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Prevalence of Cerebral Venous Thrombosis in COVID-19 Patients: A Systematic Review

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Abstract

Background: COVID-19 is a novel coronavirus that has been rapidly transmitted between individuals globally. COVID-19 has been associated with thrombotic events. A cerebral venous thrombosis is a rare form of stroke with a most common site of origin believed to be the junction of larger sinuses and cerebral veins. So, it is important to identify the prevalence and incidence of cerebral venous thrombosis among COVID-19 patients. **Aim:** To assess the prevalence of cerebral venous thrombosis in COVID-19 patients by reviewing the previous studies reported on this subject. **Method:** We searched for articles focused on our subject through PubMed and Google scholar databases. The included searching terms included "CVT, COVID-19, Prevalence, Complications, and Effect." The inclusion criteria were studies conducted on COVID-19 patients, English articles, available full-text articles, and original articles. **Result:** We got 1178 articles; only six articles were eligible for the inclusion criteria. The included articles involved a total number of 551,727 participants with a mean age ranging between 34 years and 53.3 years and covered seven countries. The incidence of CVT among COVID-19 was reported as well as risk factors and symptoms. **Conclusion:** The incidence of CVT is high among COVID-19 patients compared to the general population, patients with influenza, and those who received the mRNA vaccine, whereas the prevalence requires further studies for precise data. A management strategy or treatment regimen should be established based on the severity of CVT patients, as the mortality rate among those patients was high.

Keywords

Prevalence, CVT, COVID-19

1. Introduction

Stroke is one of the major causes of mortality and long-term disability which is usually caused by hemorrhage or arterial occlusion [1]. Cerebral venous thrombosis (CVT) is a rare form of stroke and accounts for 0.5% of all stroke cases; CVT is associated with an increased mortality rate [2] [3]. The incidence of CVT is ranging from 0.22 to 1.32 per 100,000 annually [4]. CVT is more frequent in young adults and children [4] [5] and more common among females compared to males [4]. CVT can present with a multitude of symptoms and signs, and this makes it hard to distinguish it from other neurological conditions [2]. The early identification of symptoms and management improves the overall outcomes of CVT patients [2]. The risk factors of CVT are divided into genetic risks such as inherited thrombophilia and acquired risks such as trauma, surgery, cancer, exogenous hormones, pregnancy, and puerperium [6].

The SARS-CoV-2 virus that belongs to the corona family viruses caused COVID-19 disease. It was first isolated in December 2019 [7]. The patients with COVID-19 were suffering symptoms such as fever, lack of air, dry cough, headache, diarrhea, fatigue, and throat pain [8]; however, there have been reports of multisystemic manifestations, including neurologic and thrombotic complications [9].

In this context, thrombosis following COVID-19 infection can be related to inflammation, plaque activation, endothelial dysfunction, and blood stasis [10]. There were many risk factors that have been hypothesized to contribute to thrombosis among COVID-19 patients; these factors include prothrombic events caused by cytokines storm, immobility, and reduced activity of thromboprophylaxis [11]. A study from Italy showed thrombotic events occurred in 7.7% of closed cases [12], whereas another study reported that the incidence of thrombotic complications among COVID-19 patients in intensive care unit was 31% even with prophylaxis [13].

Although attention has been given to cerebrovascular thrombotic events, few reports have addressed the risk of CVT among COVID-19 patients. The large majority of these reports are case reports, so we performed this systematic review to assess the prevalence of CVT among COVID-19 patients by reviewing previous studies that reported such subject.

2. Method and Search Strategy

This systematic review follows the PRISMA checklist guidance for systematic review and meta-analysis [14]. We revised two databases for research, including PubMed and Google scholar databases.

We used several keywords for the searching process, including "CVT, COVID-19, Prevalence, Complications, and Effect." We used these keywords in different combinations to get all articles related to our subject. All obtained titles from this primary exploration were revised, and all the studies which didn't include CVT and COVID-19 were excluded. The findings were then explored to

choose only full-text articles written in English and reporting CVT among COVID-19 patients.

3. Eligibility Criteria

We reviewed the remaining full-text articles written in English language and reported CVT among COVID-19 patients. Each of the case reports, review articles, and duplicate articles were all excluded. The inclusion criteria were original articles conducted on COVID-19 patients and experienced CVT, written in the English language, and not case reports. We showed the full description of the search strategy in Figure 1.

4. Data Review and Collection

We reviewed the abstracts of eligible articles, as well as the full article text. A pre-designed excel sheet was used to extract data of interest from the eligible

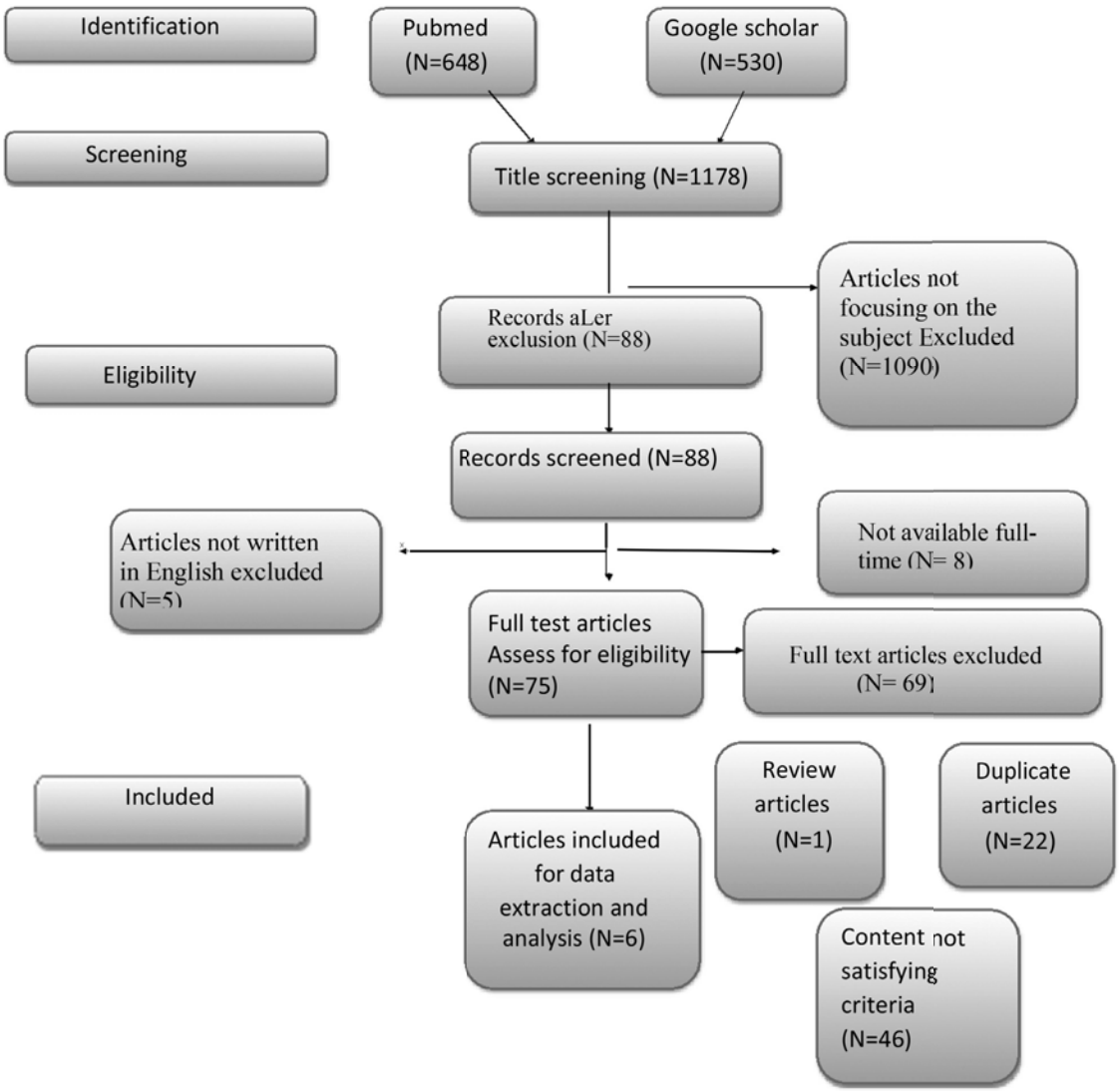

Figure 1. Planning of eligible criteria.

studies. We then revised the extracted data. We transferred the selected data to a pre-designed table to summarize the main findings.

5. Results

This systematic review included six articles that met the eligible criteria [15]-[20] (**Table 1**). There were three studies published in 2021 [15] [16] [17] and three studies published in 2020 [18] [19]. One study was case series [20], one study was an observational study [16], whereas the remaining four studies were retrospective [15] [17] [18] [19]; two studies were retrospective cohort [15] [17], one study was retrospective observational [18], and one was a retrospective study [19]. There were two multinational studies from different counties [16] [19]; one study included patients from ten centers in four countries (Egypt, Pakistan, Singapore, UAE) [16], whereas the other multinational study included patients from nine centers from three countries (Iran, USA, Singapore) [19]. Regarding the settings and strategy of the other four studies, the first study was from the USA and included two cohorts of influenza patients and individuals who received the mRNA vaccine [15]. The second study was conducted in the USA at six different tertiary care centers [17], third study was from Wuhan, China [18], and the fourth one was case series from the USA.

