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Case Report

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Right Ventricular Thrombus in a Patient on Clozapine Presenting with Hyperosmolar Hyperglycaemic State (HHS)

Siddiqi AI*

Department of Diabetes, North Manchester General Hospital, UK

***Corresponding author:** Ahmed Imran Siddiqi, Department of Diabetes, North Manchester General Hospital, UK. Tel: +447533394326; Email: ahmed.siddiqi@nhs.net

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Abstract

I describe the finding of right ventricular thrombus in a 26 years old Afro-Caribbean patient who presented with hyperosmolar hyperglycaemic state (HHS) while taking clozapine for schizophrenia. Both HHS and Clozapine are known to increase thrombo-embolic risk but neither has previously been documented to cause right ventricular thrombus. I suggest that whilst neither HHS nor Clozapine are likely to cause intra-cardiac thrombus individually they may pose a more significant risk in combination. The debate on choice of prophylactic or treatment dose of low molecular weight heparin in HHS continues. Therapeutic rather than prophylactic doses of anticoagulation should be considered in patients with HHS who have additional prothrombotic risk factors.

Keywords: Clozapine, HHS; Intra-cardiac thrombus

Introduction

Hyperosmolar hyperglycaemic state (HHS) characterized by hyperglycaemia, hyperosmolality and the absence of severe acidosis has been reported in the literature in association with both arterial [1] and venous [2] thromboembolism and the debate about therapeutic versus prophylactic approaches to anticoagulation continues [3]. The benefits of anticoagulation have to be balanced with the potential risk of major and life threatening bleeding events including intra-cranial and gastro-intestinal bleeding. Clozapine is very effective for treatment-resistant schizophrenia, and its impressive efficacy has been demonstrated in several clinical trials and a meta-analysis [4]. In addition to its unique efficacy in patients with treatment-resistant schizophrenia, clozapine possesses anti-suicidal and anti-aggressive properties, and its efficacy for treatment-resistant bipolar disorder has also been documented. However, its use has been reported to be associated with venous thromboembolism [5]. I present a case of right ventricular thrombus in a patient who presented with HHS whilst taking clozapine for schizophrenia.

Clinical Case

A 26 years old Afro-Caribbean gentleman presented to the emergency department with drowsiness, tiredness, lethargy, generalized weakness, polyuria, polydipsia, weight loss of 3 Kg over 3 weeks and generalized muscle aches and pains for 3 days. He had been short of breath on minor exertion for one week. Although drowsy he complained of generalized abdominal pain but no chest pain or urinary symptoms.Previous medical records were not available at the time of admission but his family related a history of complex schizophrenia for 10 years, unexplained diarrhoea for 3 years and obesity. Management of his schizophrenia had been challenging and he required admissions to the psychiatric unit on several occasions to manage his symptoms. He was taking clozapine for three years, loperamide for two years and lansoprazole for three years. Clozapine was used as a last resort to control his symptoms and he had been responding well to this prior to this admission. His maternal aunt suffered from type 2 diabetes. He was a non-smoker and did not drink alcohol. His schizophrenia symptoms made him leave school early and he had not worked since leaving school. He did not have many friends and spent most of his time at home leading to rising weight and BMI.

On examination his BMI was 37 kg/m^2, he was dehydrated with Glasgow Coma Scale 14/15, pulse 113/min and regular, temperature 36.4°C, BP 94/64 mmHg, respiratory rate 26/min, oxygen saturation 96% on room air.Examination of the cardiovascular system, respiratory system and abdomen revealed no abnormalities apart from tachycardia and mild general abdominal tenderness. There were no neurological abnormalities.

He had wide anion gap metabolic acidosis with pH 7.32 (7.35 -7.45) and significant hyperglycaemia. His osmolality was 404.3 mOsm/L. Investigations are summarized in **Table 1**.

