRS and flat T waves in the inferior leads; no new abnormalities were identified when compared to previous ECG. There were no signs of heart failure in the chest X-ray (**Figure 1**). At admission, the high sensitivity cardiac troponin I (hs-cTnI) level was 5,052 ng/l (normal range 0–58.05 ng/l). N-terminal pro–B-type natriuretic peptide level was 89 pg/ml (normal range 0–100 pg/ml). Creatine kinase (CK) was slightly increased, both the total and isoenzyme MB levels (271 IU/l and 15.77 ng/ml, respectively). The rest of laboratory tests remained unremarkable, without abnormal acute inflammatory markers (C reactive protein < 0.5 mg/l). No cytokine measurements nor immunofluorescence tests were carried out. The echocardiographic assessment showed mild left ventricular enlargement (**Figure 2**) with moderate left ventricular systolic dysfunction (**Supplementary Videos 1**,**2**). No changes from baseline were observed. No arrhythmic events were detected during ICD interrogation.

Neurological tests included a cranial computed tomography (CT) scan and a brain magnetic resonance imaging (MRI), which did not show any abnormalities. Cerebrospinal fluid analysis was normal: glucose and proteins levels were within normal range, leukocytes were undetectable and no oligoclonal bands were identified. The electroneurography/electromyography (ENG/EMG) conduction study during the initial acute phase revealed a moderate intensity myopathic pattern mostly affecting the lower limbs with difficulty in activating motor units. These alterations completely resolved in the follow-up ENG/EMG performed 5 days later. A bilateral muscular MRI showed appropriate thigh morphology and thickness, without abnormalities in gadolinium enhancement sequences. The autoimmunity panel was unremarkable.

Patient was evaluated through a comprehensive and multidisciplinary approach by Cardiology, Neurology and Internal Medicine. Initial treatment included acetaminophen, metamizol and colchicine. However, during the first 3 days the patient required intravenous opioids to manage the severe headache, recurrent chest pain episodes and progressive

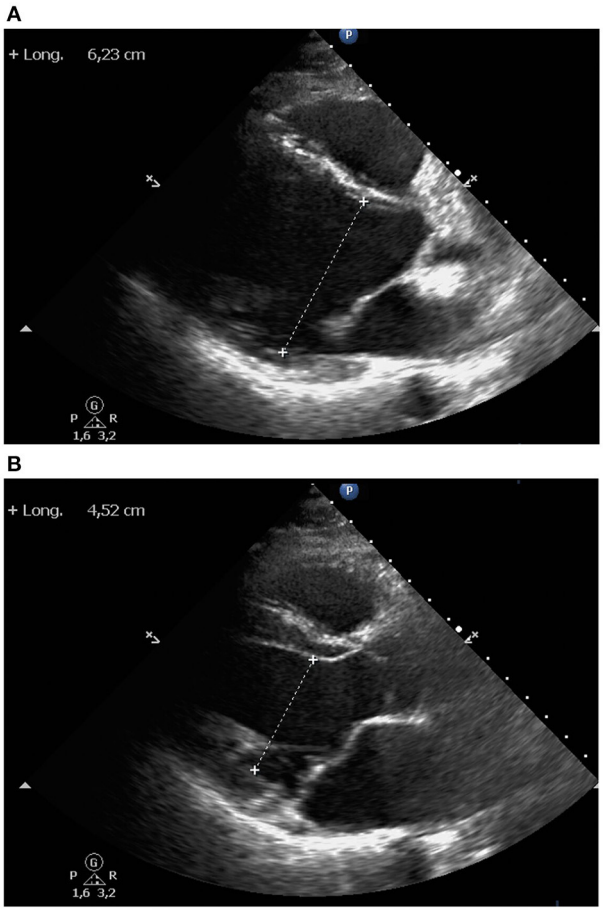

FIGURE 2 | Echocardiography. Parasternal long axis view showed mild left ventricular enlargement, both left ventricular end-diastolic **(A)** and end-systolic **(B)** diameters. Right ventricle, ascending aorta and left atrium were of normal size. Interventricular septum and posterior left ventricular wall had normal thickness. No pericardial effusion was observed.

muscular weakness. After ruling out alternative infectious agents and supported by the high suspicion of an immune-mediated etiology, intravenous steroids were suggested. Nonetheless, the patient refused to take them due to past secondary effects in the context of previous myocarditis events. At that point, aspirin was started and progressively uptitrated based upon clinical and biochemical improvement during previous myocarditis relapses and considering a significant pericardial involvement (1 g tid aspirin and 0.5 mg bid colchicine). After the fifth day of stay, symptoms progressively ameliorated and, 5 days later, the patient was discharged with mild muscle weakness and almost normal hs-cTnI levels (**Figure 3**).

During short-term follow-up, the patient did not present any episodes of chest pain nor dyspnea. Blood tests including N-terminal pro–B-type natriuretic peptide, CK, hs-cTnI and acute inflammatory markers were unremarkable. Two months later, echocardiography was repeated and showed a mild improvement of left ventricular systolic function (**Supplementary Video 3**).

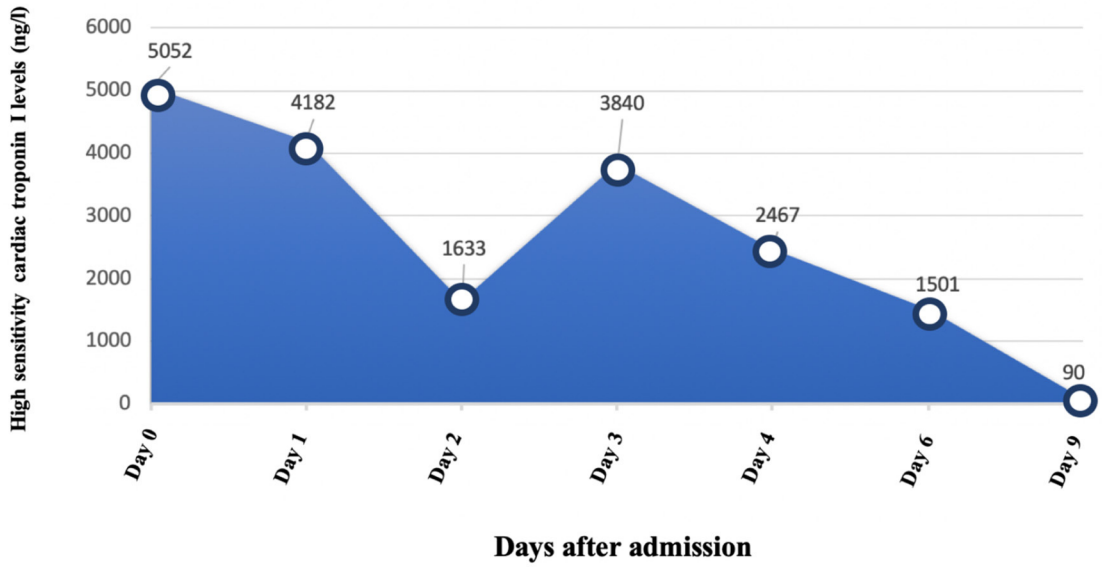

FIGURE 3 | Dynamic of high sensitivity cardiac troponin I levels. Hs-cTnI levels peaked at admission. Three days later, with ongoing recurrent episodes of chest pain, a further increase in hs-cTnI value was observed. After starting aspirin and colchicine, chest pain resolved and hs-cTnI levels progressively decreased. At discharge, hs-cTnI value was almost normal (normal range 0–58.05 ng/l).

TIMELINE

2012	Diagnose of ALVC.
September 2020	Last episode of myocarditis (without neurological symptoms).
January 2021	Administration of boost dose of mRNA Covid-19 vaccine.
February 2021 (14 days after boost dose)	Admitted for chest pain, elevated hs-cTnI and neurological symptoms.
First 3 days of admission	Recurrent chest pain despite treatment with acetaminophen, metamizol and colchicine. Stable moderate left ventricular systolic dysfunction without signs of heart failure Moderate intensity myopathic pattern in ENG / EMG
Day 4 of admission	Patient refuses to initiate steroids due to past secondary effects Aspirin is started and progressively uptitrated
5–9 days after admission	Gradual improvement of symptoms. Decline of hs-cTnI levels. Complete resolutions of abnormalities in the follow-up ENG/EMG.
Day 10 after admission	Patient is discharged

DISCUSSION

As far as we know, here we report the first suspected case of myocarditis and myopathy induced by Covid-19 vaccine in a patient with ALVC. Most of the reported systemic events of the Covid-19 vaccines were due to reactogenicity, with a typical onset within the first 24 h. These events were generally transient and resolved spontaneously. Recently, a significant number of myocarditis cases post Covid-19 vaccination have been published. The majority of the patients presented with chest pain, usually 2–3 days after the second dose of mRNA vaccination, and sometimes chest pain was preceded by fever and myalgia (4, 5).

We want to highlight some characteristics that Covid-19 vaccine-related myocarditis and ALVC have in common. First, age of onset of ALVC and vaccine-induced myocarditis are similar, ranging between 12 and 39 years.

Second, post-vaccine myocarditis has shown a male predominance, possibly related to testosterone levels, by a combined mechanism of inhibition of anti-inflammatory cells and commitment to a Th1-type immune response (6). At the same time, male patients have a three-fold-risk incidence of ALVC compared to females, develop the disease earlier and present more severe phenotypes and a higher arrhythmic risk. A possible explanation for the latter could lie in the differences of physical exercise between genders; one study found that elevated serum testosterone levels in males and decreased estradiol levels in females are independently associated with MACE (7, 8).

Third, autoantibody generation could be one of the mechanisms of myocarditis in susceptible individuals after vaccination (9). There is molecular mimicry between the spike protein of SARS CoV-2 and self-antigens, and antibodies against SARS CoV-2 spike glycoproteins have been experimentally shown to cross-react with structurally similar human peptide protein sequence, including alpha-myosin. It is possible that it may trigger preexisting dysregulated pathways in certain individuals with predisposition, resulting in a polyclonal B-cell expansion, immune complex formation and inflammation

(10, 11). The presence of serum anti-heart autoantibodies and anti-intercalated disk autoantibodies provides evidence of autoimmunity in the majority of familial and in almost half of sporadic ALVC. Increasing evidence of autoimmunity has also been recently reported with two studies identifying anti-heart, anti-intercalated disc and anti-DSG2 autoantibodies in patients with ALVC (12, 13).

Regarding our case, the diagnosis of myocarditis was made in light of recurrent chest pain and hs-cTnI elevation without an alternative explanation. Notwithstanding, the differential diagnosis between myocarditis and a hot phase of the ALVC is challenging, since most of the ECG, echocardiographic and MRI findings may overlap and, moreover, the two of them might be pathophysiologically related. Hot phases of ALVC present with chest pain and troponin rise, mimicking acute viral myocarditis and indicate a progression of the disease (14). However, the severity of the hs-cTnI peak, the positive response to anti-inflammatory drugs and the subsequent improvement in LVEF 2 months later support the diagnosis of a new myocarditis episode. Between 10 and 25% of patients included in case series of myocarditis after Covid-19 vaccination had normal values of C reactive protein. Acute inflammatory markers could more frequently be within the normal range when the cause of myocarditis is not an infectious agent. Cardiac MRI adds very useful information to the working diagnosis of myocarditis. However, our patient carried an ICD, so we did not perform this test due to image-quality and safety issues. Definite diagnosis of myocarditis relies on endomyocardial biopsy, but this an invasive procedure associated with potentially life-threatening risks, and in the daily clinical practice it is limited to a selected number of complicated clinical scenarios (15).

Myopathy diagnosis was based upon muscular symptoms, an increase in total CK and an abnormal neurophysiological study result. Artifacts related to muscle weakness and pain could have blunted the interpretation of neurophysiological study. However, the increase in CK could not be justified by the isoenzyme MB alone and thus skeletal muscle must have been to some extent involved. A muscle biopsy was initially considered, but discarded afterwards due to potential risks and subsequent patient clinical improvement.

Temporal relationship and concomitant neuromuscular symptoms suggest the boost dose could have played a significant role in the genesis of myocarditis in this case. One possible hypothesis is that the spike protein of the mRNA vaccine could have developed antibodies that in genetically predisposed patients can attack cardiac muscle proteins (sarcomeric, desmosomal, nuclear), which eventually leads to the event of myocarditis. Further research should be designed to explore predisposing factors for development of myocardial injury (genetic factors, comorbidities or autoimmunity profile). Close monitoring and surveillance after boost dose of Covid-19 vaccine could be useful in ALVC patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors contributed to the analysis and interpretation of data, wrote the manuscript, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.759119/full#supplementary-material

Supplementary Video 1 | 2D paraesternal long-axis displayed mild left ventricular dilation with moderate left ventricular systolic dysfunction. Mitral and aortic valve leaflets were thin and mobile, with good opening and closure. No pericardial effusion was observed.

Supplementary Video 2 | 2D apical four chamber showed mild left ventricular spherical remodeling, LVEF of 40% and absence of regional wall motion abnormalities. The right ventricle had normal size and systolic function. Both left and right atriums were not dilated.

Supplementary Video 3 | 2D apical four chamber 2 months after hospital discharge exhibited an elliptical-shaped left ventricle with a mild improvement in left ventricular systolic function. LVEF assessment by Simpson's method was 50%.

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CASE REPORT
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Case Report: Coexistent Wolff-Parkinson-White Syndrome and Brugada Phenocopy in a Patient With Pneumonia and Myocarditis

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Background: In recent years, Wolff-Parkinson-White (WPW) syndrome and Brugada electrocardiogram (ECG) patterns have been reported as coexistent in the same patient. In most cases, the two waveforms appeared separately. Here, we described combinations of different waveforms on one ECG, such as the Brugada pattern with delta waves and the Brugada pattern with paroxysmal supraventricular tachycardia (PSVT). Importantly, we recorded an alternate conversion of these combined ECG waveforms, which has not previously been reported in the literature. At the same time, we confirmed that the change in the waveform was related to fever by analyzing Holter data.

Case: A 48-year-old male was admitted to our hospital due to palpitations and fever. The patient had a history of a cold 3 days ago. Laboratory examinations showed an elevated neutrophil percentage (85%) and troponin I level (0.86 ng/ml). A chest computed tomography (CT) scan showed inflammation in the right lung. The diagnosis of pneumonia and myocarditis was made. ECG indicated WPW syndrome and the Brugada pattern. We recorded the dynamic changes in this combination of delta waves and Brugada waves with a Holter monitor, and we found the changes would happen when the patient's body temperature rose. The doctors thought that the patient's pulmonary infection led to fever, which caused the changes in waveform. After treatment with antibacterial therapy and supportive care, his body temperature returned to normal. The various laboratory indicators also gradually returned to normal. The doctor recommended that the patient undergo further pre-excitation bypass radiofrequency ablation treatment, but the patient refused and was discharged.

Conclusion: Delta waves and Brugada ECG patterns could appear on one ECG at the same time. There were dynamic changes of QRS complex, relating to fever.

Keywords: Wolff-Parkinson-White syndrome, Brugada phenocopy, fever, electrocardiogram (ECG), case report

INTRODUCTION

The classic WPW syndrome includes PSVT and delta waves within sinus rhythm, which are blunt and located at the beginning of the QRS complex. Its presence indicates that there is an atrioventricular sideway, which is one of the anatomical conditions of PSVT, and the diagnosis of WPW syndrome can be established if there are indications of both a delta wave and PSVT in a patient's ECGs (1–3).

Brugada waves are a typical ECG appearance in patients with Brugada syndrome. There are a high take-off ST-segment elevation ($\geq$2 mm) and inverted T wave in the leads V1 through V3, which is defined as type I Brugada pattern. Both are relatively rare arrhythmias. It is very rare for these two waveforms to appear on the same ECG.