The total number of participants was 551,727. Male gender was predominant in three studies [16] [18] [20], whereas it did not state the gender of participants in one study [17], and in the other two studies, there was female dominance [15] [19]. The mean age of patients ranged between 34 years [20] and 53.3 years [18]. the first study reported 23 patients with CVT out of 537,913 patients with COVID-19 [15]. Another study reported 20 patients had CVT and recent COVID-19 [16]. One study reported 13 patients with CVT and COVID-19 and 57 patients with CVT and without COVID-19 [19]. The case series included three patients who developed CVT with COVID-19 [20].

The findings of the included studies were various, so we could summarize the main findings into main points. Regarding the occurrence of CVT among COVID-19 patients, there were four studies reported that point [15] [17] [18] [19]; one study reported the incidence of CVT to be 42.8/million individuals after COVID-19 diagnosis, and the incidence of CVT was higher among COVID-19 patients compared to those with influenza or received mRNA COVID-19 vaccine

The same study also reported the incidence of portal vein thrombosis (PVT), which was higher compared to CVT. The incidence of PVT after COVID-19 diagnosis was 392.3/million individuals, which was also higher compared to a matched cohort of individuals with influenza or received mRNA vaccine [15].

Another study reported that only 12 patients out of 13,500 COVID-19 patients had imaging-proved CVT. The incidence of CVT was 8.8/10,000 during three months, and the incidence of CVT was found to be higher compared to the incidence of CVT among the general population, which is 5 per million annually [17]. In the third study, the prevalence of CVT, cerebral hemorrhage, and acute

Table 1. Systematic review studies of prevalence of cerebral venous thrombosis in COVID19 patients.

Author and Publication year	Study design	Population, Sample size and Age of participants	Settings/ Strategy	Results and main < findings
Taquet *et al.* 2021 [15]	Retrospective cohort	-537,913 patients diagnosed with COVID-19 -Male:45.1% -Mean age = 46.2 years -Patients with COVID-19 and CVT: 23 (100%) -Male: 30.4% -Mean age = 46.5 years	-USA -Compared with two cohorts of influenza patients and individuals received mRNA vaccine	*The incidence of CVT in the two weeks after a COVID-19 diagnosis was 42.8 per million people *The incidence of CVT among COVID-19 patients was significantly higher than in a matched cohort of people who received an mRNA vaccine and patients with influenza *The incidence of PVT after COVID-19 diagnosis was 392.3 per million people; this was significantly higher than in a matched cohort of people who received an mRNA vaccine and patients with influenza *COVID-19 is associated with a markedly increased incidence of CVT compared to patients with influenza, people who have received BNT162b2 or mRNA-1273 vaccines and compared to the best estimates of the general population incidence. compared to previously reported non-COVID-19
Hameed *et al.* 2021 [16]	Multicenter and multinational observational study	-20 patients with symptomatic CVT and recent COVID-19 -Male: 70% -Mean age = 42.4 years	-Ten centers from 4 countries participated; Egypt, Pakistan, Singapore, UAE	*Headache (85%) and seizures (65%) were the common presenting symptoms *CVT was the presenting manifestation in 13 cases (65%), 7 (35%) patients developed CVT while being treated for COVID-19 *Respiratory symptoms were absent in 45% of the patients. *The most common imaging finding was infarction (65%), followed by hemorrhage (20%). *The superior sagittal sinus (65%) was the most common site of thrombosis. *Acute inflammatory markers were raised, including elevated serum D-dimer (87.5%), erythrocyte sedimentation rate (69%), and C-reactive protein (47%) levels. *Homocysteine was elevated in half of the tested cases. *The mortality rate was 20% (4 patients); mortality is high, but functional neurological outcome is good among survivors. *COVID-19-related CVT is more common among males at older ages when compared to previously reported non-COVID-19.

Continued

Al-Mufti *et al.* 2021 [17]	Retrospective multicenter cohort	-13,500 patients with COVID-19 -Male: -Mean age = 48 years	Six different New York tertiary care centers	*12 patients (%) had imaging-proved CVT *The incidence of CVT was 8.8 per 10,000 during 3 months *The incidence of CVT is considerably higher than the reported incidence of cerebral venous thrombosis in the general population of 5 per million annually. *There was a male preponderance (8 men, 4 women) and an average age of 49 years (95% CI, 36 - 62 years; range, 17 - 95 years). *1 patient (8%) had a history of thromboembolic disease *Neurologic symptoms secondary to cerebral venous thrombosis occurred within 24 hours of the onset of the respiratory and constitutional symptoms in 58% of cases, and 75% had venous infarction, hemorrhage, or both on brain imaging *Management consisted of anticoagulation, endovascular thrombectomy, and surgical hematoma evacuation. *The mortality rate was 25%. *Early evidence suggests a higher-than-expected frequency of cerebral
Li *et al.* 2020 [18]	Retrospective observational	-221 patients with COVID-19 -Male: 59.3% -Mean age = 53.3	Union Hospital, Wuhan, China	*11 (5%) developed acute ischemic stroke, 1 (0·5%) cerebral venous sinus thrombosis (CVST), and 1 (0.5%) cerebral hemorrhage. *COVID-19 with new onset of CVD were significantly older (71.6 ± 15.7 years vs 52.1 ± 15.3 years; p<0·05), and more likely to present with severe COVID-19 (84.6% vs. 39.9%, p < 0.01) *COVID-19 with new onset of CVD were significantly more likely to have cardiovascular risk factors, including hypertension, diabetes, and previous medical history of cerebrovascular disease (all p<0·05). *COVID-19 with new onset of CVD were more likely to have increased inflammatory response and hypercoagulable state as reflected in C-reaction protein and D-dimer *Of 11 patients with ischemic stroke, 6 received antiplatelet treatment with Aspirin or Clopidogrel and 3 of them died. The other 5 patients received anticoagulant treatment with Clexane and one of them died. *The mortality rate was

Continued

Mowala *et al.* 2020 [19]	Multinational retrospective study	Two groups; Group one: -13 patients with CVST and COVID-19 -Male:38.5% -Mean age = 50.9 Group two (control): -57 CVST patient without COVID-19 -Male: 33.3% -Mean age = 36.7	Nine centers in three countries. Eleven patients from seven centers in Iran, one patient from the United States and one patient from Singapore were recruited	*of 13 patients with CVST and COVID-19; Six patients were discharged with good outcomes (mRS ≤ 2) and three patients died in hospital. *Compared to the control group, the SARS-CoV-2 infected patients were significantly older, had a lower rate of identified CVST risk factors, had more frequent cortical vein involvement, and a non-significant higher rate of in-hospital mortality *CVST should be considered as potential comorbidity in COVID-19 infected patients presenting with neurological symptoms. *Compared to non-SARS-CoV-2 infected patients, CVST occurs in older patients, with lower rates of known CVST risk factors and might lead to a poorer outcome in the COVID-19 infected group.
Cavalcanti *et al.* 2020 [20]	Case series	-3 patients developed profound neurologic injury secondary to CVT with COVID-19 -Male: 2 (66.66%) -Mean age = 34 years	USA	*One patient had thrombosis in both the superficial and deep systems; another had involvement of the straight sinus, vein of Galen, and internal cerebral veins; and a third patient had thrombosis of the deep medullary veins. *Two patients presented with hemorrhagic venous infarcts. The median time from COVID-19 symptoms to a thrombotic event was 7 days (range, 2 - 7 days). *Two patients were managed with both hydroxychloroquine and azithromycin; one was treated with lopinavirritonavir. *All patients had a fatal outcome *Severe and potentially fatal deep cerebral thrombosis may complicate the initial clinical presentation of COVID-19. *No conclusions can be drawn other than that these cases provide hints as to the accumulating evidence that COVID-19 is a serious contributor to hypercoagulation, increasing the fatality of the disease. *Heightened awareness of this atypical but potentially treatable complication of the disease.

ischemic stroke among 221 patients with COVID-19 was 0.5%, 5%, and 0.5%, respectively [18]. The last study reported the inclusion of 13 patients with CVT and COVID-19 and compared this group with another group with CVT and without COVID-19. However, the number of patients with CVT and COVID-19

was 13 patients, and it was lower than the other group with CVT and without COVID-19, which included 57 patients [19].

The risk factors associated with developing CVT among COVID-19 patients were reported in three studies [16] [18] [19]. These risk factors include elder patients [16] [18] [19], male gender [16] and severe COVID-19 [18].

The symptoms associated with the presentation of CVT among COVID-19 patients were reported in three studies [16] [17] [20]. They included headache (85%), seizure (65%), and 45% had respiratory symptoms without neurological manifestations. The major imaging findings were infarction (65%) and hemorrhage (20%). Superior sagittal sinus was the most common site of thrombosis [16]. Another study reported 58% of patients had neurological symptoms in first 24 hours of the onset of respiratory symptoms. The main radiological findings were venous infarction, hemorrhage, or both [17]. In the case series, two patients out of three had hemorrhagic venous infarction [20].

The findings regarding diagnostic markers of CVT among COVID-19 patients were reported in first study [16]. Elevation of acute inflammatory markers was found, including D-dimer (87.5%), erythrocyte sedimentation rate (69%), C-reactive protein (47%), and homocysteine (50%) [16]. Third study reported markers regarding cardiovascular disease in general; also, there was an increase in the inflammatory response and an increase in D-dimer and C-reactive protein [18].

The management of patients was reported in two studies [17] [18]. One study reported that the management was done through anticoagulation, endovascular thrombectomy, and surgical hematoma evacuation [17]. Another study reported that six patients received antiplatelet treatment with aspirin or clopidogrel, but three patients died, whereas the remaining five patients received anticoagulation treatment, and only one died [18]. The mortality rate was reported in five studies [16] [17] [18] [19] [20], and it was 20% [16], 25% [17], and 38% [18].