Table 1	Day1	Day 15
Hb (14-18 g/L)	17.8	15.4
WBC 4-11x109/L	15.8	10.8
PLT (150-450x109/L)	129	278
CRP (<10 mg/dl)	40	13
CK (24 - 195 U/L)	5867	324
Mg (0.6-1.1 mmol/l)	0.44	0.73
Na (135-145 mmol/l	160	138
K (3.5-5.5 mmol/l)	4.9	4.4
Urea (1.8-7.1 mmol/l)	16.6	6.8
Creat (46 - 92 umol/L)	233	119
PO4 (0.8-1.4 mmol/l)	1.71	
Ca (2.1-2.6 mmol/l)	2.67	2.51
ALT (5-35U/L)	127	57
Trop I (0.04-0.39ng/ml)	0.29	
Glucose (4 - 11mmol/l)	67.7	13.4
pH (7.35-7.45)	7.32	7.41
HCO3 (22-28)	17.8	23.8
Blood ketones (<0.3 mmol/l)	0.7	-

Table 1: Investigations are summarized.

Computerized tomography (CT) scan of his head and chest X ray (CXR) showed no abnormalities although the CXR was an anteroposterior projection so heart size could not be assessed accurately. Ultrasound scan of his abdomen showed fatty liver. His electrocardiogram (ECG) was normal apart from sinus tachycardia.

He was initially managed for HHS and acute kidney injury (AKI). He received antibiotics (co-amoviclax, gentamicin and metronidazole) in the emergency department to empirically treat sepsis of unknown source but these were discontinued 24 hours later as there was no convincing evidence of infection. HHS was managed following Joint British Diabetes Societies (JBDS) Inpatient Care Group HHS guidelines 2012 [6].

His medical condition slowly improved but at 36-48 hours, as his drowsiness lifted, he developed visual and auditory hallucinations so that maintaining intravenous access and fluid replacement became a challenge. On psychiatric advice benzodiazepines were introduced, clozapine was continued, and there was improvement in his psychiatric state. A repeat CT scan of his head did not find any abnormality to explain his symptoms. By day 10 the medical team noticed that despite substantial improvements in his clinical and biochemical parameters he had a persistent tachycardia even during sleep. Initially AKI, dehydration and electrolyte imbalance had been considered the likely cause of his tachycardia and later his psychiatric symptoms but the persistence of tachycardia led to a re-evaluation of the cause. An echocardiogram was completed on day 13 which suggested right ventricular thrombus.A cardiac magnetic resonance imaging (MRI) scan confirmed this finding. These scans did not show any features of myocarditis, with normal wall movement and valvular functions, ventricular sizes within the normal range and preserved ejection fractions. Cardiology multi-disciplinary team (MDT) discussion concluded that there was no cardiac cause for the intra-ventricular thrombus.

The intra-ventricular thrombus was present despite treatment with a prophylactic dose of low molecular weight heparin (LMWH) throughout this admission (Clexane 40 mg OD). At this point the LMWH dose was then increased to a full therapeutic dose (1mg/kg every 12 hours).

In view of the new findings the psychiatric team were asked to review the continued use of clozapine: although they did not feel that the evidence to implicate clozapine was strong they decided to gradually taper its dose and discontinue it over the next week. After hematology review further investigations were performed namely protein C and protein S levels (the latter measured both qualitatively quantitatively), venousDoppler's of both legs and computerized tomographic pulmonary angiogram.

He was discharged on Day 17 self-injecting Lantus insulin and taking metformin tablets. He subsequently had to be admitted to psychiatric unit twice and his glucose control remained erratic He was prescribed olanzapine by the psychiatric team but it did not seem to control his symptoms well. Olanzapine was not the ideal choice but was considered as a last resort because of treatment

refractory nature of his psychiatric condition. Olanzapine can make glycemic control more challenging and would not have been the medicine of choice in this gentleman but the refractory nature of his condition left our psychiatry team with not many choices. Psychiatry team will continue his follow up in their clinic to optimize his symptoms' control. His follow up cardiac MRI and Echocardiogram appointments have been re-scheduled a few times in view of non-attendance. We have now switched him to once a week GLP 1 agonist to help with his weight and also to improve his compliance. His Lantus dose has now been reduced to 20 units a day but metformin compliance remains patchy.

