Saudi Journal of Emergency Medicine

CASE REPORT

Neonatal near fatal flecainide toxicity; a case report

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ABSTRACT

Background: Flecainide is an anti-arrhythmic medication with a narrow therapeutic index and a high mortality rate when overdosed. Few cases of flecainide toxicity in neonates and children due to medication errors have been reported in the literature. A case of an accidental flecainide overdose in a neonate in Oman was presented.

Case Presentation: A 19-day-old newborn girl developed persistent supra ventricular tachycardia (SVT) after receiving nebulized albuterol for acute bronchitis. After unsuccessful treatment with adenosine, she was given flecainide 5.6 mg orally every 24 hours for resolution of the SVT. On day 4 of admission, the child inadvertently received 100 mg of flecainide orally due to a dose calculation error. The child developed wide complex tachyarrhythmia followed by pulseless ventricular tachycardia (VT) requiring cardiopulmonary resuscitation. Sodium bicarbonate intravenous (IV) bolus followed by an infusion was administered. The patient developed two additional episodes of pulseless VT that coincided temporally with two interruptions of the sodium bicarbonate infusion and required a high dose of inotropic support. The patient developed convulsions but her brain ultrasound was normal. Her condition stabilized on day 3 after the toxicity occurred. Repeated echo showed a normal ejection fraction (EF). The patient was discharged on propranolol and levetiracetam and was doing well on outpatient follow up.

Conclusion: Flecainide is a potentially lethal medication in overdose due to its sodium channel-blocking properties. Sodium bicarbonate remains an essential component of treatment.

Keywords: Flecainide, overdose, sodium bicarbonate, ventricular tachycardia, case report.

Introduction

Flecainide is a class IC antiarrhythmic medication which used commonly in pediatrics to treat refractory supraventricular arrhythmias [1], with a narrow therapeutic index. It blocks fast sodium channels to slow cardiac conduction, therefore, widening the QRS complex and prolonging both the QT and PR intervals [2]. Clinical presentation of toxicity ranges from noncardiac manifestations including nausea, vomiting, headache, seizures, and malignant dysrhythmias, to cardiac manifestations including bradycardia, wide complex tachycardia, cardiovascular collapse, and cardiac arrest [3]. The management strategy for flecainide toxicity has not been studied in any randomized controlled trials [1]. Successful management of sodium bicarbonate in flecainide overdose was studied by several case reports [4-7]. Additional medical therapy that showed its effectiveness included other antiarrhythmic medications, e.g., lidocaine and amiodarone, intravenous fat emulsion, and transvenous or transcutaneous pacing to treat cardiac arrhythmias [4-7]. The clinical presentation of flecainide toxicity was described and would highlight the important points in the management.

Case Presentation

A 19-day-old neonate with a weight of 2.77 kg, presented to the emergency department (ED) with acute respiratory

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Received: 29 September 2023 | **Accepted:** 10 December 2023

distress. Her initial vital signs in ED showed a heart rate (HR) of 248, a saturation of 90% in room air, blood pressure (BP) of 96/57, and respiratory rate of 70/minute. Her electrocardiogram (ECG) showed a supraventricular tachycardia (SVT) rhythm that was treated with multiple doses of adenosine with no response.

The patient was admitted to the pediatric intensive care unit with the impression of stable SVT and started on propranolol which was gradually increased to 1.5 mg/kg/dose; three doses per day, with no improvement. On day 2 of admission, the patient was started on flecainide 5.5 mg orally [per oral (PO)] every 24 hours.

Her HR significantly improved, and her vital signs remained stable with an ejection fraction of 70% on her echocardiogram (ECHO). On day 4 of admission, she received 100 mg PO of flecainide instead of 5.5 mg due to a dose calculation error at 04:45 am which was followed by immediate gastric lavage and 1 g/kg of activated charcoal. A few minutes later, the patient developed wide complex tachyarrhythmia, which evolved to pulseless ventricular tachyarrhythmia requiring cardiopulmonary resuscitation according to the standard pediatric advanced life support (PALS) protocol (Figure 1).