6. Discussion

In our review, we found there is an association between COVID-19 disease and CVT. For instance, the incidence of CVT among COVID-19 patients was 8.8 per 10,000 compared to the general population, patients with influenza, and individuals who received mRNA vaccine [17]. In the general population, the risk factors of CVT were females, young age and malignancy in elderly patients [5] [6] [21] [22]. In our review, older age and male gender were the major risk factors for CVT among COVID-19 patients. This can be attributed to the impact of COVID-19, which may change the susceptibility of patients to develop CVT.

The most common presentation of CVT in COVID-19 patients was headache, followed by seizure [16]. Thus, COVID-19 patients can have CVT without neurological manifestations. Laboratory wise, COVID-19 with CVT showed elevation in D-dimer and markers of inflammation, such as C-reactive protein [16] [18]. We found that the elevation in D-dimer levels was associated with an in-

crease in the rate of vascular complications [23].

Also, we found that the antiplatelet therapy such as aspirin and clopidogrel wasn't effective in the treatment of CVT patients. Three patients out of six patients who received that regimen died, whereas, among five patients who received anticoagulation treatment, only one patient died [18]. However, this may be attributed to the severity of CVT, and anti-platelets may be not appropriate for the conditions of patients and lead to death, which was not mentioned in the study. Another study reported using anticoagulation, surgical hematoma evacuation, and endovascular thrombectomy for CVT patients; the mortality rate reported was 25% among 12 patients [17].

7. Conclusion

The accurate incidence and prevalence of CVT among COVID-19 patients is hard to report due to the lack of the number of studies and variations between the studies and included populations. However, we could conclude that the incidence of CVT is high among COVID-19 patients compared to the general population, patients with influenza, and those who received the mRNA vaccine. This warns us and encourages us to make attention to the development of CVT among COVID-19 patients, so CVT should be suspected and expected in COVID-19 patients. Older age was the major risk factor reported. A management strategy or treatment regimen should be established based on the severity of CVT patients as the mortality rate among those patients was high.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Benign Fasciculation Syndrome Developing after COVID Vaccine (Sinovac/CoronaVac)

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Abstract

Benign fasciculation Syndrome (BFS) is related with anxiety level; it is known as fasciculation anxiety syndrome. It may also be caused by long-term use of steroid or anticholinergic, as well as nicotine, caffeine, alcohol, and exposure to insecticides and pesticides. This paper presents a benign fasciculation syndrome case developing after CoronaVac vaccination.

Keywords

Fasciculation, COVID, Vaccine

1. Introduction

The pandemic caused by the SARS-CoV-2, a new coronavirus, is the most important health problem of the 21st century. High communicability, its unprecedentedly negative effect on the healthcare systems of countries, and absence of treatments that might improve the prognosis of this disease indicate the importance of developing an effective and reliable vaccine for this disease [1]. CoronaVac is an inactive virus vaccine that has been developed in China by using conventional vaccine production technologies [1] [2]. The vaccination in Turkey has started with medical personnel in October 2020.

Benign fasciculation syndrome (BFS) is a condition having a good prognosis and characterized with the fasciculation of voluntary muscles in the body and it generally limits itself [3]. This paper presents a benign fasciculation syndrome case developing after CoronaVac vaccination.

2. Case Presentation

A 43-year-old male patient applied to our clinic with complaints of widespread fasciculation in the tongue and entire body developing 1 day after the vaccina-

tion. He had no known comorbidity or medication usage. He did not use alcohol, nicotine or caffeine. No muscle weakness or atrophy was found in neurological examination. Deep tendon reflexes were found to be normal. In routine blood tests, Ca, Mg, K, Na, B12, TSH, and T4 values were within the normal limits. Neural transmissions were observed to be normal in EMG (electromyography) examination. Using needle EMG, fasciculation was observed in resting position in all the muscles examined. Motor unite potentials (MUPs) obtained during voluntary contraction were within normal limits. Spinal cord imaging was normal. The patient was taken to follow-up and the fasciculations were completely recovered in 3 weeks by gradually decreasing. The fasciculations were re-started 2 days after the second dose of COVID vaccine and completely recovered in 2 weeks. He did not take any medication or psychotherapy. No relapse was observed.

3. Discussion

The new coronavirus disease (COVID-19), the first case of which has been reported in late 2019 and which is caused by a new-type coronavirus (SARS-CoV-2), has been announced as a pandemic by World Health Organization on 11 March 2020 [4] [5]. The communicable and life-threatening nature of the virus necessitated the vaccine studies.

Sinovac (CoronaVac) continued its third phase vaccine studies in countries including Turkey, Brazil, and Indonesia [2] [5] [6]. The prevalence of adverse effects in vaccinated group was found to be 33%, whereas the same parameter was found to be 22% in placebo group and no statistically significant difference was found with placebo, except for the pain at the point of injection. No severe adverse effect was observed and the adverse effects that have been observed include pain at the point of injection, fever, asthenia, diarrhea, and muscle pain [2] [4] [5] [6].

Benign fasciculation syndrome (BFS) is characterized with the fasciculation of voluntary muscles in the body [7]. Fasciculation may develop in any voluntary muscle group but the most remarkable ones are eyelids, arms, hands, fingers, legs, and feet. Tongue might be affected too. The fasciculation might be occasional or continuous [8]. Other common symptoms include generalized fatigue or asthenia, parasthesis, and muscle cramps or symptoms [7]. Anxiety and somatic symptom disorders and symptoms are widely reported [7]. BFS symptoms are generally not accompanied by atrophy or muscle weakness and they typically emerge when the muscle is rested. Fasciculations may pass from a part of body to another one. The exact reason for BFS is not known. It is not known if this is a disease of motor nerves, muscles, or neuromuscular endplate. It is related with anxiety level; it is known as fasciculation anxiety syndrome. Intense and long-duration exercises may cause or worsen the fasciculations [8]. BFS may also be caused by long-term use of steroid or anticholinergic, as well as nicotine, caffeine, alcohol, and exposure to insecticides and pesticides [8]. Thyroid disease

may cause similar symptoms. The other significant diseases that should be distinguished include amyotrophic lateral sclerosis (ALS) and other motor neuronal diseases, neuropathy, and spinal cord diseases.

4. Conclusion

Benign fasciculation syndrome was found to have no association with any vaccine. Fasciculation finding was not reported as an adverse effect after COVID vaccine. It was aimed to present the case that was first in the literature.

Declarations

Ethical Approval and Consent to participate: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Holoprosencephaly with Cyclopia and Proboscis in a Female Namibian Baby: A Case Report

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Abstract

We present a case of Holoprosencephaly (HPE) with cyclopia and proboscis that was delivered in Katutura Intermediate Hospital, Namibia. The mother was a 24-year-old, G2P1 with no known comorbid conditions and no history of illicit or over-the-counter drug use. Her first pregnancy was uneventful and resulted in delivery of a normal baby. She had not attended antenatal clinic by the time of her presentation with the index pregnancy and the abnormality was picked up from the booking sonar. She went into spontaneous preterm labour and delivery before the planned date for admission for termination of pregnancy and physical examination of the baby confirmed the diagnosis of Holoprosencephaly with cyclopia. The pictures presented in this article were taken after obtaining parental consent.

Keywords

Abnormality, Congenital, Cyclopia, Holoprosencephaly, Proboscis

1. Introduction

Holoprosencephaly refers to a group of disorders arising from failure of normal forebrain development, or incomplete cleavage of the prosencephalon, during embryonic life—at approximately the 18th and the 28th day of gestation (Dubourg C 2007). It is a rare condition with varying degrees of affection. In its worst form, cyclopia, fetuses do not reach full term and those that do, don't survive extra uterine life. There are several risk factors implicated in the causation of these disorders but it is not uncommon to find no single risk factor like in the

case being described in this article. Since cyclopia is incompatible with life, early antenatal attendance and identification of such cases by ultrasonography, and discussion of termination of pregnancy with the parents are of paramount importance.

2. Case Presentation

A 24-year-old G2P1 mother presented to the antenatal clinic unsure of her last normal menstrual period. She had not had any antenatal visit during the current pregnancy. Routine antenatal history taking revealed that the mother did not have any comorbidities, no history of over-the-counter or illicit drug use and no history of febrile illness during pregnancy. She had no recollection of any congenital abnormalities in her family. Her physical examination was unremarkable. Ultrasound examination showed a singleton pregnancy at an estimated gestation age 30 weeks with a single midline ocular structure (Figure 1), hydrocephaly with almost no brain tissue (Figure 2), a 2-chambered heart (Figure 3) and gross polyhydramnios (AFI of 55.3 cm).

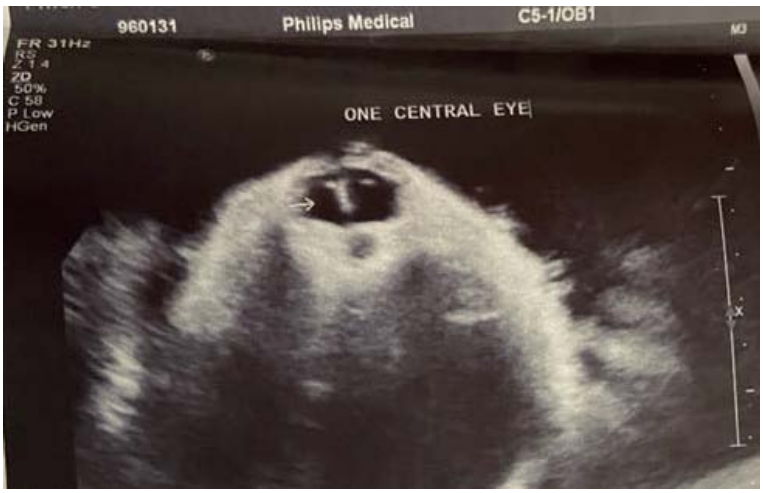

Figure 1. Ultrasound picture showing a single central eye with two pupils.