Here, we report a case in which the patient's ECG showed the combinations of these two waveforms.

MANUSCRIPT FORMATTING

Case Description

A 48-year-old male was admitted to our hospital due to palpitations and fever. These symptoms were accompanied by fever but no chest pain, cough or expectoration. The patient had a history of a cold 3 days prior. He denied a personal history of heart disease and a family history of sudden death. After admission, the patient's temperature was 38.1°C, and his blood pressure was 148/87 mmHg. Rales were heard in the right lung. His heart rhythm was regular, and no pathological murmurs were heard in any valve.

Diagnostic Assessment

The patient's first troponin I level was 0.86 ng/ml, and the neutrophil percentage was 85%. Echocardiography showed mild mitral regurgitation and left ventricular diastolic dysfunction, without segmental movement abnormalities and abnormal atrial and ventricular structures (see **Supplementary Figures 1–12**). The patient underwent three chest computed tomography (CT) scans taken 1, 4, and 12 days after admission. The CT examinations showed that the pneumonia in the upper right lung progressively worsened (**Supplementary Materials**).

The main challenges came in the form of the rare abnormality in his ECGs. There were Several ECGs and one 12-lead 24 h Holter monitor test were obtained. We identified the coexistence of paroxysmal supraventricular tachycardia (PSVT) and the Brugada wave or a delta wave and Brugada pattern in lead V2 (**Figures 1A,B**). **Figure 1C** shows a Brugada pattern without a delta wave. The height of the R wave was inversely proportional to the height of the ST-segment elevation (**Figures 2A,B**). The amplitude of the R wave had a cyclic course that moved from high to low and then back to high. The ST-segment showed the opposite changes (**Figure 2C**). These changes always happened during the night and in the early morning. Each cycle lasted from several seconds to several minutes. This phenomenon has not been reported thus far in the medical literature, and the cause is unclear.

Based on the patient's lung CT and elevated troponin, the diagnosis of pneumonia and myocarditis was made. The patient's ECGs recorded significant delta waves and PSVT, so the diagnosis of WPW syndrome was also confirmed. At the same time, the patient had no history of underlying heart disease and sudden death of family members. The typical Brugada pattern appeared on the ECG during fever, and it disappeared after the body temperature dropped. Therefore, we made the diagnosis of Brugada phenocopy. Clinicians thought the patient's pulmonary infection was the cause of the myocarditis. Fever caused by lung infection in turn caused the Brugada pattern.

Therapeutic Intervention

We were not sure whether this variability in the ECG could increase the patient's risk of sudden death. Therefore, the clinicians decided to treat the patient with antibiotics first instead of bypass ablation therapy. After the initiation of treatment, his body temperature and laboratory indicators gradually became normal (**Figure 3A** and **Supplementary Materials**). A subsequent ECG showed that the ST-segment in lead V2 had returned to baseline, while the delta wave remained (**Figure 4**). The patient's chest CT scan performed 12 days after admission showed that his lungs were still inflamed, indicating that he needed to continue anti-infective treatment; however, the patient refused and was discharged. Ten days after discharge from the hospital, the patient had a repeated chest CT. The chest CT scan showed that the inflammation in the upper right lung had disappeared (**Supplementary Materials**). One One year later, the patient was called to a follow up that not documented major aritmia except for occasional palpitations. We recommend that patients follow up another ECG to rule out the risk of sudden cardiac death, but he refused.

DISCUSSION

WPW syndrome is a clinical syndrome easily accompanied by tachyarrhythmia, also called pre-excitation syndrome. Impulses from the sinus node are transmitted down through additional channels to activate part of the ventricles earlier, causing pre-excitation in part of the ventricular muscles. This pre-excitement of the local myocardium manifests as a delta wave on the ECG, and PSVT is one of the tachyarrhythmia caused by pre-excitation syndrome. Therefore, WPW syndrome could be identified once delta wave and PSVT were recorded in one patient's ECGs.

Brugada phenocopy was first proposed by Baranchuk et al. (4), which is different from Brugada syndrome. Brugada syndrome is a hereditary ion channel disease that will causes arrhythmia. It has a higher risk of ventricular tachycardia and ventricular fibrillation. However, patients with Brugada phenocopy do not have congenital Brugada syndrome but present with the type I Brugada ECG pattern under certain specific conditions, such as exposure to some drugs (including IA and IC antiarrhythmic drugs), myocardial ischemia, fever, and other illnesses. When these triggers disappear, the ECG then returns to normal.

WPW syndrome with a concurrent Brugada wave is rarely reported. In a previous report, Eckardt et al. (5) observed 35 patients with Brugada syndrome, and they found that 10 patients

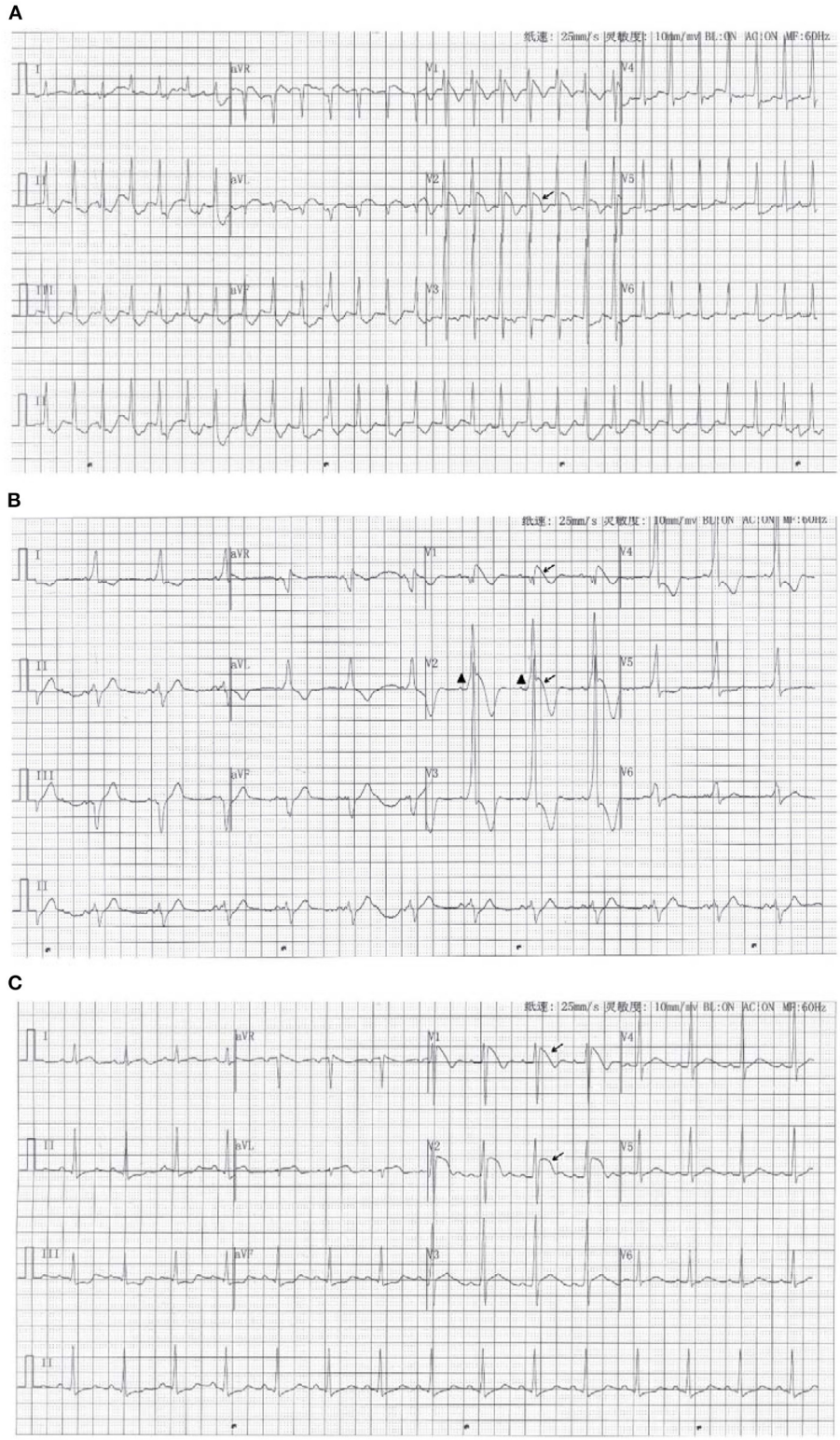

FIGURE 1 | (A) The ECG recorded in the emergency room when the patient felt palpitations. It showed the coexistence of paroxysmal supraventricular tachycardia and the Brugada pattern (arrow) on one ECG. **(B)** The ECG with the delta wave (Triangle mark) and Brugada pattern (arrow). **(C)** The ECG with only the Brugada pattern (arrow).

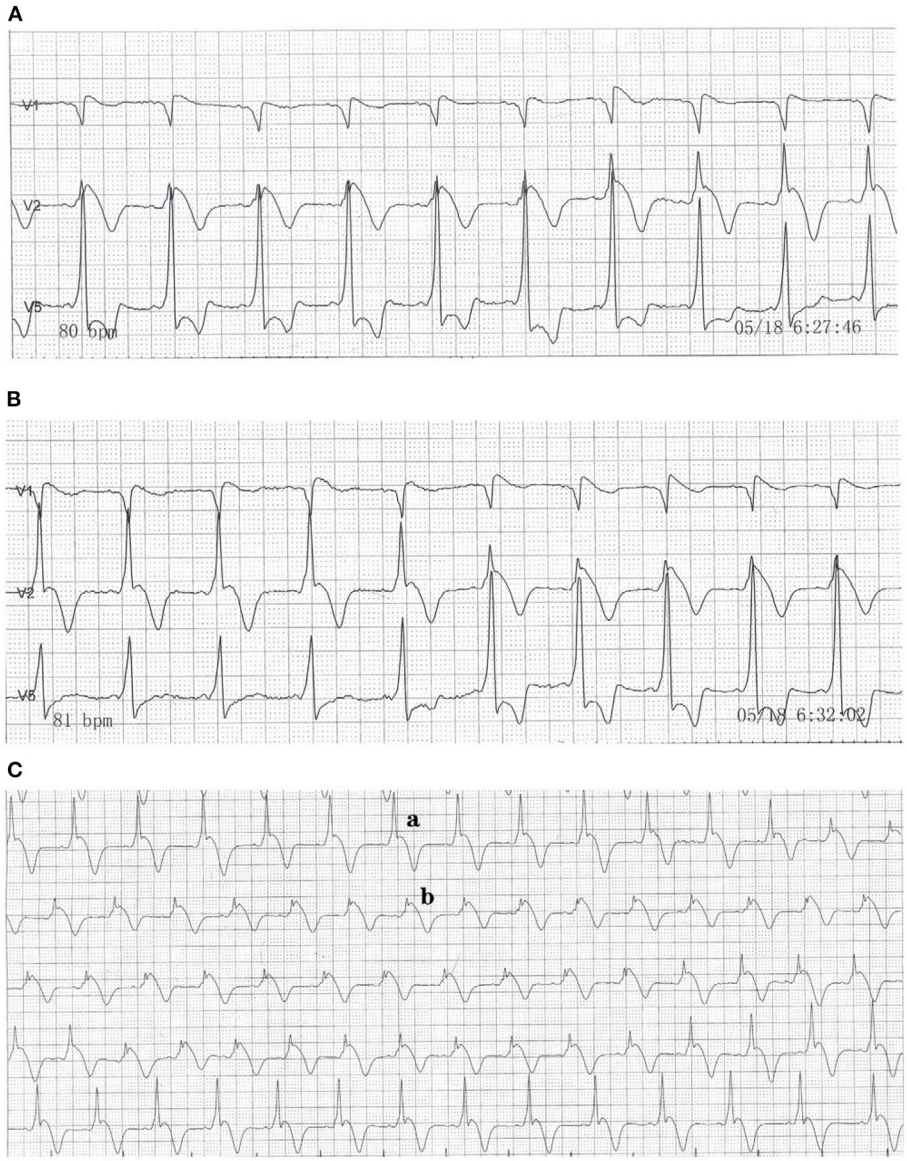

FIGURE 2 | Dynamic electrocardiogram that shows one cycle of the QRS complex. **(A)** The QRS complex began to change in leads V1, V2, and V5 at 6:27 a.m. **(B)** The change ended at 6:32 a.m. **(C)** Dynamic electrocardiogram that shows the continuous changes in the QRS complex in lead V2.

(29%) had supraventricular tachyarrhythmia. Bodegas et al. (6) reported a case of right posterior septal pathway in a patient with Brugada syndrome. However, most of these had single delta waves or Brugada waves on the same ECG.

In our case report, a type 1 Brugada pattern and a ventricular pre-excitation phenomenon appeared concurrently on one ECG. In addition, we recorded the repeated cycles of these waves. In order to explore the relationship between fever and QRS waveform changes, we re-analyzed 24 h Holter monitor, found that the waveform changes always occurred when the body temperature rose. When the body temperature dropped below 37°C, the QRS complex was relatively stable, as shown in **Figure 2C**a. When the body temperature exceeded 37°C, the QRS complex became more variable. We selected two of the most representative waveforms, **Figures 1C**, **2C**b, which meant that the QRS complex had changed once these two graphs appeared. Then we used dynamic analysis software to count the number of occurrences of the two waveforms per hour, and drew a combination diagram to reveal the relationship between the two waveforms distribution and body temperature (**Figure 3B**). From this figure, we could see that the period of waveform change and the period of fever was basically match. Therefore, fever was related to the waveform change. Comparing the waveforms before and after the change, the main difference was that the

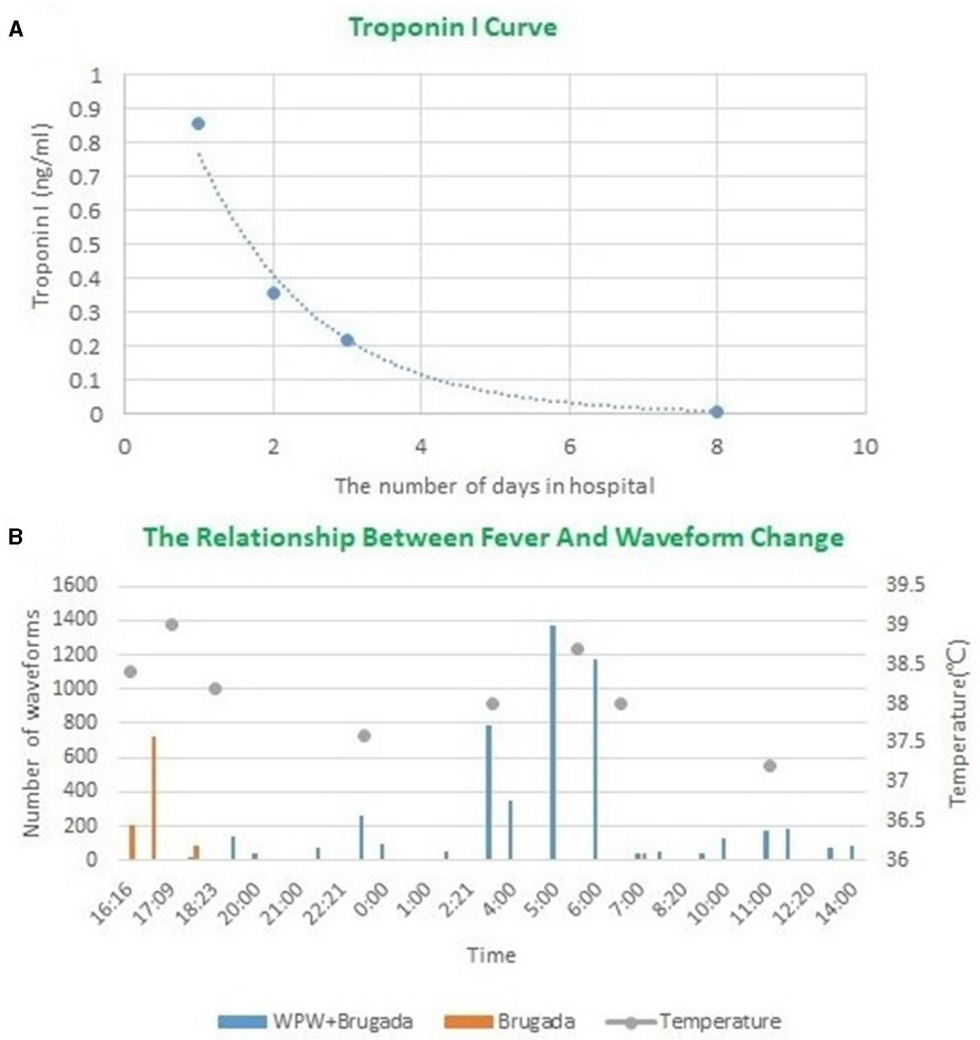

FIGURE 3 | (A) The change curve of troponin I during hospitalization. **(B)** The relationship between fever and waveform changes during 24 h Hortor monitoring period on the second day of admission. The orange mark represents **Figure 1C**. The blue mark represents **Figure 2C**b.

characteristics of Brugada pattern in the changed waveforms were more obvious. It also proved that fever was a powerful trigger of Brugada pattern (7). The dynamic variability in this association has not been reported thus far in the medical literature. And for the first time, we used statistical data to confirm the relationship between the waveform changes and fever.

