Clinical Case Reports

Open Access

CASE REPORT

Arrhythmogenic right ventricular cardiomyopathy in a patient with schizophrenia

Kenta Kawasaki[1,2], Kotaro Miyaji[2], Satoshi Kodera[2], Yoshio Suzuki[3], Junji Kanda[2] & Masayuki Ikeda[4]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Shinjuku-ku, Tokyo 160-8587, Japan
[2]Department of Cardiology, Asahi General Hospital, Asahi, Chiba 289-2511, Japan
[3]Department of Pathology, Asahi General Hospital, Asahi, Chiba 289-2511, Japan
[4]Department of Medical Informatics, Kagawa University Hospital, Miki-cho Ikenobe, Kagawa 761-0793, Japan

Correspondence
Kenta Kawasaki, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Shinjuku-ku, Tokyo 160-8587, Japan. Tel: +81 3 5363 3790; Fax: +81 3 3353 6247; E-mail: ideaal.retter@hotmail.co.jp

Funding Information
No sources of funding were declared for this study.

Received: 30 July 2014; Revised: 4 January 2015; Accepted: 20 January 2015

Clinical Case Reports **2015; 3(5): 308–314**

doi: 10.1002/ccr3.230

Key Clinical Message

People with schizophrenia are at greater risk of cardiovascular morbidity and mortality than the general population. Arrhythmogenic right ventricular cardiomyopathy is a recognized cause of sudden cardiac death in young people. This report discusses the necessity for close cardiac evaluation to reduce incidence of sudden death in people with schizophrenia.

Keywords

Arrhythmogenic right ventricular cardiomyopathy, schizophrenia, sudden death.

Introduction

Mental disorders, including schizophrenia, are associated with a high risk of morbidity and mortality. One study reported that 80% of excess deaths in people with mental disorders are caused by physical health conditions [1]. People with schizophrenia have higher rates of cardiovascular disease and mortality than the general population [2]; however, most sudden deaths remain unexplained [3]. One study has reported that one case among 51 sudden unexpected deaths in subjects with schizophrenia was associated with fibrofatty replacement of the myocardium, which may have denoted arrhythmogenic right ventricular cardiomyopathy (ARVC) [3]. Antipsychotics such as clozapine are a potential cause of cardiac sudden death because they can induce cardiomyopathy [4] and fatal arrhythmia [5]. Cardiomyopathy is reportedly rare, occurring in less than 0.1% of these patients; however, it has been suggested that other antipsychotics besides clozapine are associated with cardiomyopathy [6]. Venous thromboembolism is another potentially fatal side effect of antipsychotics [7]. ARVC is caused by fibrofatty replacement of the myocardium and can result in heart failure and sudden death from arrhythmia in young people. In an autopsy series, ARVC accounted for 10% of unexpected sudden cardiac deaths, of which nearly one-third occurred during the fourth decade of life [8]. Moreover, reduced pain perception, a widely reported but often neglected phenomenon in persons with schizophrenia [9], can have vital implications for their physical health. The present patient, who had all the risk factors described above, highlights the importance of close cardiac evaluation of persons with schizophrenia to reduce the incidence of sudden death.

Case Report

A 34-year-old man with a 12-year history of schizophrenia presented to the emergency room complaining of exertional chest pain. He had been treated with olanzapine 20 mg/day and clonazepam 2.5 mg/day for 5 years. Prior to that, his schizophrenia was controlled by risperidone 2 mg/day, etizolam 1 mg/day, nitrazepam 20 mg/day, and levomepromazine 5 mg/day. He had never taken clozapine. He had smoked 19 pack-years, but denied drinking alcohol. He had no family history of sudden death. His

© 2015 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

electrocardiogram (ECG) had been abnormal, described below, 4 years previously, with unremarkable echocardiography findings. His chest pain was localized to the left anterior region, the area changing with movement. He did not have dyspnea or palpitations. He was 180 cm tall, weighed 89 kg, and had a body surface area of 2.14 m^2. His body temperature was 37.5°C, pulse rate 90 beats/min, blood pressure 111/64 mmHg, and respiration rate 20 breaths/min with an oxygen saturation of 94% when breathing room air. Physical examination revealed no goiter or jugular venous distension. There were no crackles or rales in the lungs. No heart murmur or third heart sound was heard. He did not have peripheral coldness, orthopnea or pretibial edema and there were no signs of heart failure.