Discussion

HHS and clozapine use has been associated with both arterial and venous thromboembolism (VTE) in the literature. Left ventricular thrombus has been reported in a case study in a patient using Clozapine; however, that patient also suffered from cardiomyopathy which in itself is a risk factor for left ventricular thrombus [7]. To the best of my knowledge this is the first case in the literature with right ventricular thrombus without cardiomyopathy or valvular heart disease in a patient presenting with HHS who was taking Clozapine. The reports in the literature suggest an association of clozapine with VTE but a direct relation is still under debate [5] as the mechanism is not clear. Patients using clozapine should be alerted to this side effect as should physicians and rapid assessment for VTE is required if patients develop suggestive symptoms like swollen limbs, sudden onset of shortness of breath and pleuritic chest pain. From available literature both HHS and clozapine are independent risk factors for VTE and the combination of both may substantially increase risk, however, whether this is relevant to the development of intra-cardiac thrombus is questionable since a different etiology is probably involved [8]. Clozapine can lead to myocarditis and cardiomyopathy in rare cases [5]. Myocarditis and cardiomyopathy in turn may cause intra-cardiac thrombi [5]. The absence of chest pain and the normal Troponin I argue against myocarditis in our patient. Neither echocardiogram nor MRI of the heart showed features of myocarditis or cardiomyopathy.

Current national guidelines for the management of HHS acknowledge the increased thrombotic risk associated with HHS and recommend prophylactic LMWH for the full duration of admission [6]. As highlighted in the guideline, several regional UK hospital and previous HHS guidelines advocate the use of full therapeutic doses of LMWH, but the evidence for this is limited. Currently there is paucity of evidence as there are no randomized controlled trials available comparing prophylactic and therapeutic doses of anti-coagulation therapy in HHS patients.

The left ventricle is the high pressure chamber of the heart and thrombus generally develops in patients who have abnormalities of blood flow due to cardiac dilatation, in patients with cardiomyopathy or cardiac aneurysms [7]. In contrast the right ventricle has a relatively low pressure. One would expect the blood flow to be sluggish when blood is viscous because of high osmolality. It is difficult to determine if there is a specific threshold of osmolality which makes intra-cardiac thrombus more likely. Severe dehydration in HHS patients has also been associated with rhabdomyolysis in these patients [9]. My patient presented with high CK levels and responded well to rehydration with IV fluids. CK level in our patient was not as high as recorded in some patients in the literature. No definite cause for rhabdomyolysis in HHS patients has been found but severe dehydration is considered to be the most likely cause of muscle damage.

This case emphasizes the importance of individualized treatment plans in patients of HHS and I recommend therapeutic anti-coagulation in patients who have an additional risk factor for thromboembolism in the absence of any risk factors for bleeding.

Learning points

The development of right ventricular thrombus in this case may have been promoted by the use of clozapine. Individualization of anticoagulation in HHS is important and, in the absence of major bleeding risk factors, I suggest therapeutic rather than prophylactic anti-coagulation should be considered in HHS patients with an additional risk factor For thromboembolism **(Figure 1)**.

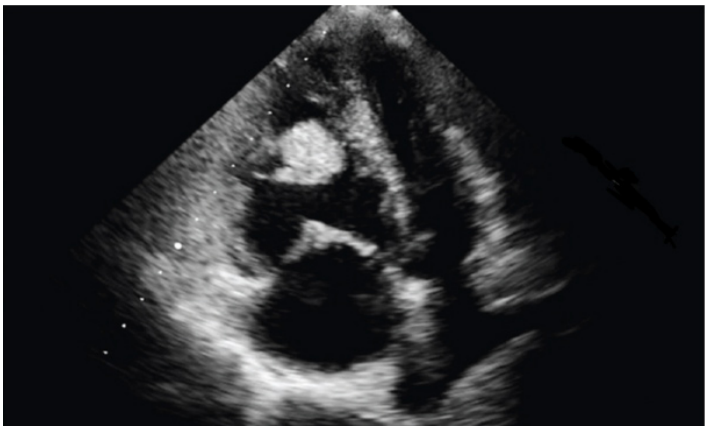

Figure 1: Right Ventricular Thrombus.

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