The most important limitation of this study was the failure to perform intracardiac electrophysiological examinations to determine if the patient had Brugada syndrome. However, in combination with the patient's family history and his present history, the doctors strongly supported the diagnosis of "Brugada phenocopy." Therefore, the correct analysis of the ECG and the comprehensive and accurate recording of the patient's medical history were particularly important.

Our case demonstrated that Coexistent WPW syndrome and Brugada phenocopy could appeared in one ECG, and appeared dynamic changes. These waveform changes was related to fever.

Patient Perspective

In previous reports, the most common cause of Brugada phenocopy coexisting with WPW syndrome was the use of drugs (8). In our report, the reason was fever that was caused by bacterial infection. The patient's troponin I level was elevated, and there were many changes on his ECGs. There remains some uncertainty regarding whether this variability on ECG indicates can increase the risk of ventricular fibrillation or sudden death. These issues made us more conservative in our treatment decisions. The clinicians directed the patient to undergo radiofrequency ablation to eliminate the bypass

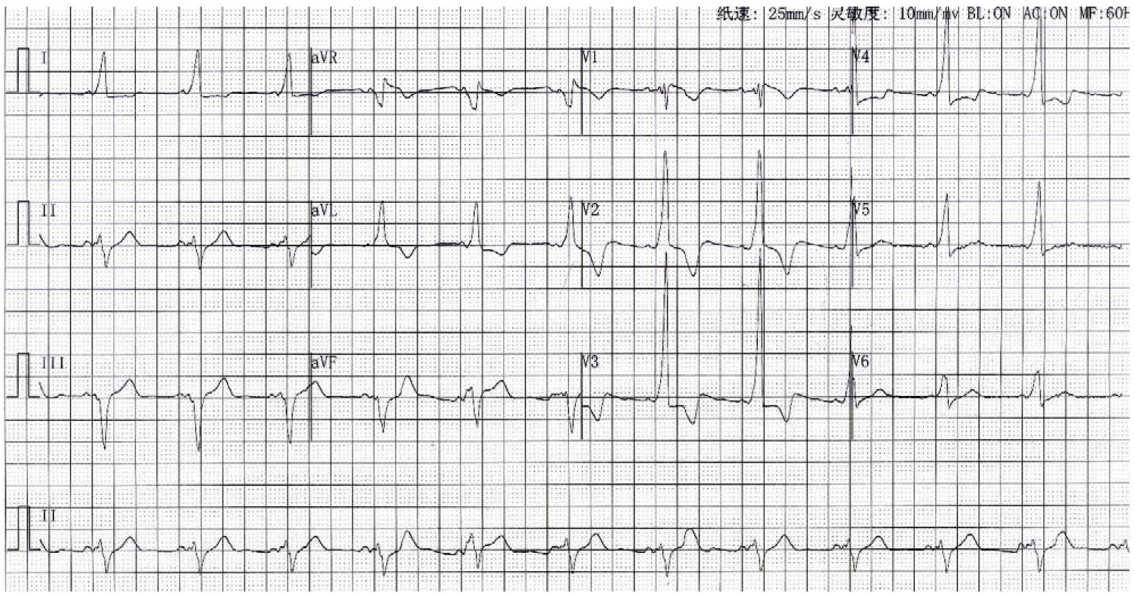

FIGURE 4 | The 12-lead ECG after antibacterial treatment.

after his condition became stable. However, the patient rejected the doctors' advice. In order to better evaluate the prognosis and risk, we included the patient in a follow-up plan.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LW analyzed and contributed to manuscript drafting. YZ and LM reviewed the literature and contributed to manuscript drafting. All authors have read and approved the final manuscript.

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CASE REPORT
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Case Report: Area of Focus of Myocardial Infarction With Non-obstructive Coronary Arteries in Eosinophilic Granulomatosis With Polyangiitis

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Background: Eosinophilic granulomatosis with polyangitis manifested as myocardial infarction with non-obstructed coronary arteries (MINOCA) is rarely reported.

Case: We report a 43-year-old male patient without any cardiovascular risk factors presenting with acute chest pain. Electrocardiogram was suggestive of acute anterior and inferior myocardial infarction. MINOCA was confirmed based on significant elevated cardiac troponin and normal coronary arteries. Cardiac magnetic resonance (CMR) imaging revealed extended late gadolinium enhancement (LGE). Further diagnosis of eosinophilic granulomatosis with polyangitis (EGPA) was based on clinical manifestations and auxiliary examination. Subsequent immunosuppressive therapy led to regression of symptoms and significant resolution of LGE on CMR.

Conclusion: Our case highlights that EGPA can be a rare cause of MINOCA. CMR is useful for differentiation diagnosis and evaluation of cardiac involvement.

Keywords: EGPA, MINOCA, case report, cardiac magnetic resonance, STEMI

INTRODUCTION

ST-elevation myocardial infarction usually occurs from plaque rupture, erosion, fissuring, or dissection, which results in an obstructing thrombus. However, in some circumstance, coronary angiography fails to reveal obstructive coronary arteries in patients clinically defined by criteria of ST-elevation myocardial infarction (STEMI) (1), and a clinically overt specific cause for the acute presentation is unclear, which is concluded as myocardial infarction with non-obstructive coronary arteries (MINOCA) (2). Eosinophilic granulomatosis with polyangitis (EGPA) is a rare, systemic, necrotizing in small- and medium-sized blood vessels vasculitis, which could cause coronaritis or MINOCA. In this case, we report a young man with clinical criteria for STEMI with normal coronary arteries, which was eventually confirmed as EGPA.

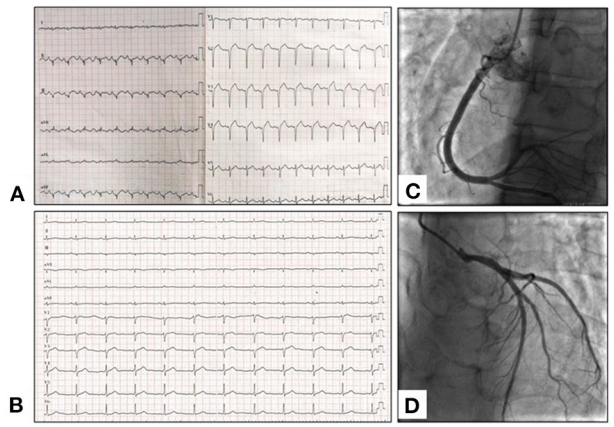

FIGURE 1 | (A) Initial ECG at the emergency room showed poor R wave progression on precordial lead and QS wave on anterior and inferior leads. **(B)** Follow-up ECG after 3-month therapy showed increased R wave amplitude in inferior leads. **(C,D)** Coronary angiography demonstrates normal coronary arteries; **(C)** Right coronary artery. **(D)** Left coronary arteries.

CASE PRESENTATION

A 43-year-old male presented to the emergency department of our hospital with a 5-day history of typical chest tightness radiating to his back. He was previously fit except for a 3-year history of recurrent cough and fever between 37 and 38°C with a significant weight loss of ∼7.5 kg. He was diagnosed as asthma and had been received regular Seretide inhaler (salmeterol and fluticasone propionated inhalation) therapy for 1 year.

In the emergency department, his electrocardiogram (ECG) showed acute myocardial infarction (**Figure 1A**). Physical examination revealed sinus tachycardia of 116 beats per minute. His blood test revealed elevated creatine kinase-MB 38 U/L (normal 0.10–4.94 U/L) and high-sensitivity troponin-T 1.19 ng/ml (normal < 0.014). The total white blood cell count was 18.97 × 10^9/L with marked eosinophilia 9.42 × 10^9/L (normal 0.05–0.50 × 10^9/L). Chest CT indicated multiple lung infiltrates and small patches of ground-glass appearance in both lungs (**Figure 2C**). Transthoracic echocardiogram (TTE) showed normal systolic and diastolic function (ejection fraction: 63%); however, increased echogenicity of endocardium and slightly reduced wall motion was detected in the basal segment of inferior wall. Thus, coronary artery disease could not be excluded. Considering it had been more than 12 h since the onset, coronary angiography (CAG) was not performed until Day 7, showing normal coronary arteries (**Figures 1C,D**). Thus, the diagnosis of MINOCA was confirmed. Cardiac magnetic resonance imaging (CMR) showed normal wall motion with inflammatory edema (**Figure 3A**), and late gadolinium enhancement (LGE) was found in multiple foci (**Figures 3B–D**).

Noticing his blood test of significant eosinophilia, we made further examinations to evaluate the underlying causes of MINOCA. The level of IgE was elevated to 3,739.00 IU/ml (normal 0–120 IU/ml). Anti-neutrophil cytoplasmic antibody was negative, while IgG and IgG4 were markedly elevated (19.10, 6.700 g/L, respectively normal: 10.13–15.13, ≤2.00 g/L, respectively) (**Figures 2A,B**). Bone marrow aspiration and biopsy were performed, and no parasites or hematological diseases were found. Furthermore, hematologic tumor cloning biomarkers were all negative.

In addition, paranasal sinus computed tomography (CT) revealed whole group sinusitis. Electromyography showed partial peripheral nerve damage in the upper and lower limbs and abnormal F waves. Since he fulfilled all the criteria of the six American College of Rheumatology (ACR) classification criteria for EGPA (3) and all other possible hypereosinophilic diseases were excluded, the diagnosis of EGPA-associated MINOCA was made.

After being diagnosed as EGPA, the patient started on intravenous methylprednisolone (40 mg/day), and his eosinophil count, CRP, IgG, IgG4, and IgE returned to normal within 1 week (**Figures 2A,B**), and the lung infiltrates obviously disappeared (**Figure 2D**). He was discharged from the hospital without any discomfort, and mycophenolate mofetil dispersible (0.75 mg QD) was added to methylprednisolone as maintenance. After 3 months, echocardiogram performed showed normal wall motion and cardiac function. ECG showed that the R wave amplitudes in lead II and avF increased significantly compared with those at the onset of MINOCA (**Figure 1B**). CMR showed regression of edema (**Figure 3E**) and significant resolutions of myocardial fibrosis (**Figures 3F–H**). Now, the maintenance dose of prednisone for this patient is gradually decreased to 17.5 mg per day, and the patient is still under follow-up.

DISCUSSION

Eosinophilic granulomatosis with polyangiitis is a systemic vasculitis with eosinophilia infiltrating small and medium-sized blood vessels in multiple organs. EGPA can be divided into three stages (4). In the prodromal stage, fever and a variety of respiratory symptoms often occur, and allergic rhinitis, sinusitis (multiple groups), and bronchial asthma often occur; the second phase is known as tissue eosinophil infiltration (including lung, myocardium, gastrointestinal tract, etc.) lasting for months to years; finally, the third stage presents as vasculitis, and multiple organ damage could occur. A diagnosis of EGPA is made when at least four out of the following criteria developed by the ACR in 1990 are presented; (1) asthma, (2) eosinophilia (>10% on differential white blood cell count), (3) mononeuropathy or polyneuropathy, (4) pulmonary infiltrates, (5) paranasal sinus abnormality, and (6) extravascular eosinophils. Myocardial abnormalities are found in more than 50% of patients with EGPA at autopsy (5). Cardiac involvement is usually the leading cause of death and is reported in 16–29% of patients with EGPA (6, 7). EGPA could involve any part of the heart and manifest as pericarditis, pericardial effusion, cardiac tamponade, congestive heart failure, or even myocardial infarction due to vasculitis of coronary vessels (7). Non-ST-elevation myocardial infarction (8–10) or STEMI with the etiologies of luminal stenosis or spasm throughout the coronary trees is reported in patients with EGPA in several cases (11–13). However, ST elevation with the etiology

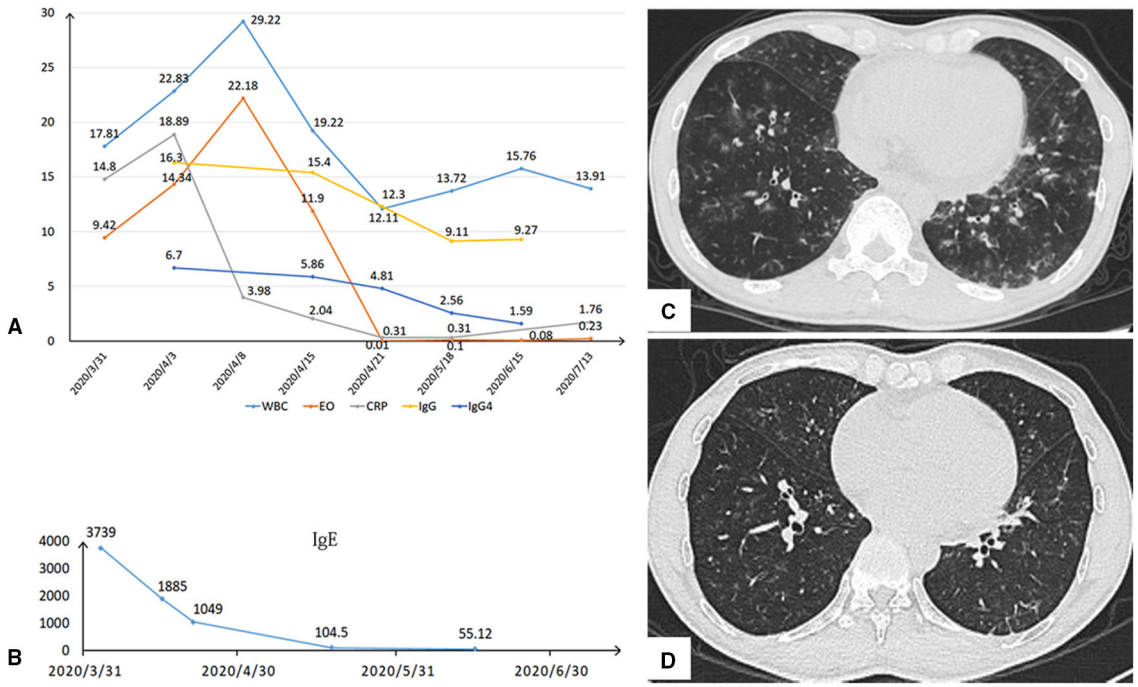

FIGURE 2 | (A,B) After comprehensive treatment, the white blood cells (WBC), eosinophilia (EO), CRP, IgG, IgG4, and IgE responded rapidly and kept dropping down. **(C)** Chest CT indicated multiple lung infiltrates and small patches of ground-glass appearance in both lungs initially. **(D)** After half-a-month antibiotic therapy, the lung infiltration infiltrates obviously disappeared.