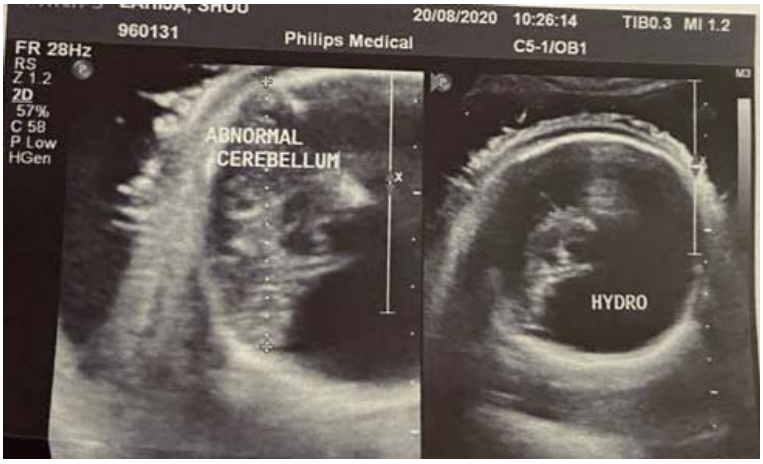

Figure 2. Ultrasound showing abnormal cerebellum and hydrocephalous.

The findings from ultrasound examination and likely outcome from the pregnancy were explained to the mother and her partner and they were counselled about termination of pregnancy, which they accepted. Labour, however, started spontaneously a day later and the mother had a vaginal delivery. The outcome was a still female baby with birth weight of 1.700 g.

At delivery approximately 3000 ml of clear amniotic fluid drained. On examination the baby had microcephaly (head circumference was 27 cm and body length of 58 cm), one diamond-shaped eye with two pupils, and absence of nose. It had a proboscis-like structure above the eye and some degree of micrognathia. See pictures below taken immediately after birth (Figure 4). A diagnosis of Holoprosencephaly with cyclopia was made.

Figure 3. Ultrasound showing a 2-chambered heart.

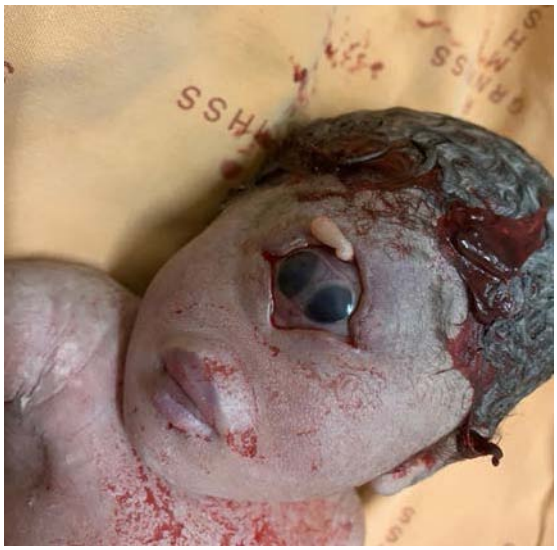

Figure 4. Photographs showing baby with a single midline ocular structure with 2 pupils and a proboscis above the eye. Photographs were taken after getting consent from parents.

Significant findings on postmortem included:

HEAD AND NECK

1) Skull: **holoprosencephaly (brain not separated into two hemispheres)**

2) Intracranial content; **microcephaly** (Brain weight; 49 **g)**

3) Orbital, nasal and aural cavities**: choana atresia**

4) Mouth, tongue and pharynx: **small round oral cavity**

5) Neck structure**: short neck**

6) Thoracic cage and diaphragm**: unremarkable**

7) Mediastinum and esophagus**: unremarkable**

8) Trachea and bronchi: **unremarkable**

9) Pleurae and lungs: unremarkable, thymus 11 g, left lung one lobe, right lung 2 lobes

Right Lung weight**: 14 g**

Left Lung weight: 18 g

10) Heart and pericardium: **one chambered heart, atriums not fully developed**

Heart weight: 12 **g**

3. Discussion

Holoprosencephaly (HPE) refers to a group of disorders arising from failure of normal forebrain development (incomplete cleavage of the prosencephalon) during embryonic life which normally takes place at approximately the 18th and the 28th day of gestation [1].

There are three classic types described in increasing severity—lobar HPE, where the right and left ventricles are separated, but with some continuity across the frontal cortex; semilobar HPE with a partial separation, and the most severe form, alobar HPE, also known as cyclopia, cyclocephaly or synophthalmia. In this condition there is a single brain ventricle and no interhemispheric fissure [2] [3]. Phenotypically the spectrum of HPE ranges from cyclopia or proboscis in the most severe cases, to midline cleft lip, a simple hypotelorism or even no anomalies in the less severe forms [1]. Babies with lobar and semilober HPE may be born alive and may survive extra-uterine life but with developmental delay and low intelligent quotient.

Cyclopia is characterized by the failure of the embryonic prosencephalon to properly divide the orbits of the eye into two cavities. It is the severest facial expression of the holoprosencephaly syndrome. It is a rare condition with sporadic occurrence. It accounts for approximately 1 in 100,000 births [4] [5]. In Namibia this is probably the first case of its kind as there is no documented literature regarding this abnormality. This concretizes the rarity of this condition. This abnormality occurs predominantly in females [6]. The reason for its predominance in the female gender is not clear yet.

There is great dysmorphism in the severely affected foetuses/babies. This index baby was delivered still (without life). The condition is not compatible with

life and usually results in miscarriage/abortion and even if the child is born alive it dies hours after birth (Winter 2015). It is thus a great contributor to perinatal mortality. It had a single central facial diamond-shaped eye with 2 pupils and proboscis, representing the nose, above the eye. The other extracranial features like polydactyl, renal dysplasia, and an omphalocele reported in other literatures (Salama 2015) were absent in the index case. Conspicuously, however, there was a one chambered heart and a very short neck.

The etiology of HPE is still not clearly understood. Heterogenous risk factors, both genetic and environmental, have been implicated. Multiple genes like sonic hedgehog, transforming growth factor beta-induced factor (TGIF), Chromosomal defects like trisomy 13, trisomy 18, and triploid are mentioned in several literatures [1] [4] [7] [8]. Environmental factors like maternal diabetes, drugs (alcohol, retinoic acid, aspirin, lithium), infections during pregnancy have also been implicated. Investigative history from the mother, however, failed to come up with any risk factor in this case.

Diagnosis: Sonography is the most helpful investigation in the antenatal diagnosis of cyclopia. The usual/normal ultrasound however may fail to pick up some features that may be helpful in making a diagnosis [9]. The imaging modality of choice is high-resolution MRI scans. In cases where MRI is not available or unaffordable, physical examination of the baby at birth offers the best diagnosis. In this case, sonar done at approximately 30 weeks, due to late booking, showed a foetus with a single ocular structure in the middle of the face, almost no brain tissue, brain was replaced with fluid and had a two-chambered heart seen. There was gross polyhydramnios with an AFI of 55.3 cm. All these were in keeping with cyclopia. At birth the baby exhibited classic features of alobar holoprosencephaly as described above.

4. Conclusion

Early recognition of these conditions during the antenatal period is of paramount importance as some, like Cyclopia (the alobar form of holoprosencephaly), are not compatible with life and others are associated with developmental delays and/or low intelligent quotient (IQ). It is therefore important to inform parents/families of the abnormality and the possible outcome during the antenatal period so that they, together with the managing medical team, decide on whether termination of pregnancy may be undertaken. All antenatal units, therefore, should incorporate routine antenatal anomaly ultrasound in their program to try to detect abnormalities like these.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Gastric Trichobezoar, Case Presentations

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Abstract

Trichobezoars are accumulations of hair casts in the stomach which is associated with trichophagia. The continuous ingestion causes mass of undigested material within the gastrointestinal, accumulating between the mucosal folds of stomach. Trichotillomania, is a mental disorder, described when someone cannot resist the urge to pull their hair from the scalp, eyebrows or eyelashes seen generally by teenagers or adolescents. A person with trichotillomania may experience repetitive pulling of hair, often without awareness, associated with anxiety and a sense of relief after pulling out hair. Consumed hair strands are beyond the pylorus into the small bowel identified as Rapunzel syndrome. Two cases of trichobezoars were encountered in our centre. They presented with nonspecific abdominal pain and abdominal mass. After investigations, with clinical correlation they were subjected to surgery, an open gastrotomy and complete removal of the trichobezoars. After surgery, the aim is to prevent recurrence by tackling the underlying cause of trichophagia which is commonly associated with trichotillomania. This case report series discusses about the management of trichobezoars.