Relevant laboratory data were as follows: serum creatine kinase concentration 145 IU/L (57–197 IU/L), CK-MB 4.6 ng/mL (<5 ng/mL), WBC count 6.5× 10^9/L (4.0–8.0 × 10^9/L), C-reactive protein 0.1 mg/dL (<0.3 mg/dL), triglyceride 158 mg/dL (50–150 mg/dL), low-density lipoproteins 103 mg/dL (60–140 mg/dL), high-density lipoproteins 41 mg/dL (40–65 mg/dL), and HbA_1c 5.1% (4.6–6.2%), all of which were in the normal range. In addition, total protein was 7.2 g/dL (6.3–7.8 g/dL), albumin 4.7 g/dL (1.7–4.9 g/dL), alkaline phosphatase 214 U/L (80–260 U/L), aspartate aminotransferase 28 U/L (11–33 U/L), alanine aminotransferase 38 U/L (6–43 U/L), lactate dehydrogenase 191 U/L (120–245 U/L), total bilirubin 0.9 mg/dL (0.2–1.2 mg/dL), brain natriuretic peptide 74.7 pg/mL (<18.4 pg/mL), D-dimer 0.5 μg/mL (<1.0 μg/mL), interleukin-6 1.6 pg/mL (<55 pg/mL), angiotensin-converting enzyme 11.0 U/L (8.3–21.4 U/L), and lysozyme 5.4 μg/mL (5.0–10.2 μg/mL).

The ECG 4 years before admission showed T-wave inversion in leads $V_{1–4}$ and incomplete right bundle branch block. The ECG on this admission showed right-axis deviation, tall R waves in V_1 lead, negative T waves in V_1 through V_5 leads with QRS duration <120 msec, suggesting incomplete right bundle branch block and right ventricular hypertrophy (Fig. 1A). There were no visible epsilon waves. A 12 lead Holter ECG performed on day 5 showed 1739 premature ventricular contractions (PVCs) in 1 day, four episodes of ventricular triplets, and 103 episodes of ventricular couplets. The morphology of the PVCs was not typical of right or left bundle branch block pattern; however, an rS pattern in V_1 and V_2 leads suggested they originated from the right ventricle. The axis of the PVCs was mostly superior; however, inferior pattern also occurred (Fig. 1B and C). Two-dimensional echocardiography on admission showed severely reduced wall motion throughout the right ventricle and akinesia, especially at the apex. A partial aneurysm associated with thrombus had formed as a result. The right ventricular outflow tract was dilated on both the parasternal long (39 mm) and short (48 mm) axes and the fractional area change was 27.7%. There was mild tricuspid regurgitation, the pressure gradient measuring 18 to 22 mmHg. An ECG gated multi-slice computed tomography scan performed on day 1 showed enlargement of the right ventricle compared with the left, degeneration of the interventricular septum (CT values <0, namely −54 HU and −80 HU) consistent with fatty tissue, and a right