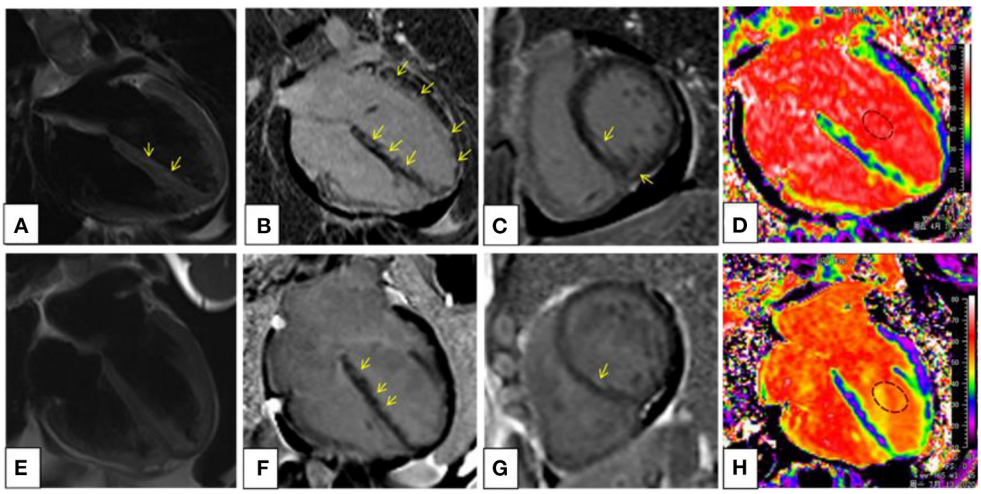

FIGURE 3 | Cardiac magnetic resonance (CMR) imaging at the baseline **(A–D)** and after 3-month prednisone and immunosuppressant therapy **(E–H)**. T2-weighted image **(A)** demonstrated small patches of high-signal intensity in mid-wall and subendocardial regions of the interventricular septum, revealing myocardial edema. On the four-chambered **(B)** and basal short-axis **(C)** view of late gadolinium enhancement (LGE), multiple foci of high-signal intensity were scattered diffusely in mid-wall and subendocardial regions in a nonischemic pattern. An extracellular volume (ECV) map **(D)** showed heterogeneously elevated ECV fraction of the left ventricular myocardium and septum; the global ECV fraction was 34.6%. On posttreatment CMR, it showed complete remission of the myocardial edema **(E)** and significantly reduced LGE **(F,G)**. The global ECV fraction decreased to 29.6% **(H)**.

of myocarditis and myocardial fibrosis in EGPA has not been reported before. In our case, the patients with EGPA without any cardiovascular risk factors presented with ST elevation without coronary arteries stenosis, and, furthermore, CMR confirmed multifocal myocarditis and replacement fibrosis as the cause of MINOCA.

Currently, Cardiac magnetic resonance is the golden criterion for the identification and characterization of myocardial fibrosis associated with myocardial infarction and other nonischemic conditions (14). What is more, a direct association between the ischemic coronary artery and myocardial infarction can be established based on the precise localization of the infarcted area on CMR. And CMR is a clinically relevant noninvasive imaging modality for the assessment of patients presenting with MINOCA (15). The myocardial characteristics of CMR can be used to identify focal edema and fibrosis with STIR T2-weighted and late gadolinium enhancement (LGE) images (16) and can assess diffuse myocardial fibrosis with elevated extracellular volume (ECV) fraction. Myocardial fibrosis detected by LGE has been related to prognosis in various cardiac conditions, and the presence of LGE likely represents a marker of severity of cardiac disease in patients with EGPA (17). In our case, the long T2 signal in interventricular septum (yellow arrow) suggested inflammatory edema (**Figure 3A**), and LGE happened in multiple foci (**Figures 3B,C**), and ECV fraction was significantly elevated in the extended LGE region (**Figure 3D**). After 3-month prednisone and immunosuppressant therapy, follow-up CMR demonstrated the resolution of high-signal intensity on T2-weighted image, attenuation of LGE in multiple foci, and decreased global ECV fraction (**Figures 3E–H**). However, ECG presentation with ST-segment elevation seemed to be a poor prognostic marker in MINOCA (15). Although ECG showed significantly better after 3-month therapy, we do not know the overall survival time of the patient. Thus, long-term follow-up of CMR and ECG should be performed. In our case, CMR is useful for differentiation diagnosis and evaluation of cardiac involvement for patients with EGPA, and an excellent follow-up way to identify internal cardiac lesion while ECG and inspection result were negative.

According to a meta-analysis of 62 patients diagnosed with EGPA with cardiac involvement (18), EGPA may mimic acute coronary syndrome with nonspecific ST-T changes or, rarely, ST elevation on ECG, the etiologies of which may be coronary vasospasm, intracoronary thrombi, coronary artery stenotic lesions or coronary ectasia. In our case, no evidence of coronary vasospasm was revealed on CAG, and, considering the patient was in the acute phase of STEMI, we did not conduct a provocation test for coronary spasm. Besides, LGE distribution within the left ventricular wall was not consistent with coronary artery territory distribution, suggesting the cardiac involvement to be a nonischemic pattern. After corticosteroids and immunosuppressive therapy, LGE was significantly attenuated, which indicated that acute myocarditis caused by EGPA may be the etiology of MINOCA, possibly the acute eosinophilic myocarditis. There are also few reported cases of ST-segment or non-ST-segment elevation myocardial infarction as the presenting feature of patients with eosinophilic myocarditis (19–21). However, in our case, the patient refused endocardial biopsy that we could not make a definite diagnosis of acute eosinophilic myocarditis. Besides, the optical coherence tomography (OCT) may be valuable in the diagnosis of atherosclerotic etiology in individuals with MINOCA (22), yet, the patient did not perform the test, which may not identify whether plaque disruption was as an underlying cause of MINOCA in this case.

CONCLUSION

This case emphasizes that cardiac involvement due to EGPA can be a rare cause of MINOCA. CMR can detect myocardial fibrosis through subendocardial or intramyocardial late gadolinium enhancement without invasion. Hence, CMR is useful for differentiation diagnosis and evaluation of cardiac involvement.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XC performed the data analyses and wrote the manuscript. YP contributed to analysis and explained the image of the cardiac magnetic resonance. JL helped the clinical case analysis and directed the coronary angiography. YD was responsible for patient follow-up. ZW helped to perform the analysis with constructive discussions and editing of the original article. YC contributed to the presentation of the published work by those from the original research group, specifically critical review, commentary, or revision. All the authors contributed to the patient care, diagnosis, and treatment.

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frontiers in Cardiovascular Medicine

CASE REPORT
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Case Report: A Case of Unusual Combination of Hypothyroidism, Myocardial Bridging, and Myocardial Infarction-Induced Left Ventricular Aneurysm

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Background: Myocardial bridging (MB) of the coronary artery is a congenital anatomical variation, which has traditionally been considered a benign condition that does not cause cardiovascular events. However, recent studies have shown that MB is associated with major adverse cardiac events, including angina, myocardial infarction, arrhythmia, syncope, and even sudden death.

Case: We report a case of a 41-year-old man who had hypothyroidism and MB associated with ventricular aneurysm following myocardial infarction. This patient was admitted to our hospital because of 11 days of sudden discomfort and pain in the chest. An electrocardiogram on admission showed an old myocardial infarction. Coronary angiography showed MB in the distal segment of the left anterior descending artery. Left ventricular angiography, which was performed using a pigtail catheter, showed ventricular aneurysm formation. Thyroid ultrasound demonstrated hypothyroidism and Hashimoto's thyroiditis. Patients with hypothyroidism and MB have a high risk of acute myocardial infarction or even sudden death.

Conclusion: Observations in our case suggest that early recognition of hypothyroidism and MB is important for risk stratification and prognosis in patients with myocardial necrosis and acute coronary syndrome. Additionally, this early recognition may have positive effects on cardiovascular outcomes in patients with hypothyroidism.

Keywords: myocardial bridging, myocardial infarction, ventricular aneurysm, percutaneous coronary, hypothyroidism

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INTRODUCTION

Myocardial bridging (MB) of the coronary artery is a congenital coronary anomaly, which has traditionally been considered a benign condition. The prevalence of MB varies greatly owing to different methods and criteria used for detection, with a much higher prevalence by intravascular ultrasound or autopsy than by angiography (1). MB is most commonly localized in the middle segment of the left anterior descending artery (LAD). Although the intramural portion is usually preserved, atherosclerotic plaques are frequently observed in the segment proximal to MB (2). MB results in compression of the coronary artery during

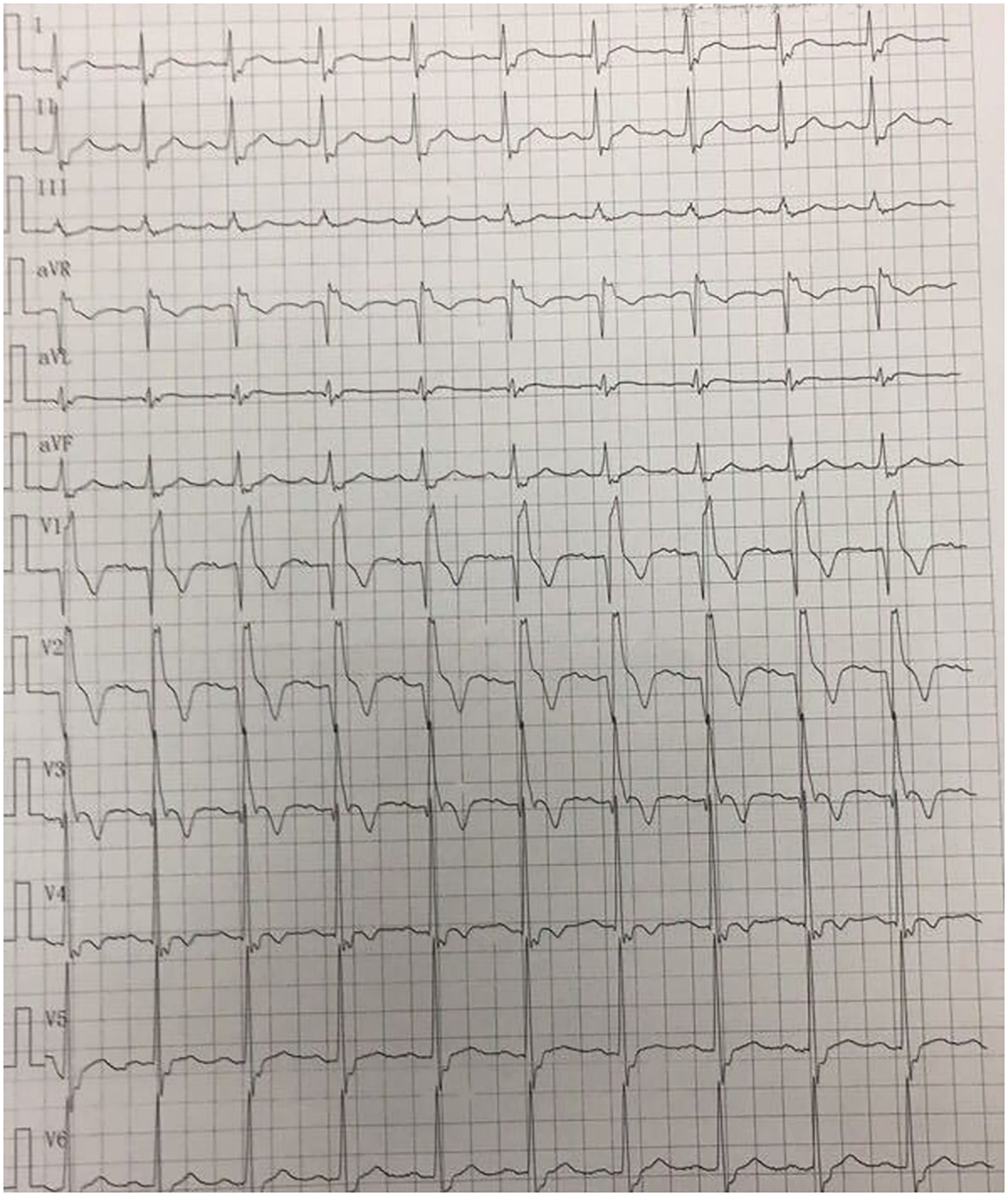

FIGURE 1 | Electrocardiogram on admission shows sinus rhythm, complete right bundle branch block, pathological Q waves in leads V1–V3, and T wave changes in some leads.

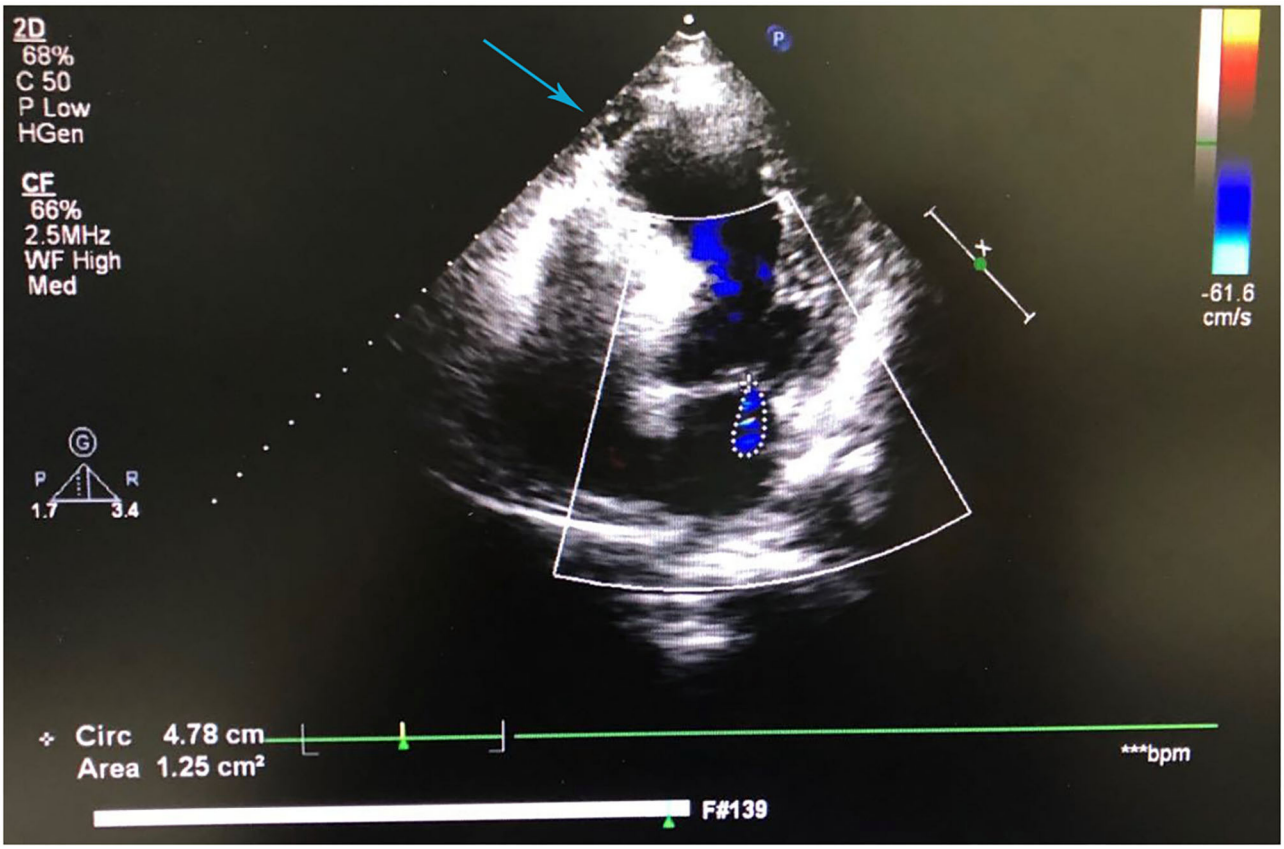

FIGURE 2 | Color Doppler echocardiography shows left ventricular apical aneurysm formation and left ventricular systolic and diastolic dysfunction.

systole, which can cause angina pectoris, myocardial infarction, left ventricular dysfunction, paroxysmal atrioventricular block, effort-related myocardial ischemia, and sudden cardiac death (3, 4). Ishikawa et al. reported pathological and anatomical evidence of MB and showed that MB was a risk factor for coronary atherosclerosis and myocardial infarction (5).