Keywords

Trichobezoar, Trichophagia, Trichotillomania, Rapunzel Syndrome

1. Introduction

Undigested material within the gastrointestinal tract is called bezoar while trichobezoar develops when consumed hair forms a hairball within the stomach. 95% of cases reported occurred in females and 72% were below 15 years of age. Symptoms may be misleading as it is nonspecific at early stage. Several manifestations of trichobezoars have been presented as intussusceptions [1] [2], pancreatitis [1] and bile duct dilatation [1]. Rapunzel syndrome requires a gastrotomy for removal and no medication has been developed to digest or fragmentate the bezoar. Endoscopic removal of the hairball would be difficult and only

successful in small bezoars [2]. In this paper we present two case reports in paediatric age group presented with abdominal mass which was discovered to be trichobezoars. From the clinical findings and the radiographic imaging done, it was unlikely the bezoars to be removed endoscopically as the bezoars were immense. Laparotomy and gastrotomy for removal of the trichobezoar was performed. After the surgery, during the recovery period, the patient was referred to the psychiatrist. From surgical point, the treatment goal is gastrotomy and removal of the trichobezoar. Child needs a psychiatric follow up to tackle the underlying mental disorder hence needing psychotherapeutic sessions adjunct with medications that would help to overcome the hair pulling impulse disorder.

2. Case Series Report

Case 1. 7 years old, girl, Malay ethnicity presented to us with nonspecific abdominal pain mainly in epigastrium region. She also complained of early satiety. Otherwise denies any odynophagia or dysphagia. No altered bowel habit or family history of malignancy. Upon further history child has habit of eating her own hair since the age of 1 year old. An examination revealed child was not septic looking, her hydration status was fair. Her abdomen was soft and not distended. A large, firm, mobile mass was felt at the epigastrium. Percussion over the mass revealed dullness. Abdominal X ray (**Figure 1**) showed a radiopaque mass within the stomach. Hence, proceeded with an ultrasound abdomen (**Figure 2**) showed an echogenic mass with intense acoustic shadow obscuring posterior structures of the stomach region measuring approximately 6.1 cm in length. The duodenum adjacent to the mass appears not dilated. After the imaging, diagnosis of trichobezoar in the stomach made and an operative procedure (open gastrostomy) removal

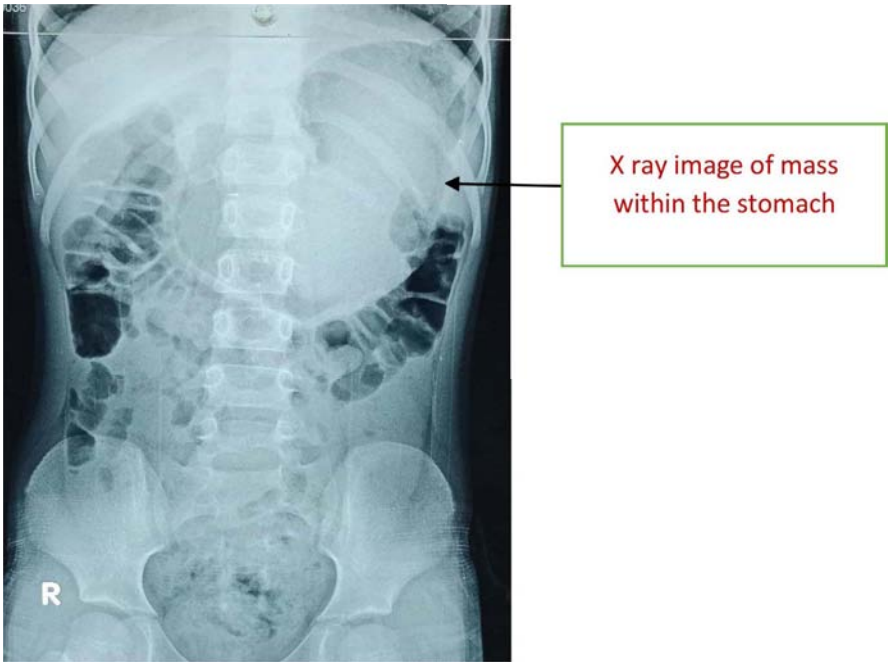

Figure 1. Abdominal X-ray showing a radiopaque mass in stomach.

of the trichobezoar (Figure 3). Gastric casting bezoar removed as shown in Figure 4. Intraoperative the stomach mucosa was examined and showed no evidence of erosions or ulcerations. After the surgery, she was allowed on fluid diet and gradually escalated to soft diet and finally normal diet. To avoid recurrence she was also referred to psychiatric department. Parents were emphasized that a psychiatrist's visit and regular check would be important to avoid recurrence.

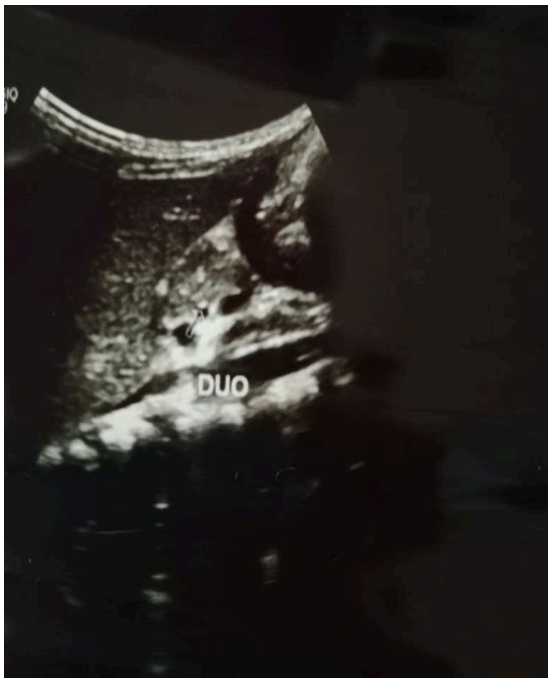

Figure 2. Ultrasound demonstrating an echo enhancing mass.

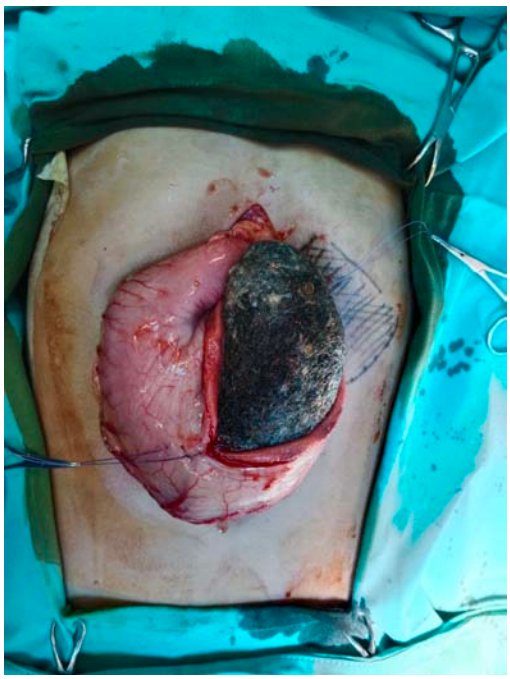

Figure 3. Vertical incision gastrostomy revealing a trichobezoar.

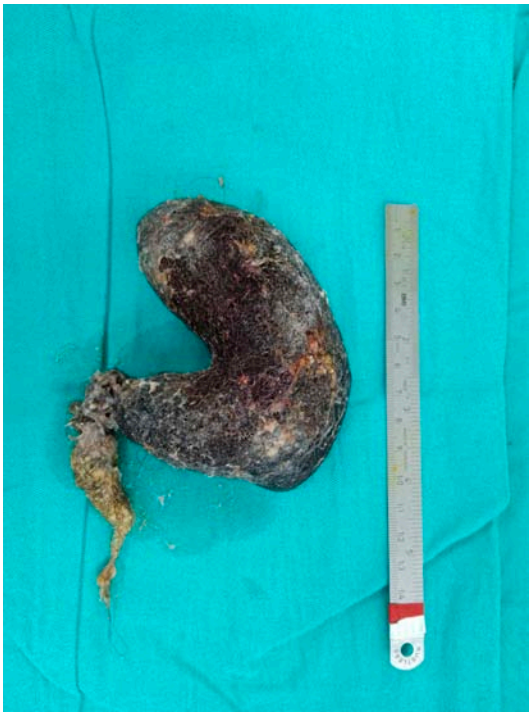

Figure 4. Gastric cast trichobezoar removed via gastrostomy.

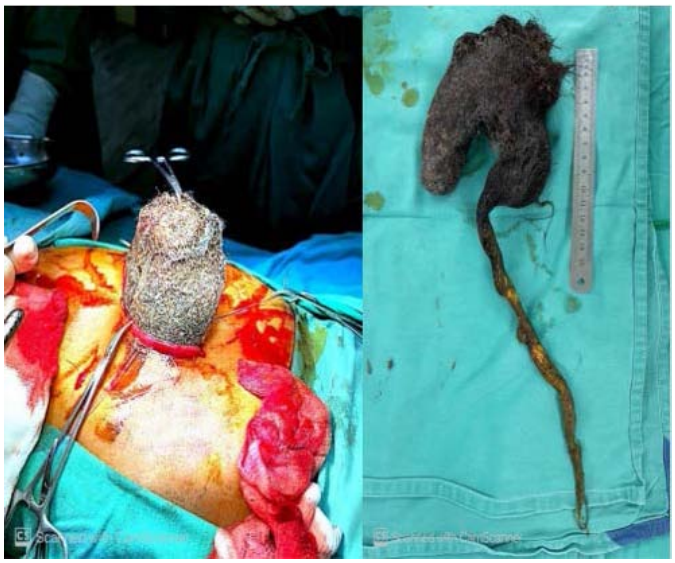

Figure 5. Vertical incision gastrostomy to deliver the huge trichobezoar.