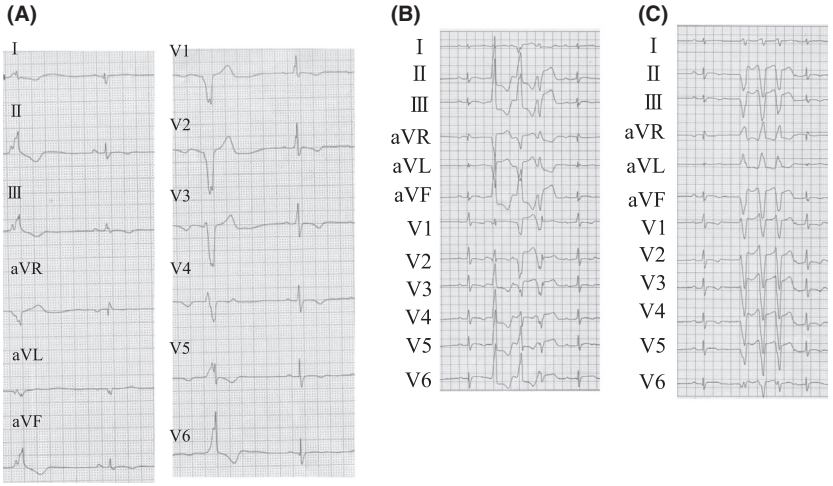

Figure 1. (A) ECG showing premature ventricular contractions and sinus rhythm. It also shows right-axis deviation, tall R waves in V_1 lead, and negative T waves in V_1 through V_5 leads with QRS duration <120 msec, suggesting incomplete right bundle branch block and right ventricular hypertrophy. (B, C) 12 lead Holter ECG showing by their morphology that the premature ventricular contractions originate from the right ventricle; the axis is mostly superior, but an inferior pattern was also observed.

© 2015 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

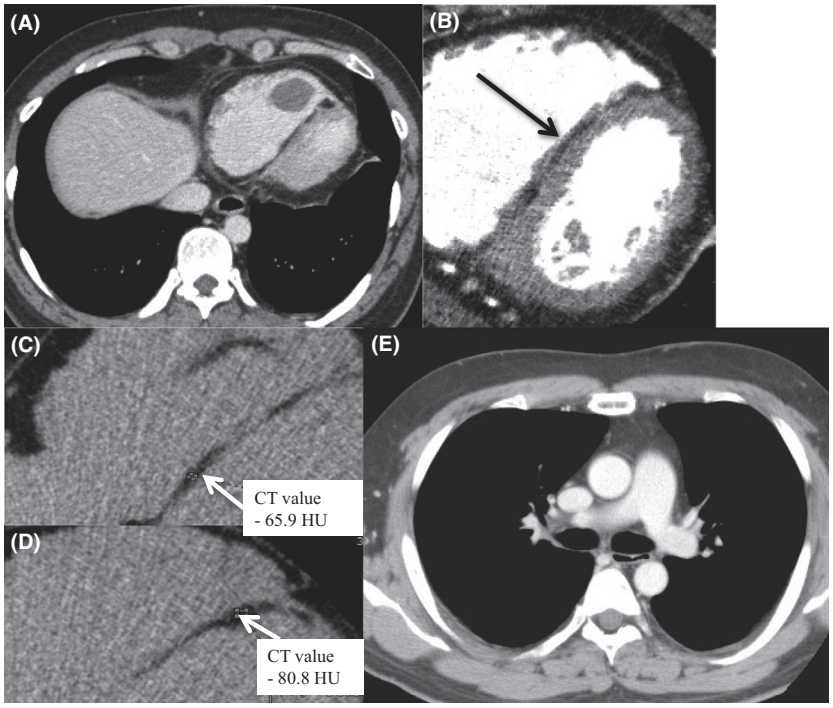

Figure 2. ECG gated multislice computed tomography scan of the heart performed on admission. (A) A right ventricular mass without contrast effect, which was thought to be a large thrombus, can be seen. (B) Degeneration of the interventricular septum (arrow). (C, D) Interventricular septum shows a CT value under 0 (−54 HU and −80 HU), which suggests fatty tissue. (E) There is no apparent dilation of the pulmonary artery or evidence of pulmonary embolism.