Ventricular aneurysm is a common complication after acute myocardial infarction. A large area of myocardial infarction and reduced or loss of local contractile force can result in left ventricular remodeling and even severe conditions, such as myocardial fibrosis, cardiac cavity dilatation, and increased ventricular wall tension. This situation then causes the ventricular wall to bulge outwards, leading to the formation of ventricular aneurysm. Ventricular aneurysm is characterized by saclike or irregular out-pouching of the heart, a thinner regional ventricular wall, and no or paradoxical wall motion. Ventricular aneurysm causes left ventricular dysfunction, arrhythmia, and mural thrombus formation and increases the risk of cardiovascular events in patients with acute myocardial infarction (6).

We present here a case of a 41-year-old man with an unusual combination of hypothyroidism caused by Hashimoto's thyroiditis, MB, and myocardial infarction-induced ventricular aneurysm. Written informed consent was obtained from the patient for publication of this case report.

CASE DESCRIPTION

A 41-year-old man was admitted to our hospital because of 11 days of sudden discomfort and pain in the chest. Approximately 3 months previously, the patient experienced chest tightness and discomfort, lasting for approximately 5 min, during exercise, excitement, and emotional upset. These symptoms were relieved with rest. He also experienced fatigue and coldness. Eleven days before admission, he had sudden onset of chest tightness and crushing pain, which persisted without relief and did not radiate to the surrounding areas. On admission, the patient showed a dull facial expression and minimal attentiveness and concentration, and his skin was rough. A physical examination showed that his vital signs were stable. His blood pressure was 120/70 mmHg, heart rate was 85 beats/min with regular rhythm, and no pathological murmurs or pericardial friction rubs were heard over each valve area after auscultation. No obvious abnormal signs were observed in the lungs or abdomen, and there was no pitting edema in the bilateral lower extremities. He denied a previous history of hypertension or diabetes. An electrocardiogram performed on admission showed sinus rhythm, complete right bundle branch block, pathological Q waves in leads V1–V3, and T wave changes in some leads (**Figure 1**). Color Doppler echocardiography revealed abnormal echoes in the mid and apical segments of the left ventricular

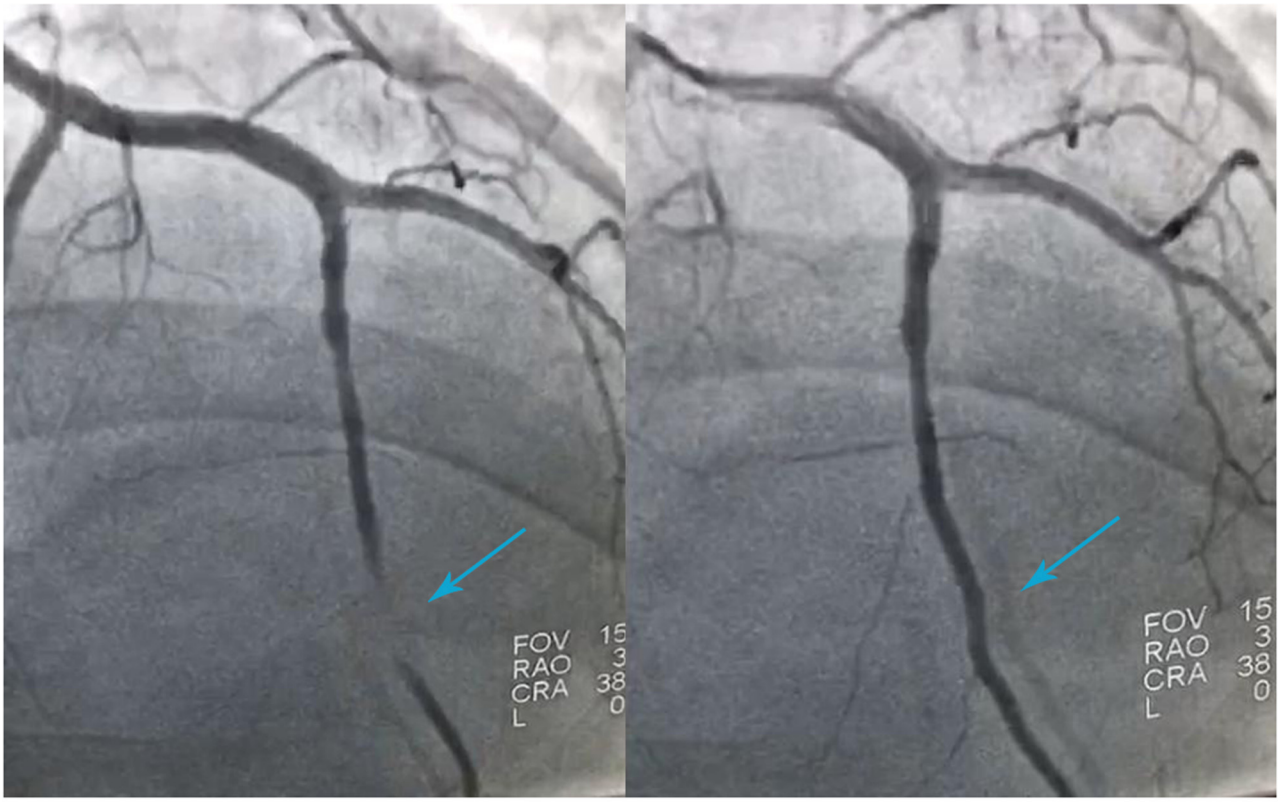

FIGURE 3 | Coronary angiography shows 40%−50% stenosis in the proximal segment of the left anterior descending artery (LAD), myocardial bridging in the distal segment of the LAD during ventricular systole **(A)**, filling of the distal LAD during ventricular diastole **(B)**, and forward flow of TIMI grade 3.

anterior wall and segmental wall motion abnormalities, which were consistent with ultrasound features of coronary heart disease. The apex of the left ventricle was dilated at the right ventricular apex. The ventricular wall was thin and the thinnest area was 17 mm. The ventricular wall bulged outwards and downwards and it showed paradoxical movements. Mural thrombus was not observed, and a left ventricular apical aneurysm had formed. The left ventricular ejection fraction was 36%. Echocardiography showed left ventricular systolic and diastolic dysfunction (**Figure 2**). Thyroid function tests showed the following: triiodothyronine (T3) level, 0.504 nmol/L; free triiodothyronine (FT3) level, 1.66 pmol/L; thyroxine (T4) level, 12.35 nmol/L; free thyroxine (FT4) level, 1.91 pmol/L; thyrotropin (TSH) level, 168.531 mIU/L; antithyroglobulin antibody (TgAb) level, 69.9I U/ml; thyroid peroxidase antibody (TPOAb) level, 486.9 IU/ml; total cholesterol (TC) level, 6.08 mmol/L; triglycerides (TG) level, 5.87 mmol/L; high-density lipoprotein cholesterol (LDLC) level, 0.97 mmol/L; low-density lipoprotein cholesterol (LDLC) level, 4.36 mmol/L; apolipoprotein A (apoA) level, 1.08 g/L; apolipoprotein B (apoB) level, 2.53 g/L; prothrombin time (PT), 14.9 s; international normalized ratio (INR), 1.14; activated partial thromboplastin time (aPTT), 57.8 s; thrombin time (TT), 111.2 s; fibrinogen (FIB) level, 3.23 g/L; aspartate aminotransferase (AST) level, 110 U/L; lactate dehydrogenase (LDH) level, 251 U/L; creatine kinase (CK) level, 169 U/L; creatine kinase-MB (CKMB) level, 10 U/L; hydroxybutyrate hydrogenase (HBD) level, 128 U/L; and troponin T level, 12.3 pg/ml. Ultrasound of the thyroid showed Hashimoto's thyroiditis. Coronary angiography showed that there was no obvious stenosis in the left main coronary artery. Additionally, 40–50% stenosis was found in the proximal LAD, plaques and MB were observed in the distal LAD, and forward flow was TIMI grade 3. There was no obvious stenosis in the left circumflex coronary artery or right coronary artery, and forward flow was TIMI grade 3 (**Figures 3A,B**). Left ventricular angiography, which was performed using a pigtail catheter, showed formation of ventricular aneurysm (**Figure 4**).

The abovementioned findings suggested the diagnosis of coronary atherosclerotic heart disease, old myocardial infarction, and ventricular aneurysm formation. Acute myocardial infarction was excluded. On the basis of our findings of thyroid function tests showing decreased T3, FT3, T4, and FT4 levels and increased TSH and TPOAb levels, hyperthyroidism was excluded, and the diagnosis of hypothyroidism and Hashimoto's thyroiditis was made.

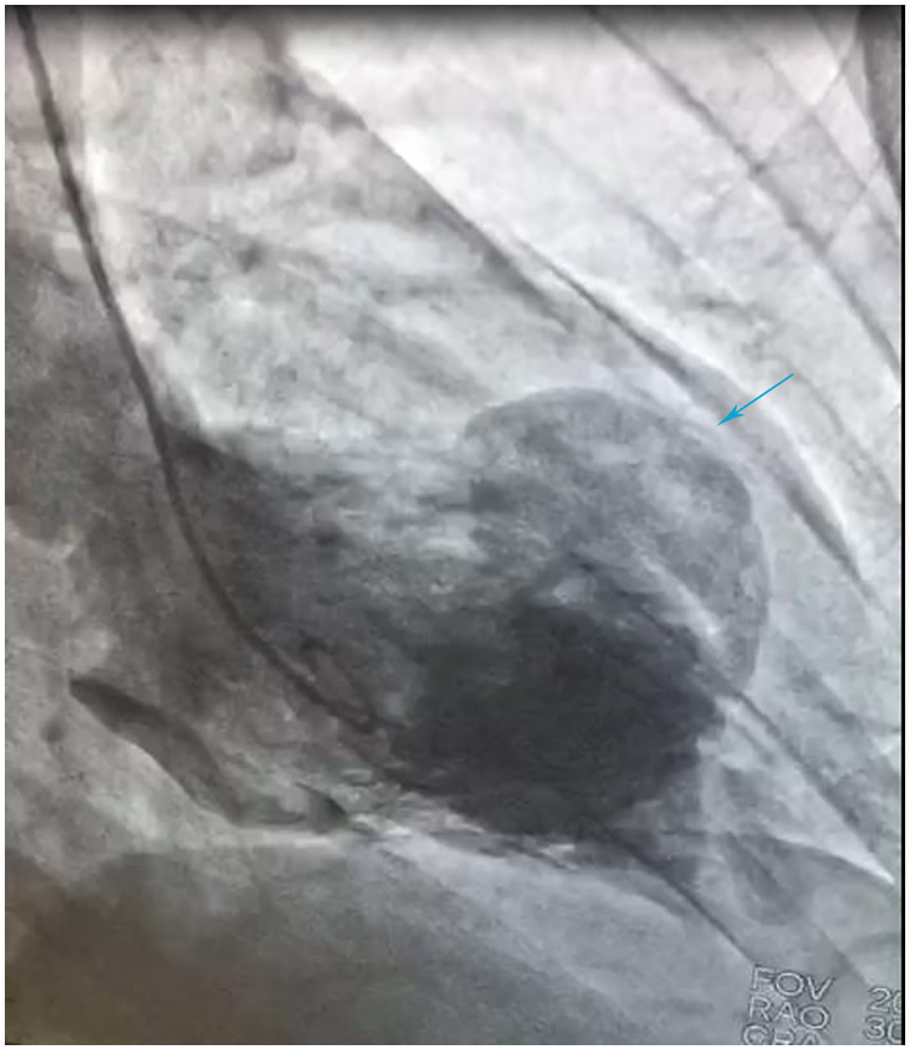

FIGURE 4 | Left ventricular angiography using a pigtail catheter shows ventricular aneurysm formation.

A total of 75 mg of clopidogrel with 100 mg of Bayaspirin was administered orally once daily to inhibit aggregation of platelets. Additionally, 20 mg of atorvastatin calcium tablets were administered orally once daily for lowering lipid and stabilizing plaques. Furthermore, a 23.7-mg metoprolol succinate extended-release tablet was administered orally once daily to slow down heart rate. The patient also received thyroid hormone replacement therapy (levothyroxine). The starting dose of levothyroxine was 12.5 μg/day with a progressive increase of 25 μg/day every 2 weeks. He was also treated with conservative medical therapy for ventricular aneurysm.

After 8 days of treatment, the chest tightness and pain of the patient were relieved, and he was then discharged. The patient was advised to follow a low-sodium, low-fat diet; take medications as prescribed; and exercise appropriately. He was not advised to consume foods containing iodine. He was asked to return to the clinic regularly every month to test thyroid function and to have echocardiography and thyroid ultrasound performed. The dose of levothyroxine was adjusted to 50 μg/day. Additionally, oral administration of clopidogrel (75 mg/day), Bayaspirin (100 mg/day), atorvastatin calcium tablets (20 mg/day), and metoprolol succinate extended-release tablets (23.75 mg/day) was continued. After 6 months of follow-up, thyroid function returned to normal. There was no complaint of chest tightness, fatigue, or coldness, and his skin was smooth and thin. He provided correct answers to asked questions, he had high attentiveness and concentration, and his condition further improved (**Figure 5**). The patient refused to receive further cardiac surgery for left ventricular aneurysm.