Case 2. A 10 years old girl presented with 4 days history of abdominal pain and vomiting with blood. She appears shaven, failure to thrive with boy-like short hair. There was a palpable mass at the epigastric aspect of the stomach. USG abdomen was unable to appreciate any mass, however computed Tomography (CT) abdomen showed a mottled gas patterned intragastric mass with linear calcification within. We proceed with laparotomy, vertical incision gastrostomy to deliver the huge trichobezoar (**Figure 5**). Incidental findings of worm ball at the jejunum were evacuated via a jejunal enterostomy 30 cm from DJ junction (**Figure 6**). A

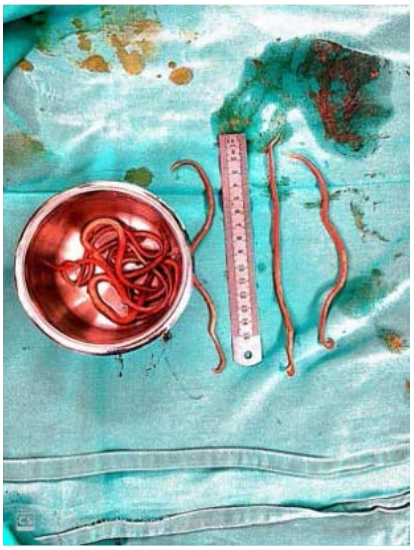

Figure 6. Incidental findings of worm ball at the jejunum were evacuated via a jejunal enterostomy 30 cm from duodenojejunal junction.

large antral ulcer 2 × 3 cm was treated conservatively. Post operatively, she was referred to psychiatry department for evaluation and discharged at day 5 post op. She was discharged with medication for deworming. Her operative wound healed unremarkably. Child showed remarkable weight improvement during 2 months clinic review. With the help from the psychiatrist, psychotherapy has prevented recurrence. Based on our clinical assessments in outpatient clinic review, child has no episode of abdominal pain and no endoscopic assessment was done to evaluate the stomach ulcer after surgery.

3. Discussion

Trichotillomania typifies an impulsive recurrent hair tugging or yanking. Trichophagia, which means *tricho*-hair and *phagia*-eating. Eating or ingesting the hair forms bezoars in the gastrointestinal tract forming a hairball in the stomach [1]. Due to indigestion of the bezoar, it emits an unpleasant odour. The enzymes in the intestines defile the protein nature of the hair, form indigested material casting the stomach [2].

In 1812 Rapunzel a young unwed girl, with long curls who was trapped in a penitentiary, high up in a tower. She lowered her hair to ground from the tower jail window, for a prince to climb up the tower to save her [3]. "Rapunzel" syndrome: hence is a hairball casting the stomach with tail extending beyond the pylorus into the small intestine or even up to the colon [4] [5]. As the bezoar obstructs the bowel lumen, patient develops intestinal obstruction. They may present with persistent vomiting, hematemesis or coffee ground vomitus due to stomach ulceration, inability to pass flatus, abdominal pain and distension. The condition may worsen as gastric ulceration may cause perforation and patient may succumb to severe sepsis and develops generalized abdominal pain due to peritonitis. Laboratories results may reveal anaemia such as due to chronic blood

loss. There are cases reported association of vitamin B 12 deficiency, hence blood results may show macrocytic, megaloblastic anaemia [6].

The operative procedure for removal of the hairball from the intestine would be an open surgery such as laparotomy and enterotomy [7]. In both of the described cases above, an open surgery (laparotomy) was done. To overcome the anaemia blood transfusion if symptomatic, hematinic such as iron tablets, folic acid and vitamin b12 tablets can be prescribed to correct the anaemia. Proton pump inhibitors to lower the gastric pH and treating the ulcers. In such cases where the hairball in the stomach is too large and extends far into small intestines such as jejunum, laparoscopic approach would be difficult. Endoscopic removal of the bezoar is also not advisable [8]. After surgery, emphasizing on importance of proper psychiatric follow up would be important, as the root cause is treated, to avoid recurrence. In our case, we referred both patients for proper evaluation and treatment of the underlying mental disorder.

The peculiarities of both cases described above are that they were females and their hair showed jiggered edges with clinical findings of mass at upper abdomen. Similar cases have been reported globally and most cases treated with gastrotomy and evacuation of the bezoar.

4. Conclusion

Parents should be aware if they notice bald patches on the scalp of their children. Ingesting hair after pulling from the scalp may cause casting in the stomach, which later may cause obstruction and ulceration or intestinal perforation. Anaemia and vitamin deficiencies from the trichobezoars may stunt their growth and development.

Consent

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Recurrent Coronary Artery Thrombosis on Triple Anti-Thrombotic Therapy, Is There a Possible Association with ChAdOx1 nCoV-19 Vaccination?

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Abstract

Background: Vaccines remain the only viable and safe option to control transmission and minimise disease sequelae during the COVID-19 pandemic. Whilst multiple vaccines are available, evidence has emerged regarding the association between the ChAdOx1 nCoV-19 vaccine, platelets and thrombosis, manifesting in thrombotic thrombocytopaenia. **Case Summary:** We report a case of recurrent coronary artery thrombosis on triple antithrombotic therapy, namely aspirin, clopidogrel, and continuous intravenous heparin, nine days after the ChAdOx1 nCoV-19 vaccine, in a 63-year-old female with no significant history of cardiovascular disease. **Conclusion:** This case may suggest that the association between platelets, SARS-CoV-2, the ChAdOx1 nCoV-19 vaccine, and coronary thrombosis may remain incompletely understood and warrants further study. Clinicians should remain on high alert if presented with similar circumstances.

Keywords

ST-Elevation Myocardial Infarction, Stent Thrombosis, ChAdOx1 nCoV-19, AstraZeneca, COVID-19, SARS-CoV-2

1. Introduction

The SARS-CoV-2 vaccinations are continuing to play a vital role in controlling the global pandemic. While ongoing compliance with the vaccination programs is of paramount importance, the rare side effects of these new vaccinations need to be recognised and treated appropriately to ensure patient safety. Evidence has

emerged of the risk of acute thrombosis in the setting of ChAdOx1 nCoV-19 (AstraZeneca) vaccination. This has led to updated guidelines from the Australian Technical Advisory Group on Immunisation recommending ChAdOx1 nCoV-19 (AstraZeneca) for those over 50 years, in line with recommendations from the United Kingdom Medicines and Healthcare Products Regulatory Agency. We present a case of coronary artery thrombosis without thrombocytopaenia whilst on dual antiplatelets and intravenous anticoagulation post initial thrombolytic therapy, nine days after ChAdOx1 nCoV-19 vaccination. Whilst the known thrombotic risk associated with the ChAdOx1 nCoV-19 vaccination remains incredibly rare, the thrombotic risk for patients with acute coronary syndromes may be increased, particularly given that the ChAdOx1 nCoV-19 vaccination is the recommended vaccine for patients over 50 years, those patients most at risk for acute coronary events.

2. History of the Case

We present the case of a 63-year-old female who developed severe retrosternal chest pain nine days after receiving her first dose of the ChAdOx1 nCoV-19 vaccination. Following acute onset of chest pain and dyspnoea she was transferred to her local regional hospital via emergency services. The time from chest pain onset to first medical contact was 59 minutes. On arrival, she had ongoing severe pain, yet was haemodynamically stable, with a blood pressure of 128/65 mmHg and a heart rate of 71 beats per minute, was afebrile at 37.4 degrees Celsius, with normal oxygen saturations and respiratory rate. Her clinical exam was normal. Given the absence of symptoms and the regional epidemiological profile at the time of presentation, she was not tested for SARS-CoV-2 virus infection.

Past medical history included ulcerative colitis, which was quiescent on azathioprine and mesalazine, and gastroesophageal reflux disease. She had a family history of ischaemic heart disease, with no other cardiovascular risk factors. She had no known clotting disorders or history of thromboembolic disease. Her vaccine status was not known at the time of presentation.

3. Investigations and Management

Her initial 12-lead electrocardiograph (ECG) demonstrated 11 mm ST-segment elevation in the anterolateral leads with reciprocal ST-segment depression (**Figure 1(A)**). Following prompt recognition of anterolateral ST-segment elevation myocardial infarction (STEMI), she was administered 300 mg loading doses of aspirin and 600 mg of the $P2Y_{12}$-inhibitor clopidogrel. Given the travel time to the nearest percutaneous coronary intervention (PCI) centre was greater than 120 minutes, she also underwent pharmacological fibrinolysis with tenecteplase which was followed by a continuous infusion of intravenous heparin. Her pain onset to fibrinolysis time was 135 minutes. Thirty minutes post fibrinolysis, she was pain free with near complete resolution of STEMI on serial ECG (**Figure 1(B)**). She was subsequently transferred the 230 kilometres by road to our PCI