The patient gained a return of spontaneous circulation (ROSC) and was intubated, ventilated, and started on noradrenaline and adrenaline infusion. A medical toxicologist was consulted by phone at 06:00 am and it was advised to start the patient on sodium bicarbonate boluses followed by infusion and intravenous 20% lipid emulsion (ILE) 1.5 ml/kg over 2-3 minutes as intravenous (IV) bolus followed by infusion of 0.25 ml/kg/minute for 1 hour. The patient received five doses of sodium bicarbonate boluses of 1 mmol/kg at about 10 minutes intervals slow push followed by infusion initially 0.5 mmol/kg/hour then increased to 1.5 mmol/kg/hour. Hence, the patients' wide QRS improved (Figure 2).

The child was continued on sodium bicarbonate and intralipid infusion. She received another dose of sodium bicarbonate at 08:30 am as she became bradycardia during central line insertion and then her HR stabilized at 90 beats\minute. At 11:20 am, she was on bicarbonate infusion at a rate of 1.5 mmol/kg/hour, venous blood gas (VBG) done at that time showed pH of 7.67, PCO_2 69, PO_2 22, HCO_3 79, BE 52, and lactate 3.2.

Based on the findings, the sodium infusion was decreased by the treating physician down to 1 mmol/kg/hour, and intralipid infusion was stopped. Another VBG was taken at 13:36 pm, where it showed metabolic alkalosis with pH of 7.7, PCO_2 29, PO_2 4, HCO_3 36, BE 16, and lactate 3.9. Therefore, sodium bicarbonate was reduced further down to 0.5 mmol/kg/hour.

Four hours later at 17:30 pm, the child started to develop wide complex tachycardia and was arrested for a second time. She had been resuscitated according to PALS protocol and sodium bicarbonate infusion increased up to 1.5 mmol/kg/hour and she revived without any sodium bicarbonate boluses. At this point, a bolus of intralipid emulsion was given and the infusion restarted again with a rate of 0.25 ml/kg/minute.

At 19:45 pm, the patient developed her third arrest with pulseless wide complex tachycardia, when she had been resuscitated for 8 minutes, received two boluses of sodium bicarbonate, and the infusion was increased up to 3 mmol/kg/hour. She was on high vasoactive support including epinephrine infusion 0.08 mcg\kg\minute, norepinephrine infusion 0.12 mcg\kg\minute, and dopamine infusion 14 mcg\kg\minute.