DISCUSSION

Chest pain is the most common reason for visiting a doctor for patients with MB, most commonly occurs during exertion or exercise, and may also occur at night during sleep and during emotional stress. In the present case, MB was located in the distal

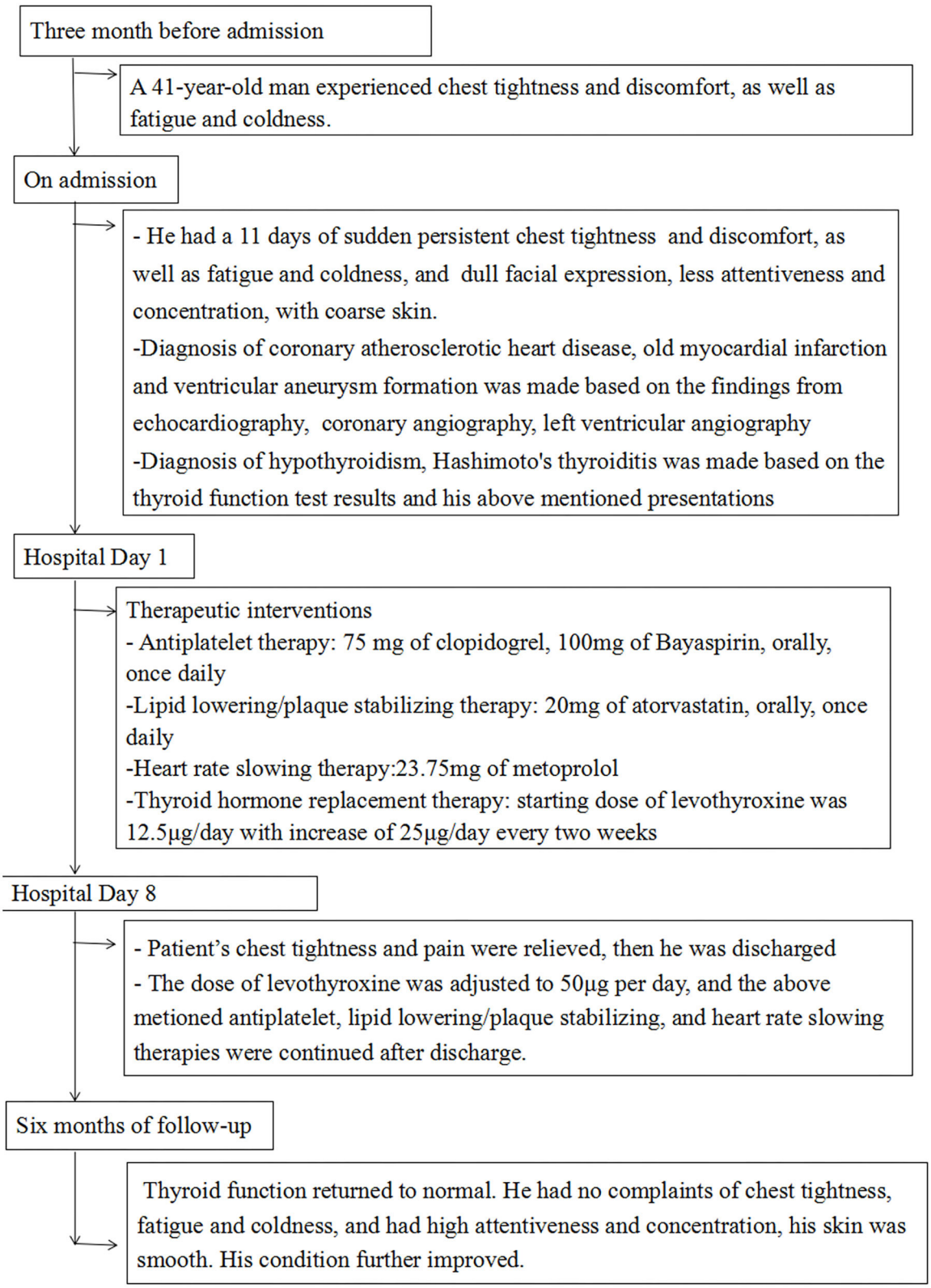

FIGURE 5 | Timeline showing the clinical course in this patient.

segment of the LAD and was not found in the middle segment, and it caused chest pain. This led to myocardial infarction and formation of left ventricular apical aneurysm. The mechanisms by which MB causes chest pain include reduced coronary blood flow and abnormal endothelial function, thrombosis, and coronary spasm (7). MB can induce coronary heart disease. The reason for this induction may be that MB causes compression of the artery during systole, resulting in delayed diastolic relaxation, reduced coronary flow reserve, and decreased blood perfusion. Additionally, repeated compression of the arteries in regions near MB during systole can cause endothelial dysfunction and changes in hemodynamics, thus increasing the risk of coronary artery atherosclerotic stenosis.

Ishikawa et al. found that unstable plaque-related lesion characteristics are more common in MB and coronary arteries near MB are more susceptible to rupture, causing myocardial infarction in young people (8). Therefore, MB is considered a new anatomical risk factor for coronary atherosclerosis. MB initiates the development of atherosclerotic lesions and promotes progression of atherosclerosis at its proximal segment. Compression of the mural coronary artery by MB can be relieved and disappear during diastole. However, fixed stenosis may also exist at the proximal segment, which reduces coronary blood flow to a certain extent. Additionally, coronary artery occlusion and spasm caused by myocardial contraction of the bridge exacerbate myocardial imbalance of supply–demand (9). Increased systolic compression of the coronary artery and a shortened diastolic coronary filling time caused by tachycardia under stress conditions also exacerbate this imbalance.

The present case had Hashimoto's thyroiditis, also known as chronic lymphocytic thyroiditis, which is an autoimmune disease, and it can cause hypothyroidism. Patients with hypothyroidism have endothelial dysfunction, increased platelet activation, and increased cardiovascular risk. Hypothyroidism leads to hypercholesterolemia, increased levels of low-density lipoprotein cholesterol, and hypertriglyceridemia, promoting the development of atherosclerosis and coronary heart disease (10, 11). Studies have shown that a large number of immune cells, including macrophages and T cells, accumulate in atherosclerotic lesions. Adhesion molecules and cytokines released by these cells further activate the immune response and participate in the formation of atherosclerosis (12–14). Many autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and antiphospholipid antibody syndrome, are associated with arteritis, accelerated progression of atherosclerosis, and increased cardiovascular risk (15). Therefore, Hashimoto's thyroiditis may be associated with autoimmunization in patients or inflammatory arteritis, thereby leading to atherosclerosis. However, this possibility needs to be confirmed by further studies.

The findings of the current case suggested that MB initiated the development of coronary atherosclerotic lesions. Our patient had abnormal thyroid function caused by Hashimoto's thyroiditis or hypothyroidism, and the TSH level was elevated. TSH is one of the hormones involved in regulating lipid metabolism. High TSH levels are a risk factor for hypercholesterolemia and hypertriglyceridemia, which have an adverse effect on the lipid profile and lead to an increase in morbidity and mortality from coronary heart disease (16). Therefore, our patient received secondary prevention therapies for coronary heart disease, such as antiplatelet, lipid-lowering/plaque-stabilizing, and heart rate-slowing therapies. He also received thyroid hormone replacement therapy for hypothyroidism. After 6 months of follow-up, the patient had a good prognosis.

Hashimoto's thyroiditis, which is an autoimmune disease, not only promotes progression of atherosclerosis in arterial segments proximal to MB but also promotes progression of atherosclerosis in the entire arterial segment. Hashimoto's thyroiditis and MB increase the risk of acute coronary syndrome, and patients with this condition and MB are prone to adverse cardiovascular events, such as acute myocardial infarction. The combination of immune responses and low thyroid function contributes to progression of coronary atherosclerosis in the entire arterial segment, with more significant progression than hypothyroidism alone.

Manifestations of MB-related myocardial ischemia are not uncommon. Patients with MB have a high risk of acute myocardial infarction or even sudden death. Findings from our case suggest that early recognition of hypothyroidism and MB is important for risk stratification and prognosis in patients with myocardial necrosis and acute coronary syndrome. This early recognition may have beneficial effects on cardiovascular outcomes in patients with hypothyroidism.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Qingyuan People's Hospital, the Sixth Affiliated Hospital of Guangzhou Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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CASE REPORT
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Sintilimab-Induced Myocarditis Overlapping Myositis in a Patient With Metastatic Thymoma: A Case Report

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Although immune checkpoint inhibitor (ICI)-related myocarditis has been widely discussed, a lot of gaps and challenges in its clinical course and rational intervention remain elusive. We present the case of a 33-year-old man with a history of metastatic thymoma who developed dyspnea and muscle weakness 1 month after the first dose of sintilimab. He was asymptomatic but found to have a mild elevation of troponin-T and a moderate increase of creatine kinase 20 days after the infusion. Although the scheduled second dose was deferred, he developed dyspnea, left bundle branch block, and left ventricular enlargement that is suggestive of Grade 3 ICI-related myocarditis, complicated with myositis/myasthenia gravis 10 days later. Fortunately, his response to intensive immunosuppressive therapy was good.

Keywords: immune checkpoint inhibitor, sintilimab, myocarditis, myositis, myasthenia gravis

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INTRODUCTION

Immune checkpoint inhibitor (ICI) has emerged as a revolutionized therapy across multiple refractory malignancies. Programmed cell death receptor 1 (PD-1) or programmed cell death ligand 1 (PD-L1) is among the most established targets for immunological tumor depletion. However, while T cells are inflamed against tumor cells, undesired withdrawal of tolerance to self-antigens has created a wide spectrum of immune-related adverse events (irAEs) (1). ICI-related myocarditis as one of the life-threatening irAEs has been broadly discussed in the previous publications (2), but the gap of knowledge remains in terms of its clinical pattern (3). Sintilimab, a human monoclonal antibody targeting PD-1, was recently approved in China and launched extensive clinical trials (4). In this case study, we reported a rare case of myocarditis overlapping myositis/myasthenia gravis (MG) induced by sintilimab with the description of an "incubation" before the onset of severe symptoms.

CASE PRESENTATION

A 33-year-old male with a history of metastatic thymoma was admitted with dyspnea, palpitation, and muscle weakness 1 month after the first infusion of sintilimab. He had received multiple lines of therapy before a high expression (50%) of PD-L1 was detected by immunohistochemical examination. He had no history of hypertension, diabetes, dyslipidemia, smoking, or drinking. He was given the first dose of 200 mg sintilimab intravenously after a normal baseline assessment including cardiac biomarkers, ECG, and echocardiography. A total of 24 days later, proactive

monitoring before the next dose revealed an elevated serum troponin-T (TnT) of 69 ng/ml (normal < 14 ng/l), N-terminal probrain natriuretic peptide (NT-proBNP) of 154 ng/ml (normal < 88 ng/ml), and creatine kinase (CK) of 1,324 IU/L (normal 19–226 IU/l), though the patient was asymptomatic with unremarkable ECG and echocardiography. The second dose of sintilimab was deferred; however, he quickly developed dyspnea, palpitation, and muscle weakness in 10 days. Physical examination on admission showed a normal body temperature of 36.5°C, a regular heart rhythm of 78 bpm, and a mildly high blood pressure of 140/90 mmHg. Ptosis and dysarthria were noted, but no edema in the lower limbs. Markedly increased TnT (1,566 ng/ml), NT-proBNP (1,339 ng/ml), or CK (25,692 IU/l) level was alarmed. ECG demonstrated a new complete left bundle branch block with a QRS duration of 156 ms. Echocardiography indicated a dilated left ventricle (LV) with an LV end-diastolic dimension of 58 mm, but a preserved ejection fraction of 61%. Therefore, the diagnosis of Grade 3 ICI-related myocarditis, MG was suggested, and a combination therapy of methylprednisolone (2 mg/kg/d), human immunoglobulin (20 g/d for 5 days), and pyridostigmine (180 mg/day) was given. Within a few days after the treatment, his symptoms significantly improved, while the LV reduced to a normal size and the QRS complexes resumed a normal morphology (**Figures 1A–D**).

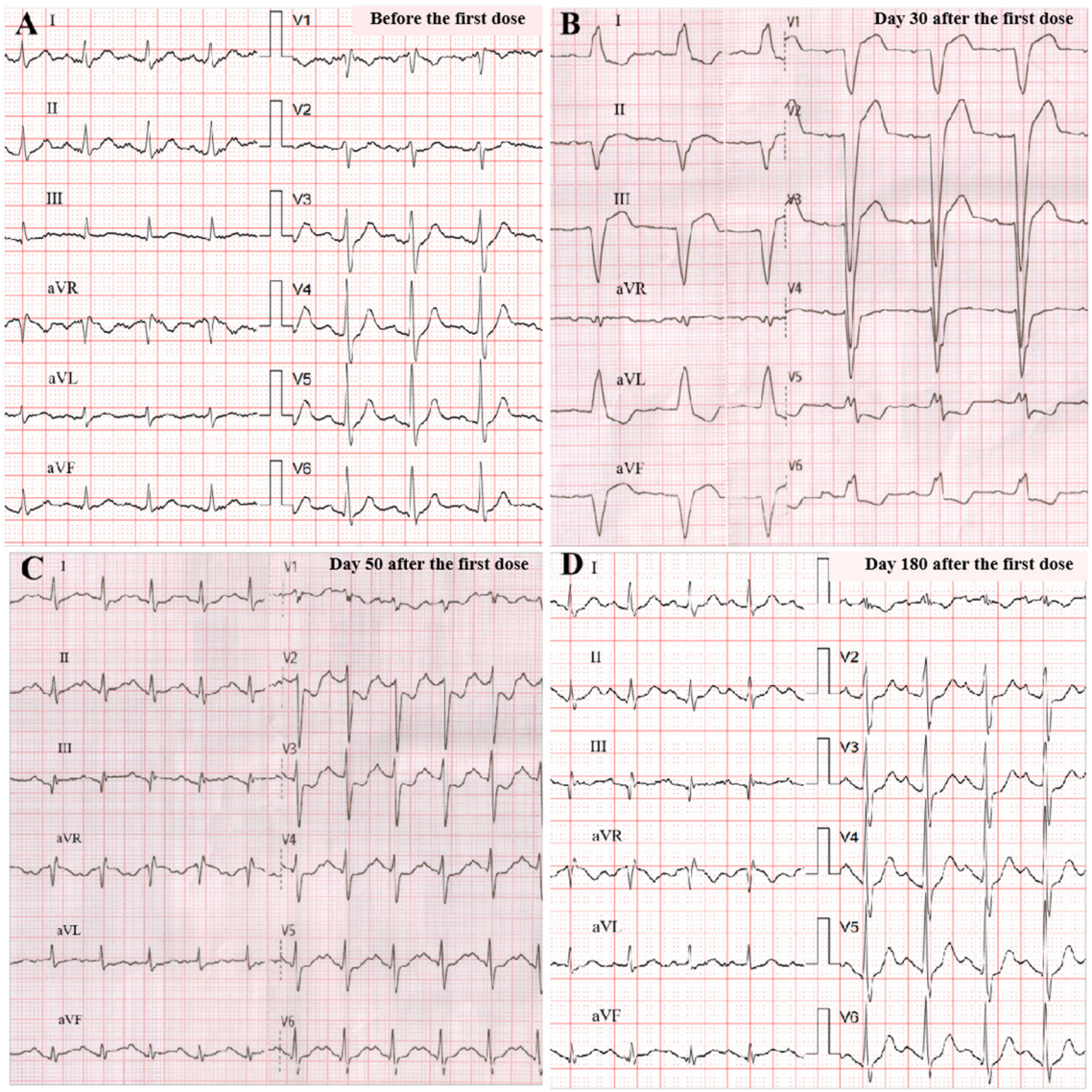

FIGURE 1 | ECG changes. Before programmed cell death receptor 1 (PD-1) inhibitor treatment (sinus 104 bpm, normal QRS of 106 ms) **(A)**; on admission (sinus 73 bpm, wide QRS of 156 ms, left bundle branch block) **(B)**; at discharge (sinus 125 bpm, normal QRS of 118 ms) **(C)**; at 6-month follow-up (sinus 113 bpm, normal QRS of 110 ms) **(D)**.