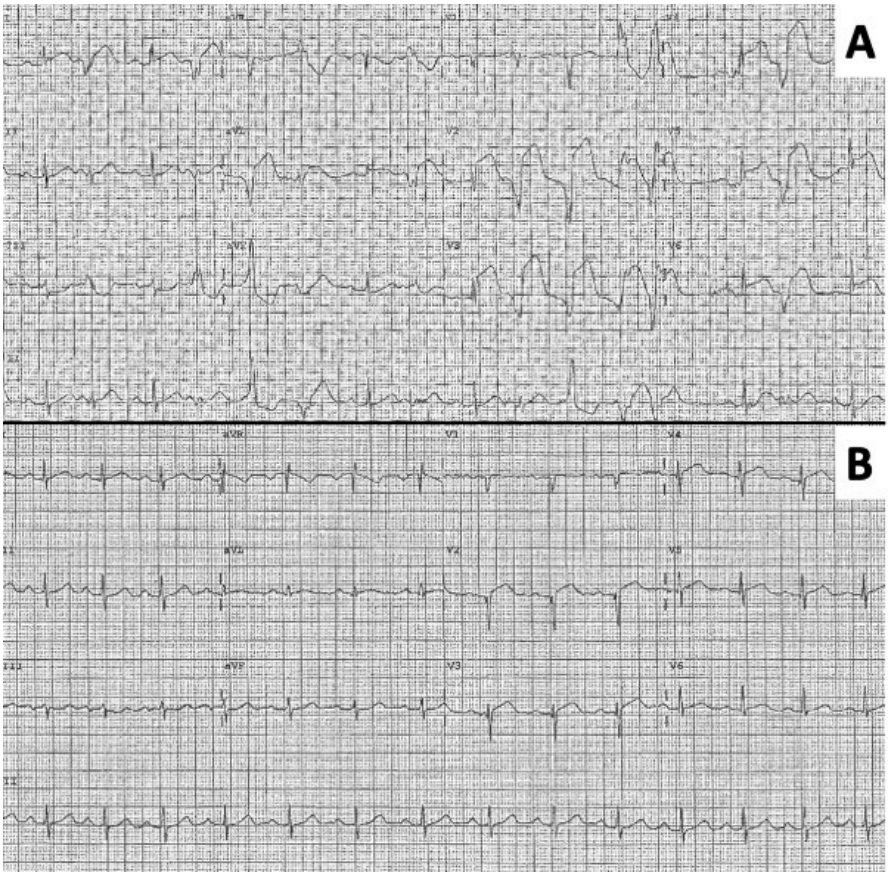

Figure 1. Anterolateral ST-segment Myocardial Infarction. 12-lead ECG pre (A) and post (B) thrombolysis.

capable tertiary hospital.

Upon arrival, she remained haemodynamically stable and pain free. Her admission ECG demonstrated sinus rhythm with anterior q waves, without evidence of acute ischaemia (**Figure 2(A)**). Her laboratory findings were unremarkable, with the exception of an elevated cardiac troponin I of 116,013 ng/L (reference value, <26 ng/L). Of note, her platelet count was normal at 291,000/mm^3 (reference value, 150,000 - 400,000/mm^3). Within two hours of arrival, day 10 post ChAdOx1 nCoV-19 vaccination and four hours post thrombolysis, she experienced recrudescence of severe chest pain with corresponding 5 mm anterior ST-segment elevation on her ECG (**Figure 2(B)**) and was promptly taken for emergency coronary angiography.

Coronary angiography, via right radial access, demonstrated mid-vessel occlusion of the left anterior descending artery (LAD) (**Figure 3**). Occlusion was predilated and treated with a 2.75 × 34 mm Resolute Onyx (R-Onyx, Medtronic, CA, USA) zotarolimus-eluting stent and post-dilated with 3.0 NC balloon at high pressure achieving a good angiographic result (**Figure 4**), however slow antegrade flow was noted in the distal artery after the post-dilatation (Thrombolysis in Myocardial Infarction (TIMI) Grade II). She was therefore maintained on a continuous infusion of intravenous heparin. Intravascular imaging was not

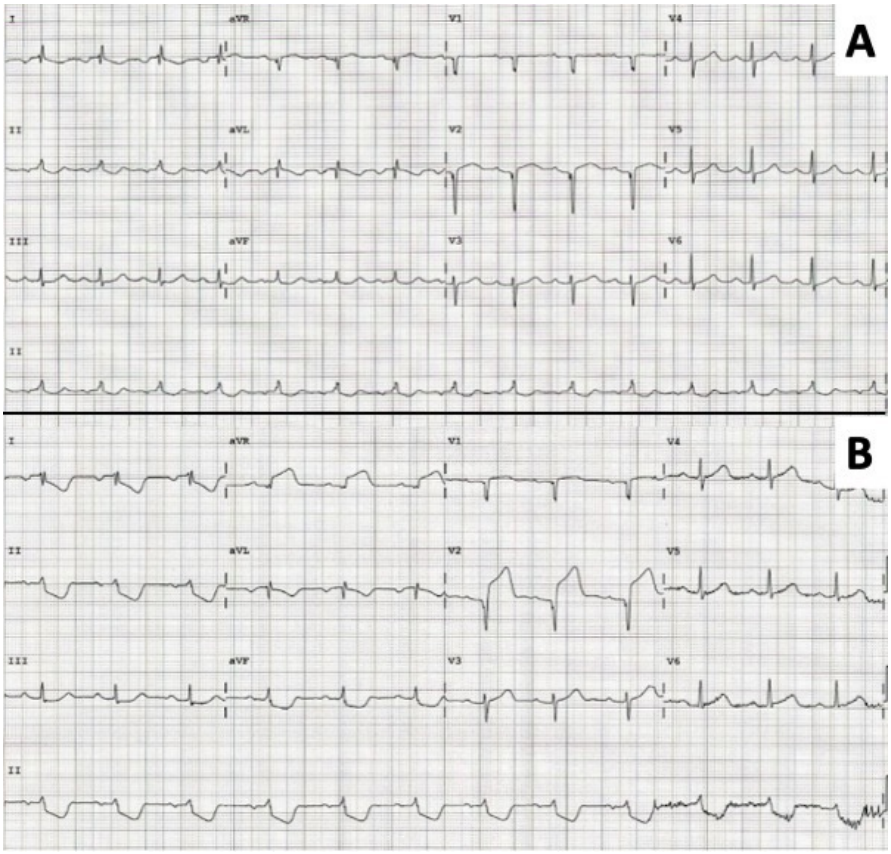

Figure 2. Failed thrombolysis. Arrival 12-lead ECG (A) without acute ischaemic changes, and following onset of chest pain (B) on dual anti-platelet and heparin infusion.

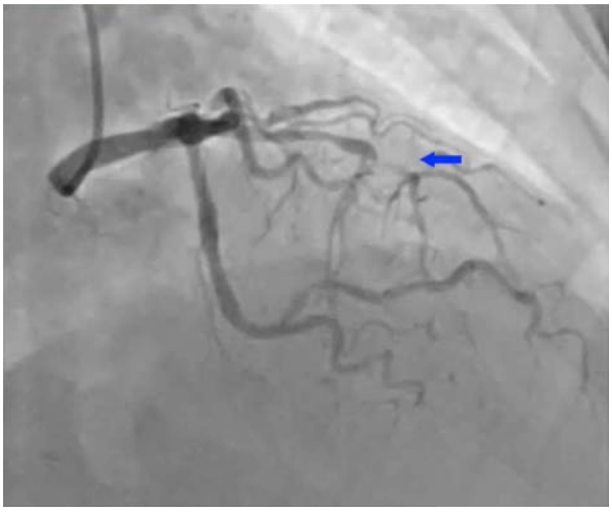

Figure 3. Coronary angiogram. Mid-vessel occlusion (blue arrow) of the LAD.e.

undertaken due to the lack of availability within the regional setting.

Post coronary angiogram she remained pain free for two hours. Whilst on triple antithrombotic therapy, her chest pain returned with ECG demonstrating acute change from sinus rhythm with anterior q-waves post PCI (**Figure 5(A)**) to a new right bundle branch block with concurrent 3 mm anterior ST-segment

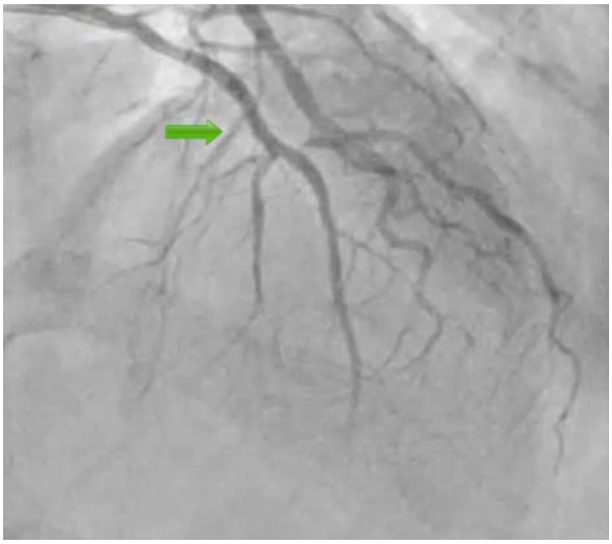

Figure 4. Coronary angiogram and PCI. Post PCI and stent insertion (green arrow) of the LAD occlusion with distal TIMI II flow.