ventricular mass with no contrast effect that was thought to be a large thrombus (Fig. 2A–D). Because the putative thrombus was not swinging and was high-echo, we did not assess it as fresh thrombus. There was no dilation of the pulmonary artery or evidence of pulmonary embolism at any level (Fig. 2E). Magnetic resonance imaging performed on day 6 showed a remarkable enlargement of the right ventricle compared with the left (Fig. 3A), and probable fibrofatty replacement, particularly in the interventricular septum (Fig. 3B and C). Fluorodeoxyglucose positron emission scanning was negative for cardiac sarcoidosis and other inflammatory diseases. ECG gated myocardial scintigraphy with 99 m technetium performed on day 14, showed that the contractility of the left ventricle was normal by end systolic volume 34 mL, end diastolic volume 79 mL, and ejection fraction 58% (Fig. 4A and B). The right ventricular pressure (29 mmHg/6 mmHg) was not high when measured by cardiac catheter on day 13. The left ventricular end diastolic pressure was 16 mmHg, right ventricular end diastolic pressure 9 mmHg, the cardiac output was 5.7 L/min, and cardiac index 2.7 L/min/m^2 (Fick). We were unable to measure the pulmonary capillary wedge pressure because of the risk of causing new embolism from the existing thrombus. Although dilation of the right ventricle was present, the patient was hemodynamically stable and his physical examination and catheter data supported the contention that he was not overloaded. We therefore concluded that the dilation of the right ventricle was attributable to cardiomyopathy. The coronary arteries were intact on coronary angiography (Fig. 5A and B). Right ventriculography showed a round translucency at the apex of the right ventricle, which was suspected to be thrombus (Fig. 6A and B).

Taking all the above data together, our case met the four major criteria of ARVC 2010 (global or regional dysfunction and structural alterations, tissue characterization of wall, repolarization abnormalities, and arrhythmias), confirming our diagnosis of ARVC [10].

We injected an intravenous bolus of 3000 units of heparin on the day of admission and subsequently intravenously infused 20,000 units per day. On day 12, we replaced the heparin with warfarin, maintaining an international normalized ratio of 2 to 3. Because his nonsustained ventricular tachycardia was triplet at its longest, we did not implant an implantable cardioverter-defibrillator. However, we did administer 5 mg/day of carvedilol, increasing it to 20 mg/day in the outpatient clinic, and 25 mg/day of losartan. Beta-blockers are recommended for hemodynamically stable arrhythmias, whereas an