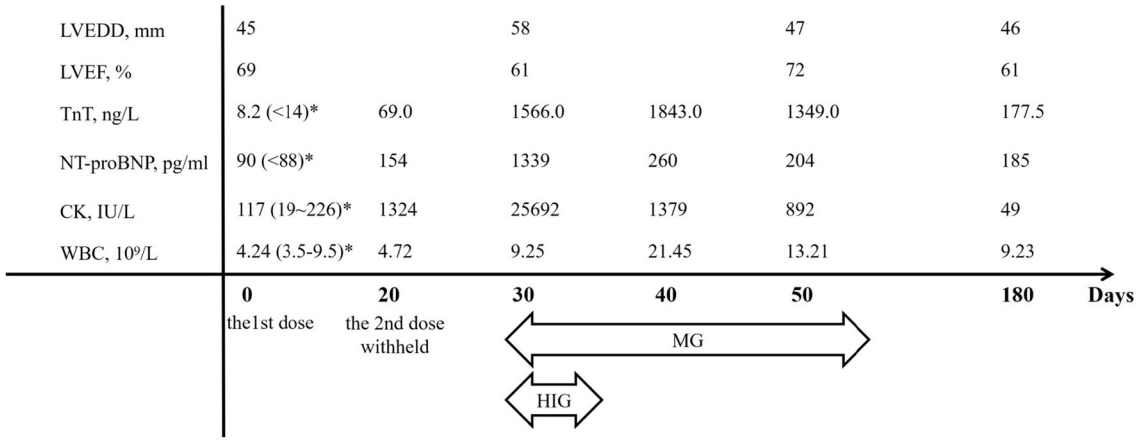

FIGURE 2 | The chronological changes of major parameters. CK, creatine kinase; HIG, human immunoglobulin; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MG, methylprednisolone; NT-proBNP, N-terminal pro-brain natriuretic peptide; TnT, troponin-T; WBC, white blood cell count. *Normal ranges in parentheses.

He maintained oral prednisone in a tapering regimen for 6 months. The chronological changes in biomarkers and LV parameters with immunosuppressive treatment are shown in **Figure 2**.

DISCUSSION

Few ICI-based therapies were available for patients with thymoma in China. Clinical trials reported that severe irAEs occurred in 15% of the patients, with pneumonitis being the most frequent (4). Previous publications with other ICIs suggested 25 and 11% of concomitant myositis and MG among myocarditis, respectively (5), which indicated common inciting autoantibodies. Patients with preexisting autoimmune disease (AD) are potentially more susceptible to irAEs. A phase 2 study of pembrolizumab observed a higher incidence of cardiac and muscular abnormalities in patients with thymic carcinoma and a notable predilection to Asians. (6) Two recently reported cases of sintilimab-induced myocarditis and myositis or MG demonstrated some similarities in clinical pattern with other ICIs (7, 8). Comparatively, the current case showed an early onset after the first dose, a preceding asymptomatic period, a dramatic change of ECG, and a better outcome in a younger patient. Given, the recognized association of thymoma to AD, it would be rational to be alerted when treating this cohort (9).

With CD8+ T cell infiltration on endomyocardial biopsy being the cardinal feature of ICI-related myocarditis, changes detected by other noninvasive tools, such as ECG, echocardiography, and cardiac magnetic resonance are heterogeneous and inconclusive (3). Despite not being indicative to specific etiology, elevated troponin is the most sensitive marker of myocardial damage (10). In this case, a slight elevation of high-sensitive TnT was noted in proactive monitoring before the scheduled second infusion (usually 14–21 days after the first dose), which may not necessarily suggest overt myocarditis in the clinical settings other than ICI induced. Nonetheless, it was followed by a 2-week silent "incubation" period before an abrupt change into acute symptomatic heart failure with demonstrated electrical and structural abnormalities in the LV. We address this course because the progression in asymptomatic patients with only mild changes of cardiac biomarkers is not fully delineated, which could be a transient alteration, or as in our case, a preceding sign of a more severe event. Current consensus recommends holding the ICI without additional prophylaxis for this cohort, yet the evidence is mostly empirical (11).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Z-xY: contributed to data analysis, writing of the article, and editing of the figure. XC: contributed to imaging analysis and editing of the figure. S-qT: contributed to the literature search and clinical record collection. QZ: contributed to the clinical care of the patient, study design, and critical review of the article. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Series: Extracorporeal Shockwave Myocardial Revascularization Therapy Improves Ischemic Response, Functional Capacity, and Quality of Life in Indicated CABG-Stable Angina Pectoris Patients

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Introduction: Extracorporeal shockwave myocardial revascularization (ESMR) is included in the guidelines only for patients with refractory angina pectoris having no option for invasive revascularization. We intend to report a case series with ESMR therapy is indicated patients with coronary artery bypass grafting-stable angina pectoris (CABG-SAP) who refuse the surgery, irrespective of angina symptoms.

Methods: We review medical records of patients with SAP admitted to ESMR therapy in Dr. Hasan Sadikin General Hospital, Bandung, Indonesia from January 2018 to December 2019. Recorded variables at baseline and after therapy extracted, namely, (1) ischemic response, double product, and (2) functional capacity measured as metabolic equivalent (MET) using treadmill test; (3) six-minute walking test distance achieved; and (4) quality of life using SF-36 Questionnaire.

Results: A total of four indicated patients with CABG-SAP from 50 to 75 years old were included in this study. At baseline, one patient is CCS class I and two patients are CCS class II with SDS ranging from 3 to 17. Ischemic response improved in all the patients. The double product improved in patient 1 9,600–14,872 mm Hg × bpm, patient 2 9,460–10,640 mm Hg × bpm, and patient 4 17,220–20,480 mm Hg × bpm. The functional capacity improved in Patient 1 8.07–8.91 METs, patient 2 1.91–4.01 METs, patient 3 3.45–6.39 METs, and patient 4 3.9–4.43 METs. The 6-min walking distance improved in patient 1 540–570 m and patient 2 345–405 m. The CCS class, bodily pain, and general health domain scores improved in all patients.

Conclusion: ESMR therapy might be beneficial for indicated patients with CABG-SAP to improve ischemic response, functional capacity, and physical component of quality of life.

Keywords: cardiac shock wave, case series, functional capacity, stable angina, quality of life

INTRODUCTION

Coronary artery disease (CAD), including stable angina pectoris (SAP), remains the leading cause of mortality and morbidity in Indonesian adults (1–3). The current SAP treatment guideline mainly focuses on medical therapy and invasive revascularization approaches (1). Studies showed that invasive revascularization therapy leads to better anginal pain reduction and improved quality of life than using medication alone (4). However, approximately, one-third of patients with CAD in Indonesia refuse invasive treatment approaches (5).

The mechanism that precipitates angina in patients with SAP highly correlates with the multifaceted mechanism of chronic myocardial ischemia (6). Imbalances of oxygen supply-demand, anaerobic metabolism, sympathetic activation, and myocardial perfusion have been postulated to influence myocardial ischemia (7). In addition, coronary collaterals could also affect myocardial perfusion, improving myocardial ischemia (8). Exercise and some emerging non-invasive treatments have been studied to improve microvascular circulation in patients with CAD (9–11).

Extracorporeal shockwave myocardial revascularization (ESMR) is a non-invasive procedure that has a beneficial effect in patients with SAP having no option for invasive revascularization and refractory angina (12). In a triple-blind randomized clinical trial of patients with refractory angina, ESMR therapy demonstrated significantly improved myocardial perfusion during 6-month follow-up compared to medical therapy alone (9). A recent meta-analysis comparing ESMR vs. optimal medical therapy alone in patients with refractory angina shows a significant improvement in the 6-min walking test distance achieved and quality of life measured using the Seattle angina questionnaire (13). A limited study describes the efficacy of ESMR to treat indicated invasive revascularization patients with SAP. We report our case series of indicated patients with CABG-SAP, irrespective of angina status undergoing ESMR therapy.

METHODS

We conducted a retrospective case series study of prospectively collected data of patients who have completed ESMR therapy in the Department of Cardiology and Vascular Medicine, Dr Hasan Sadikin General Hospital, Bandung, Indonesia, between January 2018 and December 2019. The inclusion criteria were patients with SAP who completed nine ESMR therapy sessions and indicated a CABG procedure after angiography. The exclusion criteria were a history of invasive revascularization. We collected data from medical records concerning clinical characteristics, ESMR therapy protocol, baseline evaluation, and postintervention evaluation. In this report, we focus to report data of 6-min walking distance, treadmill test, and quality of life measured using the Canadian Cardiology Society Class (CCS Class) and the Short Form-36 (SF-36) questionnaire before and after ESMR therapy. Another report for perfusion and contractility changes is published elsewhere (14). The study was approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung (No. LB.02.01/X.6.5.284/2020) and signed individual consent for this report was waived.

RESULTS

We included records of four patients with SAP having Syntax scores ranging from 32 to 43. All the patients are suggested for CABG procedure by their interventional cardiologist. However, the patient refuses to surgery approach and they undergo ESMR therapy in our center based on clinician referral. Clinical and demographic features are shown in **Tables 1**, **2**. The mean age was 60 years old (range 50–75 years old) consisted of three males and one female. Patients 1, 3, and 4 were diagnosed with the three-vessels disease (3VD), and Patient 2 was diagnosed with 3VD with left-main involvement. Patient 2 has a history of myocardial infarction. The mean left ventricular ejection fraction was 62.5 $\pm$ 3.69%. The mean of Summed Stress Score (SSS), Summed Difference Score (SDS), and Summed Rest Score (SRS) were 17.25 $\pm$ 9.8, 9.5 $\pm$ 5.9, and 7.75 $\pm$ 5.5, respectively. Patients 1, 2, and 4 have hypertension as risk factors, Patient 1 also has psychological stress as risk factors, and Patient 4 has smoking and diabetes as risk factors. All four patients have no history of invasive revascularization and refused the CABG procedure. All four patients completed ESMR therapy in addition to their optimal medical therapy.

This therapy consisted of nine sessions for 3 months with three sessions per week and was performed on the 1st, 5th, and 9th intervention weeks. During the 1st, 5th, and 9th intervention weeks, the shockwave was delivered to the target spots segments of the left ventricle, respectively, for 30 min each session. A 3-week therapy-free interval was kept after the 1st and 5th therapy weeks (15).

At first, shockwave (SW) is delivered to the border zone to induce neovascularization from the segment with adequate blood supply to the ischemic zone. The ischemic zone was divided into specific target spots based on one focus zone of the SW applicator to achieve optimal therapy. The SW applicator was fixed at the measured distance when end-diastole. An inflatable silicone cushion was filled, and the ultrasound gel was used for optimal delivery of shockwaves into the body. Low-intensity SW (100 impulses/spot) were delivered to the target spot under

TABLE 1 | Included patients characteristics.

Variable	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Male	Male	Male	Female
Age (years)	54	61	75	50
BMI (kg/m^2)	26.6	25.3	24.6	24.6
Blood pressure (mmHg)	90/70	120/70	140/90	140/90
Heart rate (bpm)	53	63	56	81
CAD history (years)	10	2	2	2
Coronary stenosis				
LAD	Yes	Yes	Yes	Yes
LCX	Yes	Yes	Yes	Yes
RCA	Yes	Yes	Yes	Yes
LM	No	Yes	No	No
SYNTAX score	41	32	43	40
History of myocardial infarct	No	Yes	No	No
Biplane simpson LVEF (%)	62	63	58	67
SPECT				
Areas with reduced blood infusion	Left ventricular apex, apical lateral wall, and middle until basal inferolateral wall	Left ventricular apex, apical anterior wall, apical lateral wall, and middle inferolateral wall	Left ventricular middle until basal inferior wall, and anteroseptal apex	Left ventricular apical anteroseptal wall, basal anteroseptal wall
SSS	31	13	17	8
SDS	17	3	11	7
SRS	14	10	6	1
Risk factor				
a. Non-modifiable				
- History of premature CAD in first-degree relatives	No	No	No	Yes
b. Modifiable				
- Obesity	Yes	No	No	No
- Hypertension	Yes	Yes	No	Yes
- Hypercholesterolemia	No	No	Yes	No
- Diabetes Mellitus	No	No	No	Yes
- Smoking	No	Yes	No	Yes
- Stress	Yes	No	No	No

BMI, body mass index; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society Class; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main artery; LVEF, left ventricular ejection fraction; RCA, right coronary artery; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

electrocardiographic R-wave gating. The target spot is different for each individual, and if there were five target spots, the total SW are 500 impulses (15). The target spot is determined using the single-photon emission CT (SPECT) test and defined as areas with reduced blood infusion. An example of SPECT examination report represented by Patient 1 is given in **Figure 1**.

During 3 months after ESMR therapy, post-ESMR evaluations were collected. Therapy efficacy in this study is presented in **Table 3**. Patient 2 experienced limiting angina at baseline during the treadmill stress test that improved after ESMR therapy. The ischemic response is improved in patient 1 positive to negative, patient 2 suggestive to negative (**Figure 2**), and patients 3 and 4 positive to suggestive ischemic responses. The double product (DP) improved in patient 1 9,600–14,872 mm Hg × bpm, patient 2 9,460–10,640 mm Hg × bpm, and patient 4 17,220–20,480 mm Hg × bpm. The functional capacity improved in patient 1 8.07–8.91 METs, patient 2 1.91–4.01 METs, patient 3 3.45–6.39 METs, and patient 4 3.9–4.43 METs. The 6-min walking distance improved in patient 1 540–570 m and patient 2 345–405 m, but deteriorated in patient 3 435–405 m and patient 4 450–425 m.

After ESMR, there are improvements of CCS Class in patient 1 CCS III to I and patient 2 CCS II to I. In addition, our case series demonstrated the various effect of ESMR therapy on quality of life measured using SF-36. The bodily pain domain score improved in all the patients as seen in patient 1 60–90, patient 2 58–80, patient 3 65–78, and patient 4 58–68. The general health domain score improved in all the patients as seen in patient 1 65–85, patient 2 40–65, patient 3 70–75, and patient 4 65–75. On medical records, there are reductions of ß-blocker dose in patients 1 and 2. Also, there are additions for antianginal medication such as trimetazidine in patients 1 and 4. During a 3-month follow-up period, no major adverse cardiovascular events (MACEs) such as death, myocardial infarction, coronary revascularization, stroke, and hospitalization because of heart failure were recorded in all the patients.

TABLE 2 | Medications history of included patients.

	Before ESMR	After (3-month) ESMR
Patient 1	Clopidogrel 1 x 75 mg	Clopidogrel 1 x 75 mg
	Bisoprolol 1 x 10 mg	Bisoprolol 1 x 5 mg
	Amlodipine 1 x 5 mg	Amlodipine 1 x 5 mg
	Candesartan 1 x 16 mg	Candesartan 1 x 16 mg
	Glyseril-tri-nitrate 2 x 2.5 mg	Glyseril-tri-nitrate 2 x 2.5 mg
	Atorvastatin 1 x 40 mg	Trimetazidine 2 x 35 mg
		Atorvastatin 1 x 40 mg
Patient 2	Aspirin 1 x 80 mg	Aspirin 1 x 80 mg
	Bisoprolol 1 x 10 mg	Clopidogrel 1 x 75 mg
	Amlodipine 1 x 10 mg	Bisoprolol 1 x 7.5 mg
	Candesartan 1 x 16 mg	Amlodipine 1 x 10 mg
	Glyseril-tri-nitrate 2 x 2.5 mg	Candesartan 1 x 4 mg
	Hydrochlorothiazide1 x 25 mg	Glyseril-tri-nitrate 2 x 2.5 mg
	Atorvastatin 1 x 20 mg	Atorvastatin 1 x 20 mg
Patient 3	Aspirin 1 x 80 mg	Aspirin 1 x 80 mg
	Bisoprolol 1 x 10 mg	Bisoprolol 1 x 10 mg
	Glyseril-tri-nitrate 2 x 2.5 mg	Glyseril-tri-nitrate 2 x 2.5 mg
	Atorvastatin 1 x 40 mg	Furosemide 1 x 20 mg
		Atorvastatin 1 x 40 mg
Patient 4	Clopidogrel 1 x 75 mg	Clopidogrel 1 x 75 mg
	Bisoprolol 1 x 10 mg	Bisoprolol 1 x 10 mg
	Amlodipine 1 x 10 mg	Amlodipine 1 x 10 mg
	Candesartan 1 x 16 mg	Candesartan 1 x 8 mg
	Glyseril-tri-nitrate 2 x 2.5 mg	Glyseril-tri-nitrate 2 x 2.5 mg
	HCT 1 x 12.5 mg	Trimetazidine 2 x 35 mg
	Atorvastatin 1 x 40 mg	Atorvastatin 1 x 40 mg

DISCUSSION

Based on the current guidelines, the position of ESMR therapy is recognized as a potential treatment for refractory angina (1). Previous clinical studies of ESMR found beneficial effects for patients with refractory angina pectoris that do not have options for invasive approaches (13). However, most EMSR therapy trials only include a small sample of patients for each group (16–18). Trials with large samples are needed to increase the power of this therapy.