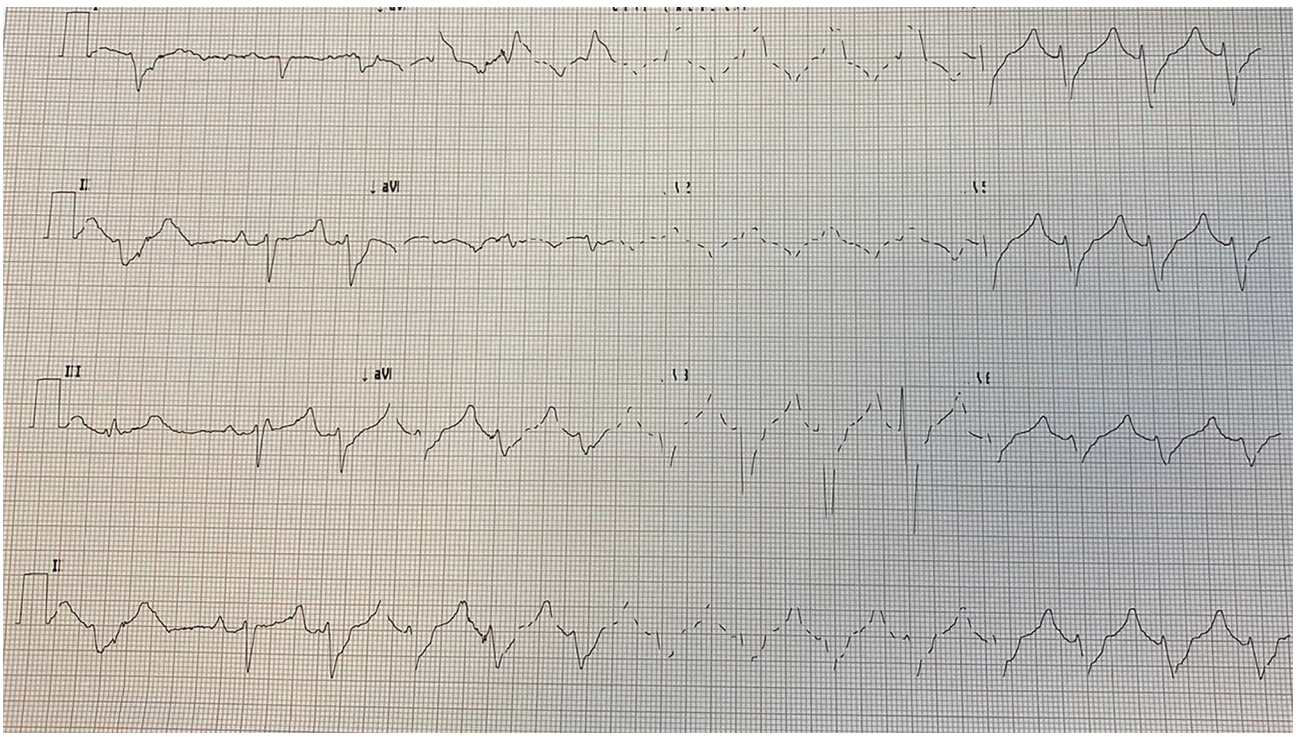

Figure 1. *ECG before the cardiac arrest.*

Following this, the child was transferred to a facility with extracorporeal membrane oxygenation (ECMO) services. This center is 2 hours away by ground transportation. On arrival at the center, she required a transcutaneous pacemaker for severe bradyarrhythmia and started on isoprenaline infusion 0.05 mcg\kg\minute. Her ECHO reported tiny patent ductus arteriosus with normal rest of the study. On day 3 post toxicity, she started to improve (HR 100, BP 90\45) and was only on one inotrope. Her ECG showed normal sinus rhythms (Figure 3).

The child suffered from brief episodes of tonic-clonic convulsions on day 4 post the medication error which was controlled with levetiracetam 42 mg orally twice a day. Her head ultrasound report was normal and no electroencephalogram was done. On day 5, the patient was extubated successfully in good condition, well perfused, and off of inotropes. Her Holter study was reported as normal with no significant tachy or brady arrhythmia.

On day 6, the patient was started on propranolol 1 mg three times a day (TID) and was discharged home