 © 2015 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

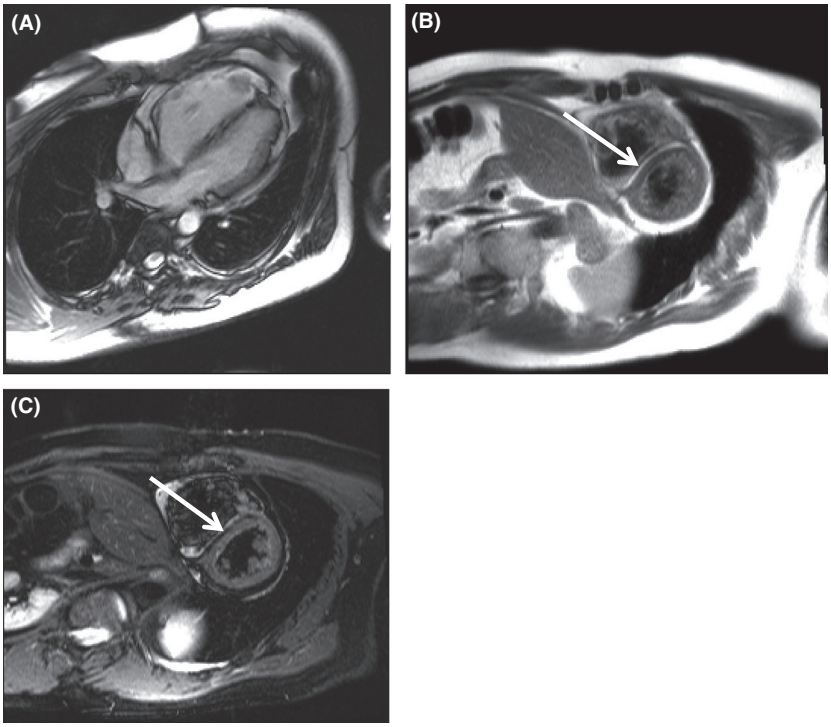

Figure 3. Magnetic resonance imaging, (A) MRI image from a balanced steady-state-free precession sequence. The right ventricle is much larger than the left. (B) T2 half-Fourier-acquisition single-shot turbo spin-echo image. There is a large area with high intensity signal in the ventricular septum (arrow). (C) Short inversion time inversion-recovery image. The high-intensity area (arrow) identified in figure (B) now has a low-intensity signal, suggesting that this signal is originating from fatty tissue.

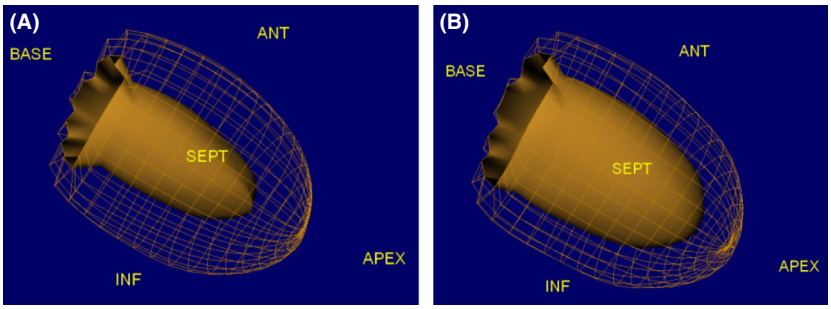

Figure 4. Myocardial scintigraphy showing the contractility of the left ventricle is normal. (A) End systolic volume 34 mL (B) End diastolic volume 79 mL, ejection fraction 58%.

implantable cardioverter-defibrillator is indicated in patients who have cardiac arrest or syncope [11]; we acted in accordance with these recommendations. The patient received no diuretics during his clinical course.

After 4 months, a follow-up echocardiography was performed and the ejection fraction was 46% by Pombo (LVDd 65 mm, LVDs 53 mm) with diffuse hypokinesis of the heart wall.

One year after commencement of anticoagulation therapy, the thrombus had resolved. We performed an endomyocardial biopsy, which confirmed fatty infiltration of the right ventricle, which is compatible with the diagnosis of ARVC (Fig. 7). Brain natriuretic peptide concentrations did not change significantly, being 49.9 pg/mL 4 months after his hospitalization, 45.9 pg/mL at 12 months, 54.8 pg/mL at 21 months, and 57.4 pg/mL at 35 months. The patient is doing well with New York Heart Association functional classification 1. Repeated Holter ECGs have shown no deterioration in his nonsustained ventricular tachycardia and no episodes of

© 2015 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

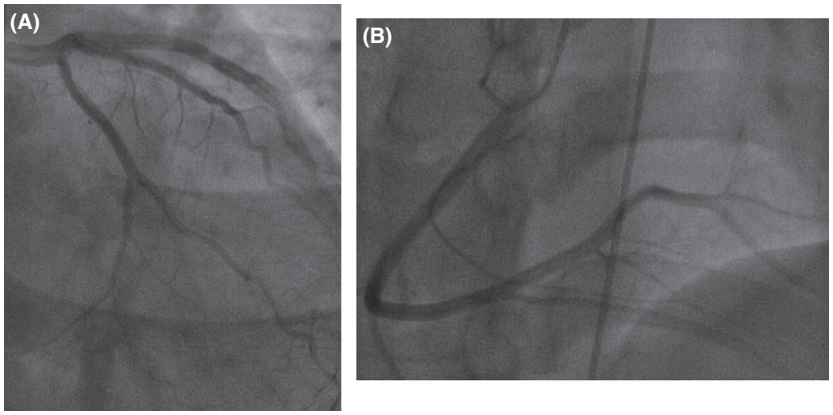

Figure 5. Coronary angiogram (A) The left anterior descending and circumflex arteries show no evidence of coronary artery disease. (B) The right coronary artery shows no evidence of coronary artery disease.