This case series demonstrated its novelty by evaluating the use of ESMR therapy in patients with SAP currently indicated to CABG procedure, irrespective of angina symptoms. Therefore, the included patients are not yet defined as patients with refractory angina pectoris. In our study, ESMR therapy could improve ischemic response, functional capacity, angina symptoms, and physical component quality of life, especially in bodily pain and the general health domain.

Extracorporeal shockwave myocardial revascularization (ESMR) therapy works by triggering the inertial collapse of micro-sized bubbles, which exert shear stress-like forces on myocardial tissue. Therefore, stimulating angiogenesis induction of growth factors, namely, vascular endothelial growth factor (VEGF) and nitric oxide synthase (NOS) (19). In animal studies, increased VEGF and NOS concentration after ESMR therapy was also observed. These substances stimulate the process that increases collateral growth, myocardial remodeling, and left ventricular compliance (20). In previously published trials, ESMR therapy was demonstrated to improve myocardial perfusion, clinical symptoms, and functional capacity in patients with refractory angina pectoris (16–18).

The mechanism that induces angina might differ based on coronary conditions in patients with refractory angina and SAP that still indicated invasive revascularization. In patients with refractory angina, anginal pain is mainly due to other factors beyond significant large coronary stenosis, such as microvascular coronary disorders and vasospasm (12). Whereas, in indicated patients with CABG-SAP, significant epicardial stenosis is present, causing a significant mismatch of oxygen demand in the myocardium, provoking angina and reduced quality of life (21).

As demonstrated in this case series, ESMR therapy could improve ischemic response and functional capacity in patients with remaining significant stenosis in epicardial coronary circulations. It may be postulated that ESMR, with its mechanism, could improve myocardial microcirculation and coronary collaterals (9). This improvement leads to improved myocardial ischemia response and improves functional capacity and physical component of quality of life. Therefore, our small case series might broaden the clinical study of ESMR therapy to this population than its previous use in refractory angina.

In our patients, Ischemic response improved as shown in the double product, ischemic electrocardiogram (ECG) changes findings and maximal functional capacity during treadmill stress test after ESMR therapy. Trial of ESMR therapy in patients with refractory angina pectoris by Shkolnik et al. (22) comparing 35 patients undergoing ESMR with 37 patients undergoing placebo demonstrated improvement of exercise duration during treadmill test with the mean increase in the exercise duration was 32.8 $\pm$ 83.3 s at 3-months and 48.8 $\pm$ 106.5 s at the 6-months follow-up in the ESMR therapy group compared with 68.3 $\pm$ 119.5 and 80.4 $\pm$ 128.8 s in the placebo group. Although exercise duration in ESMR groups does not show better than placebo in that trial, the number of patients with ischemic response recorded during peak exercise decreased significantly to only 18 patients in the ESMR group compared with 33 patients in the placebo group at 6-month follow-up. These findings mean that non-cardiac reasons may limit exercise duration in the included patients. In addition, in our findings, ESMR improves myocardial oxygen consumption, as shown in the improvement of double product. Therefore, an improvement in the double product could reflect an improvement of exercise tolerance that correlates with myocardial activity (23).

In the context of 6-min walking distance evaluation after ESMR therapy in patients with refractory angina pectoris, a trial by Weijing et al. (24) comparing 46 patients in ESMR therapy with 41 patients receives medical therapy. That study demonstrated an improvement of 6-min walking distance from 331.7 $\pm$ 62.3 to 403.1 $\pm$ 61.2 m in the ESMR therapy group compared 319.3 $\pm$ 69.3 to 336.7 $\pm$ 71.1 m in the medical therapy group. However, our case series only demonstrate an improvement of the 6-min walking distance

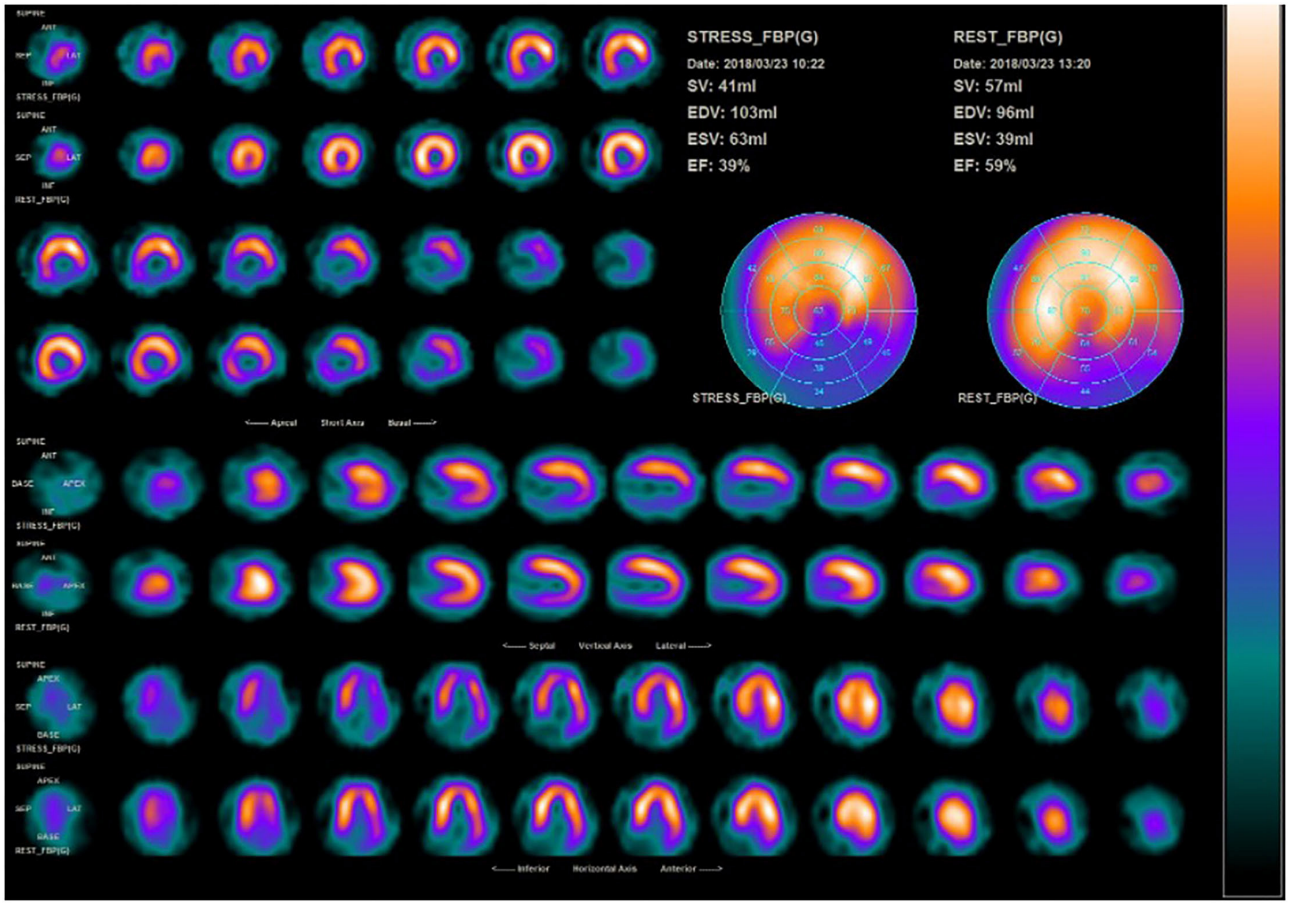

FIGURE 1 | SPECT examination of patient 1 before ESMR therapy.

TABLE 3 | The effect of ESMR therapy to ischemic response, functional capacity, and quality of life.

	Patient 1		Patient 2		Patient 3		Patient 4	
	Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Functional capacity								
Treadmill stress test								
Chest pain during test	+ at recovery	+ limiting angina	+ limiting angina	-	-	-	-	-
Ischemic response	+	-	±	-	+	±	+	±
METs	8.07	8.91	1.91	4.01	3.45	6.39	3.59	4.43
DP (mmHg*bpm)	9,600	14,872	9,460	10,640	10,920	10,890	17,220	20,480
6MWD (m)	540	570	345	405	435	405	450	425
Quality of life								
Angina	+	+	+	+	+	+	+	-
CCS class	III	I	II	I	I	I	I	-
SF-36								
Physical health								
FP	50	80	65	70	70	50	55	35
RP	0	0	0	75	0	0	0	50
BP	68	90	58	80	65	78	58	68
GH	65	85	40	65	70	75	65	75

(Continued)

TABLE 3 | Continued

	Patient 1		Patient 2		Patient 3		Patient 4	
	Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Mental health								
RE	0	0	0	100	33	0	0	33
VT	60	20	30	55	45	75	65	45
MH	84	60	40	64	76	80	84	72
SF	63	75	63	88	75	62	100	63

+, positive ischemic response; -, negative ischemic response; ±, suggestive ischemic response; 6MWD, 6-min walking distance; BP, bodily pain; CCS Class, Cardiovascular Canadian Society Class; FP, physical function; GH, general health; METs, metabolic equivalents; MH, mental health; RE, role limitations due to emotional health; RP, role limitations due to physical health; SF, social function; VT, vitality.

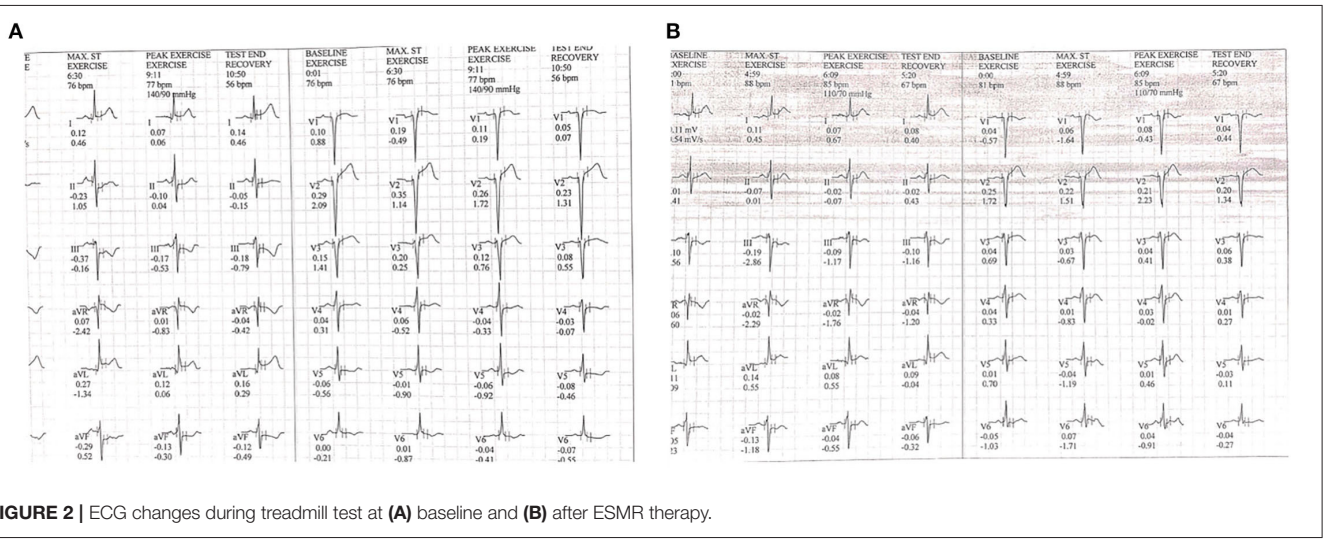

FIGURE 2 | ECG changes during treadmill test at **(A)** baseline and **(B)** after ESMR therapy.

achieved only in Patients 1 and 2. The 6-min walk distance measures the maximum distance that a person can walk in 6 min. This test might be reflecting the capability of patients in normal daily activities and related to mobility ability (25). Although it has good reproducibility, the 6-min walk test is not without limitations. The test does not provide insight into the individual functional capacity. Its results can be affected by several unrelated independent factors, namely, age, height, weight, impaired cognition, and patient motivation. Therefore, these factors should be considered when interpreting the test results (26). Deterioration of the 6-min walk distance achieved after ESMR therapy in Patients 3 and 4 may be due to advanced age, diabetes, and smoking activity that can negate and shorten a 6-min walk distance (27, 28).

In this study, CCS Class improved in all the patients. In addition, we also measured quality of life using SF-36. This questionnaire contains parameters that can assess the physical and mental health of patients (29). We found that after ESMR therapy, Patient 2 has improved in physical and mental health domain quality of life. Improvement in ischemic response and functional capacity in Patient 2 leads to improvement in physical performance. In general, improvement in physical performance is linked to improvement in quality of life (30). The bodily pain and general health domain of physical health component quality of life scores improved in all patients in our case series after ESMR therapy. Concordance with our findings, a meta-analysis study found ESMR therapy could improve CCS class up to one severity class (13). Another study by Schmid et al. (18) demonstrated improvement of general health, physical function, and vitality domain in 11 patients with refractory angina after ESMR therapy.

This case study had some limitations. Since the data were derived retrospectively from medical records, several factors cannot be controlled such as reasons and strategies for medications modifications that could be affected post-therapy evaluation. In our report, there are changes in the dose of ß-blocker dose and the addition of anti-ischemic medications in some patients that might be affecting their exercise tolerability. Also, only four patients were assessed in this study, limiting clinical interpretations of this study. Last, due to the lack of a control group, our findings may result in high bias and cannot be justified as a clinical recommendation.

Our report will stand out its novelty that represents the effect of ESMR in patients with SAP that not defined as patients with refractory angina pectoris. This report will complement our previous report for positive changes in myocardial perfusion

and contractility in the included patients (14). Therefore, our findings could broaden the target population for further clinical studies of ESMR therapy in various subsets of patients with SAP. Future trials using ESMR therapy that includes patients with SAP suitable for invasive revascularization are needed to confirm our findings. The study should be with control groups, and confirmatory myocardial function and perfusion evaluation are needed along with functional capacity assessment to match clinical improvement. We are concerned that ESMR therapy did not replace the position of the invasive approach to treating significant epicardial stenosis in patients with SAP.

CONCLUSION

There are improvements of ischemic response, functional capacity, and physical component quality of life in four indicated patients with CABG-SAP who received ESMR therapy evaluated in this study. We are concerned that there are marked limitations in our study. Therefore, more rigorous studies with controlled trials and large samples are needed to confirm these findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MA and ES: conception, design, supervision, materials, data collection and processing, analysis and interpretation, writing, and critical review. DA: conception, design, supervision, materials, funding, analysis and interpretation, and critical review. BT: conception, design, supervision, materials, data collection and processing, analysis and interpretation, literature review, writing, and critical review. MH: supervision, materials, data collection and processing, analysis and interpretation, writing, and critical review. FM: supervision, materials, funding, analysis and interpretation, and critical review. PR and EN: materials, data collection and processing, analysis and interpretation, writing, and critical review. NT: analysis and interpretation, literature review, writing, and critical review. All authors contributed to the article and approved the submitted version.

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