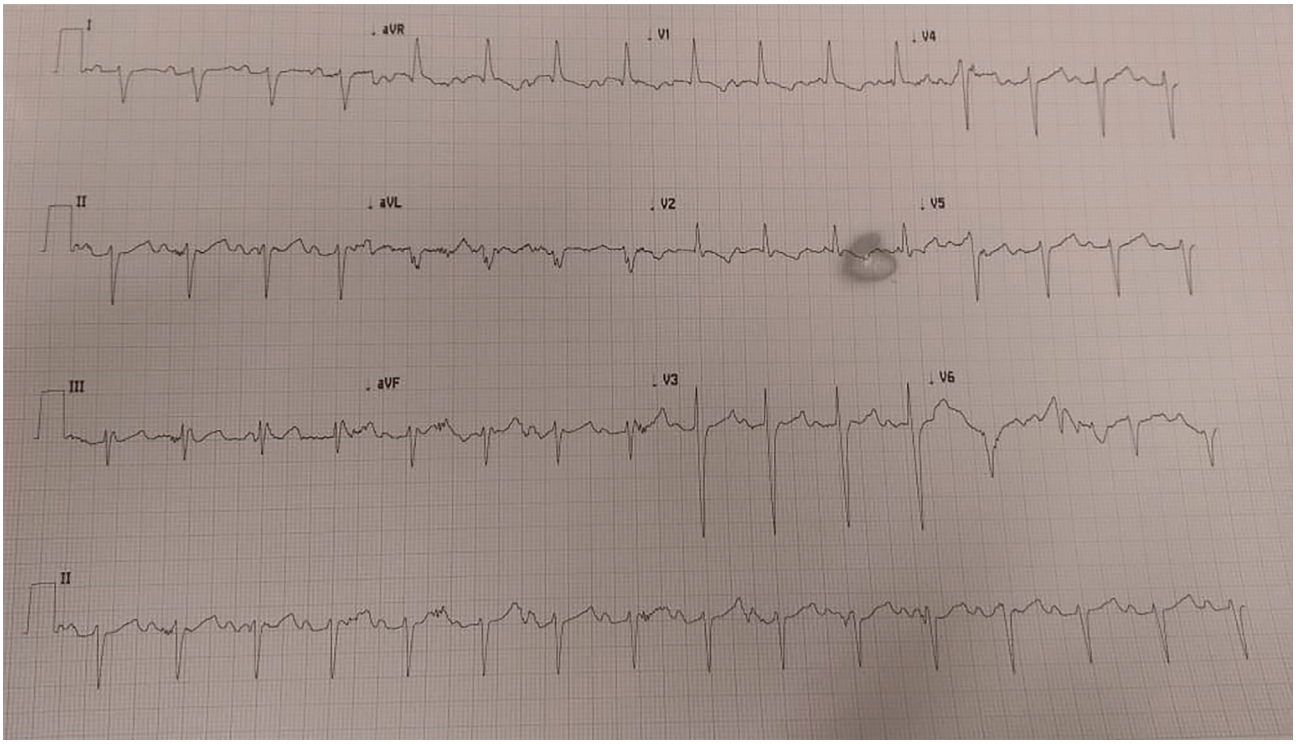

Figure 2. *Post ROSC ECG after sodium bicarbonate infusion.*

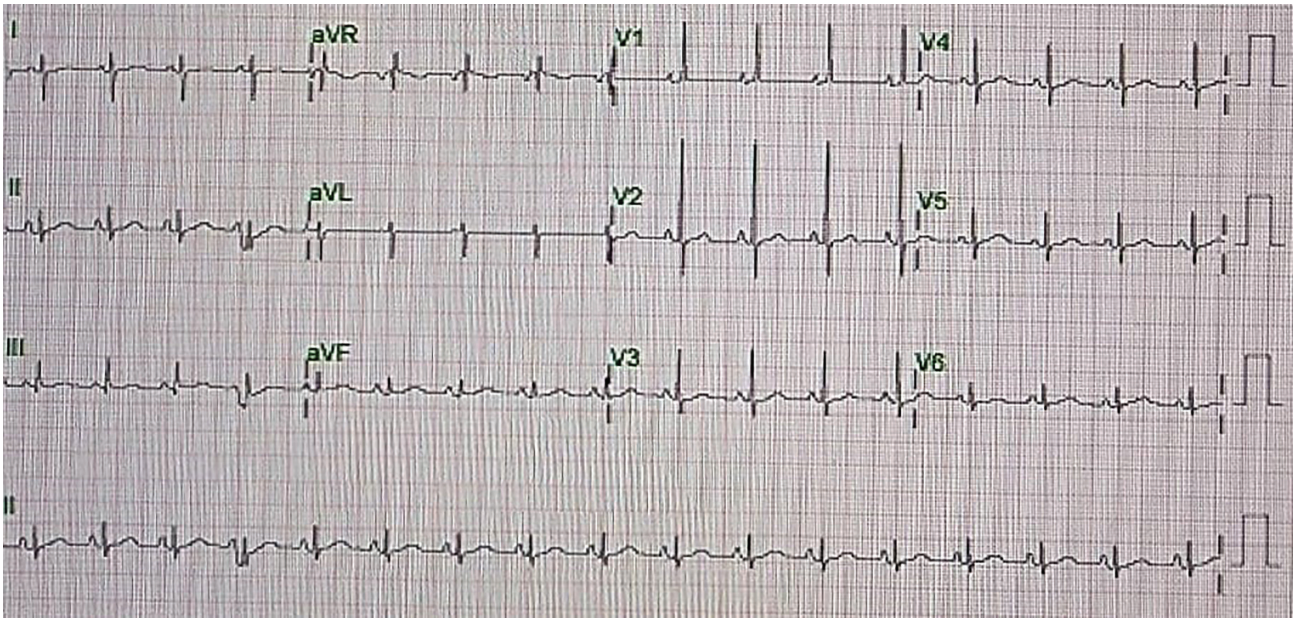

Figure 3. *Patient's ECG after stabilization.*

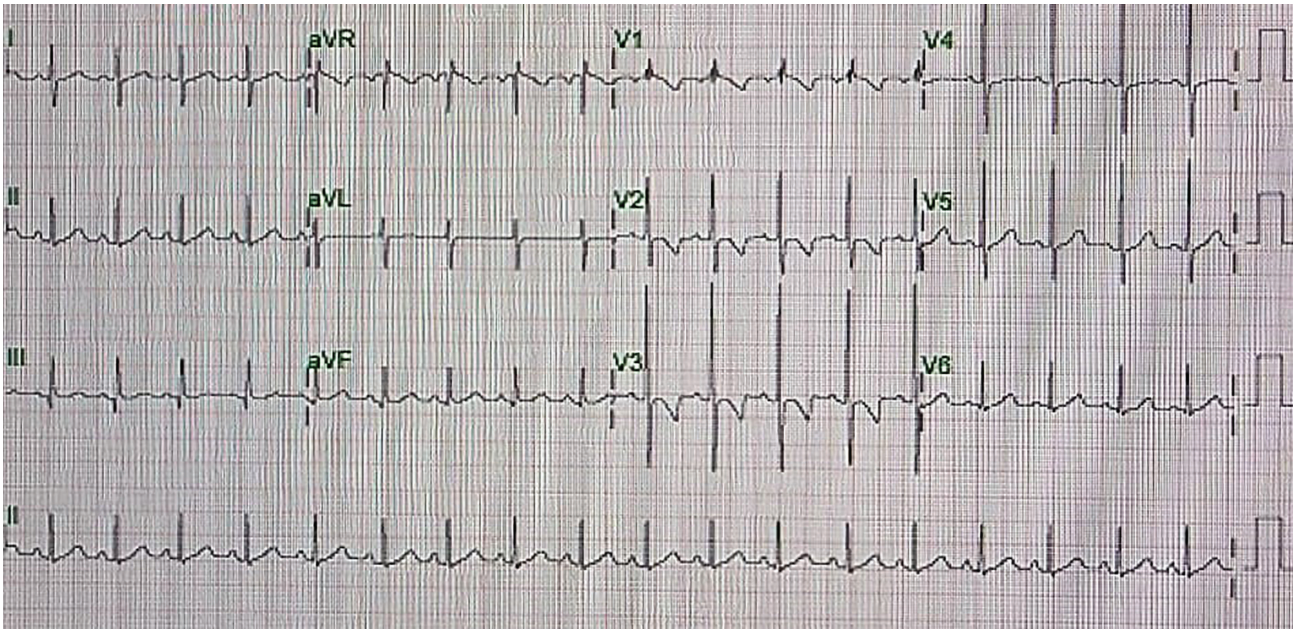

Figure 4. *Patient's ECG on follow up 2 weeks after the discharge.*

on September 1st, 2021 (day 9 post toxicity) with propranolol 1 mg TID for 30 days and levetiracetam 42 mg orally twice a day for 90 days. She was followed up on September 14th, 2021 and February 8th, 2022; when her levetiracetam and propranolol were stopped. The patient was doing well after that in her follow up on October 25th, 2022 with good milestones and had no complaints as shown in the patient's ECG on follow up (Figure 4).

Discussion

Because of the high oral bioavailability of oral flecainide (90%), and slow rate of elimination, the management of its toxicity can be challenging [8]. The presentation and successful treatment of a neonate was described, who suffered from severe intoxication and hemodynamic instability after a medication error. Although sodium bicarbonate is the mainstay of management in flecainide overdose, in severe toxicity, an integrated approach with sodium bicarbonate, ILE, and immediate availability of extracorporeal support besides other supportive management is recommended.

Flecainide is a derivative of procainamide and a class 1C antiarrhythmic drug that is used to prevent and treat conditions such as paroxysmal SVT, Wolf-Parkinson-White syndrome, atrioventricular nodal re-entrant tachycardia, AV re-entrant tachycardia, atrial fibrillation and atrial flutter [9]. It has a narrow therapeutic index with goal therapeutic levels ranging from 0.2 to 1 μg/ml although, toxic levels as low as 0.7 μg/ml have been reported with a mortality rate of approximately 22.5% [1,3,10]. Death was reported even at a double dose [11] and it can cause arrhythmia at therapeutic doses in patients with underlying coronary artery disease or structural heart disease [12].

Flecainide blocks fast sodium channels causing prolonged depolarization of the myocytes which therefore inhibits ventricular ectopy, resulting in the widening of the QRS complex and prolonging both the QT and PR intervals [1,2]. The frequency of ECG changes in overdose includes 50% QRS widening, 30% PR prolongation, and 15% QTc prolongation [13].