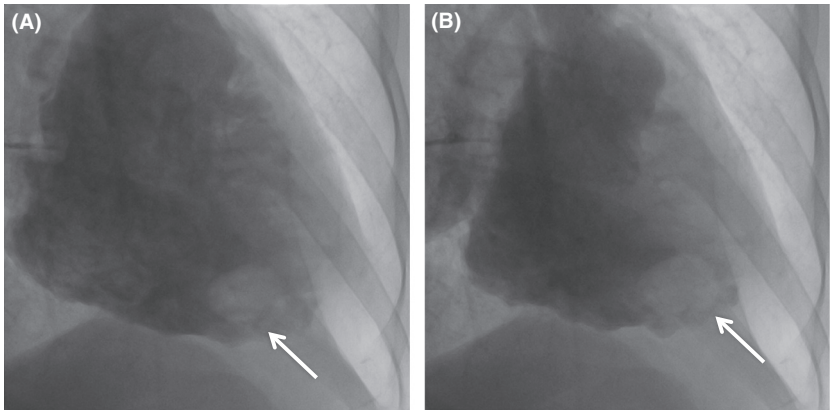

Figure 6. Right ventriculography. (A) Diastole (B) Systole. The round translucency at the apex (arrow) of the right ventricle is thrombus.

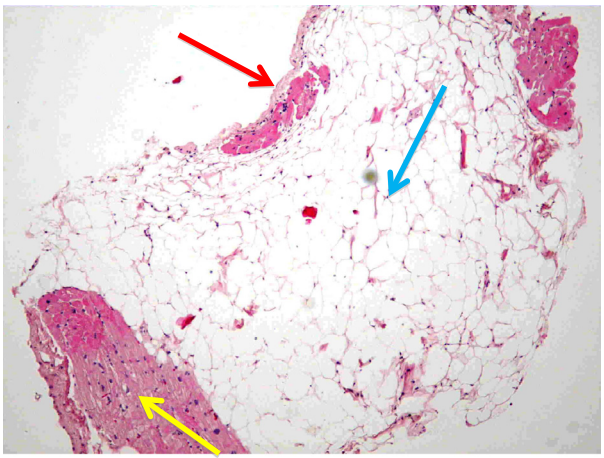

Figure 7. Histological findings on endomyocardial biopsy. The red arrow is the endocardium. Fatty infiltration extends into the subendocardium (blue arrow). The remaining myocardium is normal (yellow arrow). No lymphoid infiltration or epithelioid cell granulomas are present. (hematoxylin and eosin stain; ×40).

suggestive pulmonary embolism including dyspnea was observed. When he was prescribed olanzapine by another hospital, we suggested that the psychiatrist change the medication.

Discussion

We here present the case of a man with schizophrenia treated with olanzapine whom we recently diagnosed as having ARVC associated with a thrombus in the right ventricle; he had been found to have an abnormal ECG 4 years prior to presentation to our institution. We considered myxoma as a differential diagnosis, but ruled it out because serum interleukin-6 concentrations were normal, there was no stalk on the putative tumor and myxomas in the right ventricle are rare (3–4%) [12]. As for the low D-dimer, the sensitivity for a thrombus is 91.67% [13] and concentrations of D-dimer are different for mobile and nonmobile thrombi [14]. Embolism can cause sudden death: our patient had multiple risk factors for