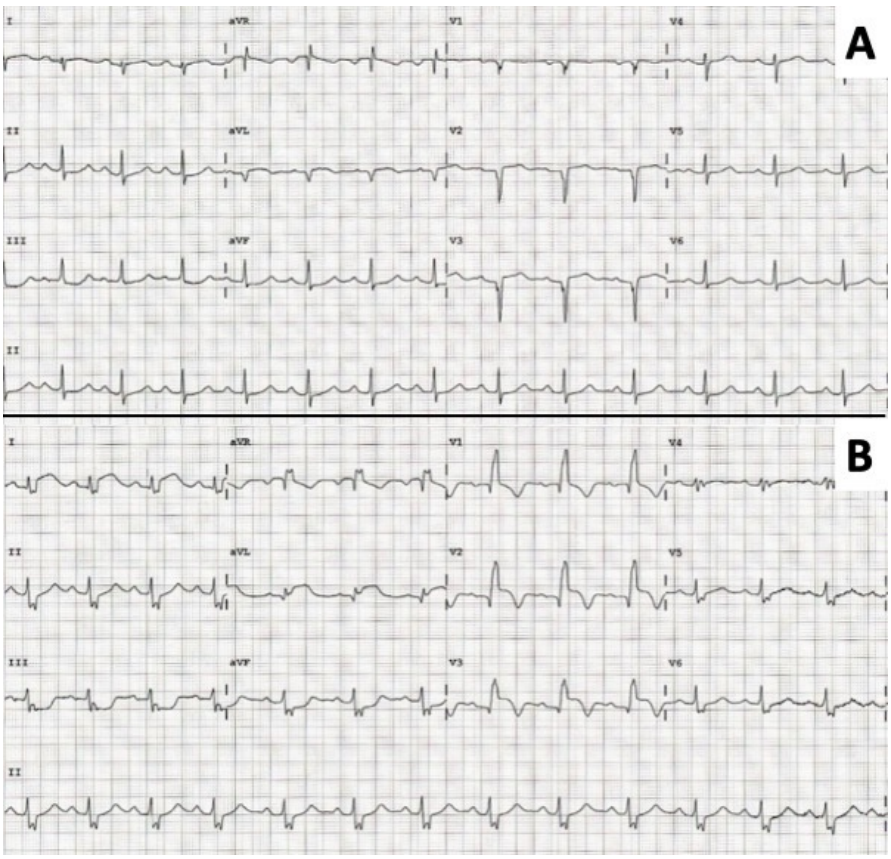

Figure 5. Anterior ST-segment myocardial infarction post PCI. 12-lead ECG post recent left anterior descending artery stent (A) and upon return of chest pain (B).

elevation (**Figure 5(B)**). She was commenced on a glyceryl trinitrate infusion and urgently transferred for repeat coronary angiography, which revealed occlusive, acute stent thrombosis (**Figure 6**). Following intracoronary thrombectomy

via an export aspiration catheter (MedtronicAVE, Santa Rosa, CA), further prolonged balloon angioplasty at low and intermediate pressures was performed for the residual thrombus, achieving improved flow albeit some distal embolization (Figure 7). She was commenced on an infusion of glycoprotein IIb/IIIa antagonist, tirofiban.

4. Outcome and Follow Up

Our patient remained pain free and stable post repeat coronary angiogram and was transferred to the intensive care unit for monitoring. Her platelets remained stable and within the normal range throughout her admission and a heparin-induced-thrombocytopaenia test was negative. She was subsequently discharged home day four post presentation.

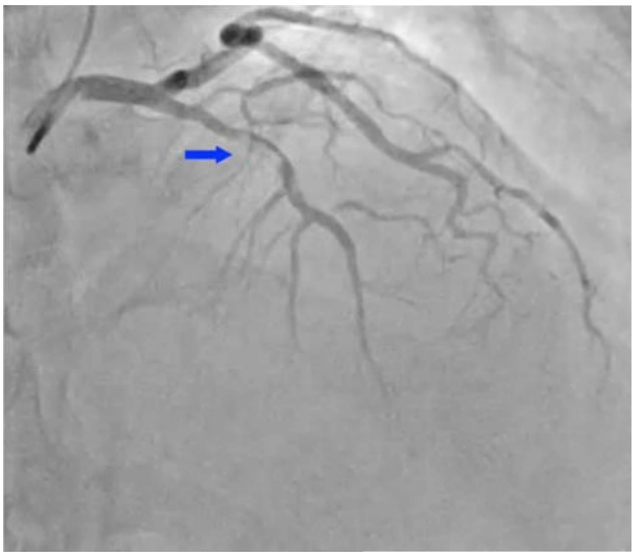

Figure 6. Acute stent thrombosis. Repeat angiography demonstrating acute stent thrombosis (blue arrow).

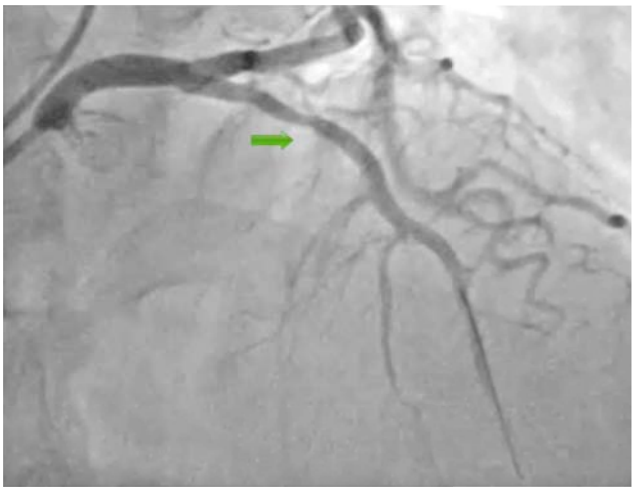

Figure 7. Acute stent thrombosis. Resolution of stent thrombosis post thrombectomy and balloon angioplasty (green arrow) with improved LAD flow.

5. Discussion

This case represents recurrent coronary thrombosis due initially to failed thrombolysis and subsequently to acute stent thrombosis. Whilst failed thrombolysis is not uncommon, occurring in up to 40% of patients [1], acute stent thrombosis, within 24 hours, is exceedingly rare, occurring in 0.8% of patients [2]. What is particularly unusual in this case is the consecutive occurrence of outcomes whilst on triple antithrombotic therapy, namely that of aspirin, clopidogrel and continuous heparin infusion. Procedural or device related causes of acute stent thrombosis cannot be completely ruled out in the absence of intravascular imaging, which was unfortunately unavailable within the regional facility.

Clopidogrel resistance must also be considered as a possible cause for acute stent thrombosis. Whilst stent thrombosis on clopidogrel is reported in both the PLATO, at 1.9% [3], and TRITON-TIMI 38, at 2.4% [4], trials, it is important to consider that these outcomes did not occur whilst on a continue heparin infusion, and related to subacute, late and very late stent thrombosis, as per Academic Research Consortium [5], at twelve and fifteen month follow up respectively, rather than the acute stent thrombosis seen in our patient. Whilst clopidogrel resistance has been suspected in acute stent thrombosis [6], these also have occurred on dual rather than triple antithrombotic therapy.

Furthermore, the management of acute stent thrombosis, in addition to invasive thrombectomy and stent balloon angioplasty, includes triple antithrombotic therapy [7], so the development of acute stent thrombosis within two hours of stenting in our patient is noteworthy. A single similar case report exists, that of failed thrombolysis, rescue PCI, followed by sequential acute and subacute stent thrombosis, whilst on triple antithrombotic therapy, occurring in an asymptomatic SARS-CoV-2 positive patient [8].

As the SARS-CoV-2 pandemic has progressed, evidence has emerged of the increased cardiovascular complications of infection, including that of acute coronary syndrome [9], yet the pathogenesis remains incompletely understood. Hypotheses for coronary complications include inflammatory mediated cytokine excess and decreased activation of platelet Mas receptors, with resultant platelet activation, aggregation and thrombosis [10]. Recent interest has also included SARS-CoV-2 vaccinations, particularly ChAdOx1 nCoV-19, an adenovirus vectored vaccine, and its rare side-effect on platelets resulting in thrombotic thrombocytopaenia [11]. Whilst these adverse events are well described and recognised in the clinical setting, reports of patient presenting with acute coronary syndromes post SARS-CoV-2 vaccinations, without thrombocytopenia [12] [13] [14], when considered with the demonstrated activation and aggregation of platelets by adenovirus vaccine vectors via unknown platelet receptors [15], suggest further research is required to ensure patient safety.

Whilst the overall safety and efficacy of the ChAdOx1 nCoV-19 vaccine is well documented [16], the occurrence of rare sequential platelet associated complications in our patient whilst on triple antithrombotic therapy, only previously do-

cumented in a SARS-CoV-2 positive patient, may suggest the association between platelets, SARS-CoV-2, the ChAdOx1 nCoV-19 vaccine, and coronary thrombosis remains to be elucidated. Causality to the ChAdOx1 nCoV-19 vaccine is not claimed in this case and authors acknowledge the possible procedural, device and pharmaceutical causes that may have contributed to our patients' outcomes. This case however highlights possible avenues for further research.

The importance of SARS-CoV-2 vaccinations in controlling the global pandemic cannot be understated. It is vital to recognise that these vaccines are not only efficacious but safe [16]. This case of recurrent coronary artery thrombosis whilst on triple antithrombotic therapy and without clinical or serological evidence of heparin induced thrombocytopaenia, demonstrates the need for ongoing investigation, and for clinicians to remain on high alert if presented with similar circumstances.

6. Learning Points

- Fibrinolysis remains first line treatment of STEMI in healthcare setting greater than 120 minutes from PCI capable centres. Transfer to PCI capable centres should be initiated post fibrinolysis due to the risk of failed therapy.
- Recurrent chest pain and ST-segment elevation post thrombolysis and PCI always require prompt management, however increased suspicion for recurrent thrombosis post ChAdOx1 nCoV-19 vaccination may be prudent.
- Whilst stent thrombosis is relatively rare in the modern era, patient, device, and procedural related factors can be contributing factors and require appropriate assessment.
- Further investigation may be required to completely understand the relationship between platelets, SARS-CoV-2, the ChAdOx1 nCoV-19 vaccine, and thrombotic events.
- ChAdOx1 nCoV-19 vaccine remains a safe vaccination and is vital in the SARS-CoV-2 pandemic response.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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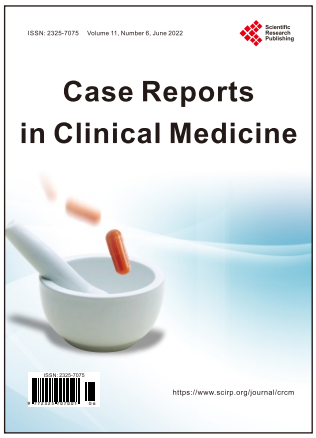

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