The patient developed wide QRS with a duration of 169 ms followed immediately by pulseless ventricular tachyarrhythmias. Furthermore, a QRS complex duration of greater than 200 ms has been shown to be a predictable sign of the need for mechanical circulatory support [10].

Nausea and vomiting, bradycardia, hypotension, and new or worsening arrhythmias are the most common effects of flecainide toxicity but edema, tremors, confusion, stupor, convulsions, or death can be present [14]. Profound cardiovascular collapse can rapidly occur after significant toxicity and is associated with a relatively high mortality. The presented patient developed sudden cardiovascular collapse immediately after the overdose followed by cardiac arrest.

Sodium bicarbonate is recognized as an effective therapy for hypotension and arrhythmias [8]. Although the exact molecular mechanism is not completely understood, increases in both sodium ion concentration and pH have been shown to reverse the flecainide effect in canine Purkinje fibers. This phenomenon is thought to be mediated by competitive inhibition and electrostatic repulsion preventing flecainide binding. Alkalinization also facilitates flecainide dissociation from the sodium channel - binding site [14]. The presented patient responded to the initial sodium bicarbonate boluses and infusion. Unfortunately, once the infusion rate reduced, she developed another cardiac arrest. This highlighted the importance of close monitoring of the sodium bicarbonate infusion in cases with flecainide-induced arrhythmias.

Additional medical therapies that have been used for flecainide overdose include antiarrhythmic

medications, lipid emulsion therapy, and transvenous or transcutaneous pacing to treat cardiac arrhythmias [4-7]. Although success has been reported with the use of intravenous fat emulsion for such cases [7], it is unlikely that it played a major role in the presented case as the patient developed two cardiac arrests with the sodium bicarbonate infusion discontinuation despite being on lipid infusion. Amiodarone and lidocaine have been reported as effective, although the mechanism is not clear [5,6]. Overdrive pacing has not been effective in tachyarrhythmias but pacing is effective in treating significant bradyarrhythmia [4].

Mechanical circulatory support with ECMO has been previously reported in cases of life-threatening flecainide toxicity after the failure of medical therapy [7]. ECMO is the preferred method of mechanical support in this type of toxicity as it maintains the hepatic and renal perfusion (and therefore, function), and also helps to accelerate the drug's elimination. The presented patient was about to be started on ECMO, but she improved on day 3 post toxicity [7].

Flecainide-induced dysrhythmias are often refractory to the standard treatment of cardioversion with usual therapies (i.e., amiodarone, lidocaine, and defibrillation) [6]. Previous case reports disclosed that frequent sodium bicarbonate boluses or infusion, ILE administration, and ECMO are the mainstay of treatment in refractory cases.

Flecainide toxicity can cause seizures due to sodium channel blockage proprieties; however, there is no enough data about the best choice of antiepileptic medications to be used during overdose. The presented patient responded well to levetiracetam which is known to have a novel mechanism of action through an interaction with the synaptic vesicle protein 2A [15]. Therefore, more study is needed to assess its effectiveness in managing seizures in flecainide toxicity.

Conclusion

Flecainide is a lethal medication in an overdose due to its sodium channel-blocking properties. It causes wide complex tachyarrhythmias and hemodynamic collapse refractory to standard management. While it cannot be concluded with certainty if one treatment was solely responsible for the improvement observed in the presented patient. Furthermore, using a high dose of sodium bicarbonate is recommended for treating flecainide overdose. ILE and extracorporeal support should be considered in refractory cases. Furthermore, a study is needed to assess the role of levetiracetam in managing seizures in patients presented with flecainide toxicity.

List of Abbreviations

BP	Blood pressure
ED	Emergency department
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ECHO	Echocardiogram
HR	Heart rate
ILE	Intravenous lipid emulsion
PALS	Pediatric advanced life support
ROSC	Return of spontaneous circulation
SVT	Supraventricular tachycardia
TID	Three times a day
VBG	Venous blood gas

Conflict of interest

The author declared that there is no conflict of interest regarding the publication of this case report.

Funding

None.

Consent for publication

Informed consent was obtained from the participant.

Ethical approval

Ethical approval is not required at our institution for an anonymous case report.

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