© 2015 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

sudden cardiovascular death, namely antipsychotics, ARVC, and a large thrombus in the right ventricle. The thrombus could have formed because of disturbed heart function. As for differential diagnoses, we considered dilated cardiomyopathy (DCM), sarcoidosis and ARVC. Pathologically, the myocardium is replaced with fat in subjects with ARVC: our investigations were highly suggestive of fatty infiltration and our patient met the criteria for diagnosis of ARVC [10]. Sarcoidosis was ruled out based on fluorodeoxyglucose positron emission scanning findings, and laboratory data for angiotensin-converting enzyme and lysozyme. A case of DCM induced by clozapine has been reported [15], but different from the report, our patient had never taken clozapine and the marked reduction in left ventricular function in the reported case was not present in our case. Fatty infiltration in a patient with DCM has been reported; however, the clinical characteristics, including left ventricular function, differed from those of our case [16]. We believe the disturbance in our patient's heart function caused by ARVC was responsible for his thrombus formation; however, thrombi are relatively rare in patients with ARVC, the reported annual incidence being 0.5/100 patients [17]. As for olanzapine, there are several reports of it causing embolism [18]. The thrombus could be attributable to olanzapine, ARVC, and dyskinesia. Furthermore, olanzapine could have induced ARVC because not only clozapine [4], but also other antipsychotics [5] are associated with an increased risk of cardiomyopathy.

As to our patient's chest pain, this can be a symptom of ARVC [11]; the differential diagnosis is pulmonary embolism. According to European Society of Cardiology guidelines [19], his revised GENEVA score was three points, which is classified as low risk. There was no evidence of massive pulmonary embolism on the CT; however, the thrombus in the right ventricle suggested he was at a high risk of it. Given his slightly low oxygen saturation and chest pain, we could not rule out microembolism. Conversely, although his thrombus has resolved, he still occasionally experiences chest pain. It is possible that psychotic factors play a part. Furthermore, low oxygen saturation can be associated with overweight [20]. He had a low-grade fever on admission that resolved spontaneously, so we did not consider infection likely.

Discussing about the inconsistency between echocardiographic parameter and scintigraphy, in five of six echocardiography measurements, left ventricular diastolic diameter was 61–62 mm and systolic diameter was 44–47 mm and ejection fraction by Pombo method ranged 45–53%. Only the data for 4 months stated above have the data of LVDd 65 mm, LVDs 53 mm. It has been suspected that the sampling point on the echocardiography has been different only this time, compared to the other examinations. There are some reports that argue visual assessment of ejection fraction correlate well with formal method [21, 22], but when there is inconsistency between two methods like our case, it is important to make sure the accuracy of the data.

Although, our patient's chest pain prompted evaluation of his heart, ARVC is usually asymptomatic [11]. An abnormal ECG should prompt further investigation [23]: our patient may have had ARVC 4 years prior to his presentation to our institution.

We conclude that patients with schizophrenia, especially those who are taking antipsychotics, should be asked about chest discomfort and carefully evaluated by ECG periodically to prevent sudden cardiac death.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Conflict of Interest

The authors declare no competing interests.

References

1. Lawrence, D., K. J. Hancock, and S. Kisely. 2013. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. BMJ 346:f2539.
2. Curkendall, S. M., J. Mo, D. B. Glasser, M. Rose Stang, JK. Jones. 2004. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. J. Clin. Psychiatry 65:715–720.
3. Ifteni, P., C. U. Correll, V. Burtea, JM. Kane, P. Manu. 2014. Sudden unexpected death in schizophrenia: autopsy findings in psychiatric inpatients. Schizophr. Res. 155:72–76.
4. Taneja, A. K., J. Wong, and J. Bayliss. 2009. Antipsychotic-drug-induced dilated cardiomyopathy. BMJ Case Rep. 2009. pii::bcr.09.2008.0958.
5. Coulter, D. M., A. Bate, R. H. Meyboom, M. Lindquist, IR. Edwards. 2001. Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. BMJ 322:1207–1209.
6. Jolly, K., M. D. Gammage, K. K. Cheng, P. Bradburn, MV. Banting, MJ. Langman. 2009. Sudden death in patients receiving drugs tending to prolong the QT interval. Br. J. Clin. Pharmacol. 68:743–751.
7. Farah, R. E., N. M. Makhou, R. E. Farah, MD. Shai. 2004. Fatal venous thromboembolism associated with antipsychotic therapy. Ann. Pharmacother. 38:1435–1438.

© 2015 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

8. Tabib, A., R. Loire, L. Chalabreysse, D. Meyronnet, A. Miras, D. Malicier, et al. 2003. Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. Circulation 108:3000–3005.
9. Wojakiewicz, A., D. Januel, S. Braha, K. Prkachin, N. Danziger, D. Bouhassira, et al. 2013. Alteration of pain recognition in schizophrenia. Eur. J. Pain 17:1385–1392.
10. Marcus, F. I., W. J. McKenna, D. Sherrill, C. Basso, B. Bauce, DA. Bluemke, et al. 2010. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/ dysplasia: proposed modification of the task force criteria. Circulation 121:1533–1541.
11. Basso, C., D. Corrado, F. I. Marcus, A. Nava, G. Thiene, et al. 2009. Arrhythmogenic right ventricular cardiomyopathy. Lancet 373:1289–1300.
12. Reynen, K. 1995. Cardiac myxomas. N. Engl. J. Med. 333:1610–1617.
13. Rajappa, M., T. N. Sunil Roy, A. Raj, V. Trehan, and V. Mallika. 2013. D-Dimer assay as a non invasive test for the diagnosis of left atrial thrombi in Indian patients with rheumatic MS. Afr. Health Sci. 13:584–589.
14. Yasaka, M., K. Miyatake, M. Mitani, S. Beppu, S. Nagata, T. Yamaguchi, et al. 1991. Intracardiac mobile thrombus and D-dimer fragment of fibrin in patients with mitral stenosis. Br. Heart. J. 66:22–25.
15. Makhoul, B., I. Hochberg, S. Rispler, ZS. Azzam. 2008. Dilated Cardiomyopathy: an unusual complication of clozapine therapy. Nat. Clin. Pract. Cardiovasc. Med. 5:566–570.
16. Guo, X., Y. Dai, L. Cui, Q. Fang. 2014. A novel dystrophin deletion mutation in a becker muscular dystrophy patient with early-onset dilated cardiomyopathy. Can. J. Cardiol. 30(956):e1–e3.
17. Wlodarska, E. K., O. Wozniak, M. Konka, W. Rydlewska-Sadowska, A. Biederman, P. Hoffman. 2006. Thromboembolic complications in patients with arrhythmogenic right ventricular dysplasia/ cardiomyopathy. Europace 8:596–600.
18. Kannan, R., and D. K. Molina. 2008. Olanzapine: a new risk factor for pulmonary embolus? Am. J. Forensic Med. Pathol. 29:368–370.
19. Authors/Task Force Members, Konstantinides, S. V., A. Torbicki, G. Agnelli, N. Danchin, D. Fitzmaurice, N. Galiè, et al. 2014. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC) Endorsed by the European Respiratory Society (ERS). Eur. Heart J.; pii: ehu283.
20. Hakala, K., P. Mustajoki, J. Aittomäki, and A. R. Sovijärvi. 1995. Effect of weight loss and body position on pulmonary function and gas exchange abnormalities in morbid obesity. Int. J. Obes. Relat. Metab. Disord. 19: 343–346.
21. Gudmundsson, P., E. Rydberg, R. Winter, and R. Willenheimer. 2005. Visually estimated left ventricular ejection fraction by echocardiography is closely correlated with formal quantitative methods. Int. J. Cardiol. 101: 209–212.
22. Shahgaldi, K., P. Gudmundsson, A. Manouras, L. A. Brodin, and R. Winter. 2009. Visually estimated ejection fraction by two dimensional and triplane echocardiography is closely correlated with quantitative ejection fraction by real-time three dimensional echocardiography. Cardiovasc. Ultrasound 7:41.
23. Marcus, F. I., and A. Abidov. 2012. Arrhythmogenic right ventricular cardiomyopathy 2012: diagnostic challenges and treatment. J. Cardiovasc. Electrophysiol. 23:1149–1153.

© 2015 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.