Cardiology in the Young

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New onset of protein-losing enteropathy in a patient with Fontan circulation after COVID-19 vaccination: dread the cure or the disease?

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Brief Report

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Abstract

We present the case of a 31-year-old female with Fontan circulation who developed signs of protein-losing enteropathy 10 days after second COVID-19 vaccination. After standard investigations for identification of potential triggers for protein-losing enteropathy, we concluded that coronavirus disease 2019 (COVID-19) booster vaccination could have been the most probable underlying trigger. Prompt investigation of new symptoms post-vaccination in high-risk patients is necessary.

Introduction

Protein-losing enteropathy is one of the most challenging complications occurring in approximately 5–12% of patients with a Fontan circulation and is associated with increased morbidity and mortality.[1] It is characterised by abnormal loss of serum protein into the interstitial lumen leading to a drop in the intravascular oncotic pressure. Patients can present with variety of symptoms and signs, including weight gain, peripheral oedema, ascites, pericardial or pleural effusion, as well as with chronic or intermittent diarrhoea associated with abdominal bloating and pain.[2]

Protein-losing enteropathy's severity can vary from mild and transient to a permanent condition characterised by periods of relapse and remission. The exact pathogenesis is poorly understood with multiple potential underlying mechanisms, which may be present at the same time. One of the potential triggers is viral infection that can cause a transient increase in the enterocyte membrane's permeability.[3]

Although coronavirus disease 2019 (COVID-19) vaccination was proven to be safe in patients with underlying cardiovascular conditions, adverse effects have been reported.[4,5] Hereby, we present a case report of a female patient with a Fontan circulation and protein-losing enteropathy development following COVID-19 booster vaccination.

Case presentation

A 31-year-old female was born with congenitally corrected transposition of the great arteries, pulmonary stenosis, ventricular septal defect, and persistent left superior vena cava. She initially underwent percutaneous balloon pulmonary valve valvuloplasty at age 3 years. At age 6 years, she underwent right-sided bidirectional Glenn operation and ligation of persistent left superior vena cava. At age 13 years, extra-cardiac total cavopulmonary connection was completed.

She presented to the hospital in June 2021 with significant peripheral leg oedema (Figure 1), which started approximately 10 days after her second COVID-19 vaccination with viral vector vaccine. She did not present with dyspnoea or ascites and no signs or symptoms of infection. On physical examination, she was normotensive with oxygen saturation of 96% on room air. Electrocardiogram showed sinus rhythm. Echocardiogram was similar compared to previous studies and showed unobstructed Fontan pathway, normal systolic function of systemic right ventricle in the context of moderate tricuspid valve regurgitation, and normally functioning aortic valve. Blood tests revealed a new finding of decreased levels of total protein and albumin at 50 g/L and 31 g/L, respectively. Brain natriuretic peptide level was mildly elevated at 39 ng/L (normal < 20 ng/L), but stable compared to previous measurements. Faecal Alpha 1 antitrypsin level was increased at 2.23 mg/g (normal < 0.5 mg/g). Based on these findings, protein-losing enteropathy was suspected, and investigations to identify potential underlying mechanism were undertaken.

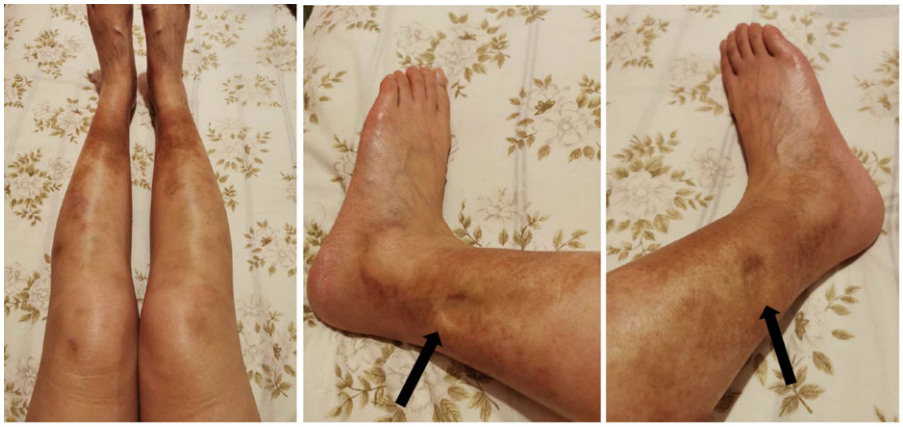

Figure 1. Peripheral oedema (arrows) in a female patient with Fontan circulation who was subsequently diagnosed with protein-losing enteropathy.

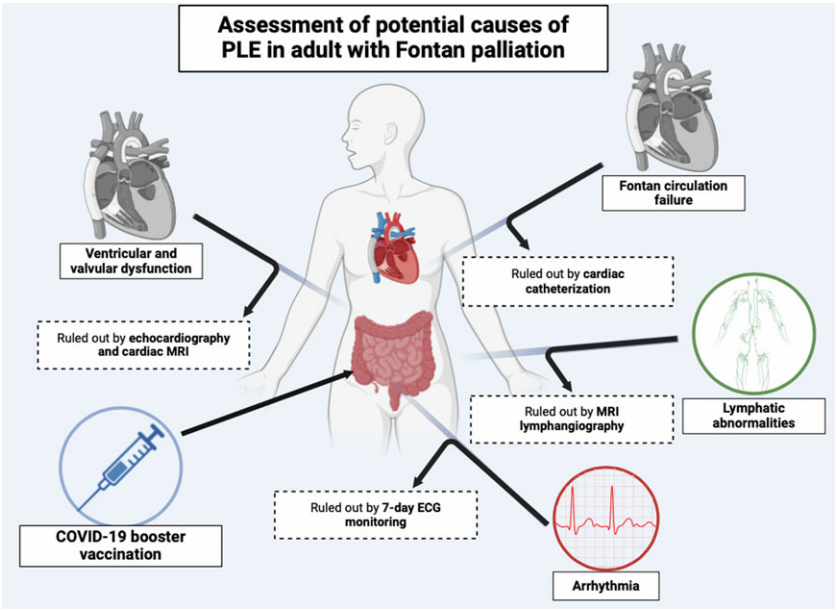

Figure 2. Protein-losing enteropathy in patient with Fontan circulation. Illustration of potential causes of protein-losing enteropathy which were ruled out in our patient. Abbreviations: PLE = protein-losing enteropathy.

No proteinuria was detected. Liver MRI revealed normal liver structure. No arrhythmias were detected on a 7-day ECG monitoring. Lymphatic abnormalities were ruled out by MRI lymphangiography. Right-heart catheterisation revealed low pressures in her Fontan circulation (mean pressure 6 mmHg) with no significant transhepatic (2 mmHg) or transpulmonary gradient (3 mmHg).

Based on these findings it was concluded that the most probable trigger for protein-losing enteropathy was COVID-19 booster vaccination (Figure 2).

High-protein and low-fat diet were prescribed. Furosemide 40 mg once daily was initiated, leading to improvement of her leg oedema after a few weeks of treatment. Subsequently, the patient stopped the furosemide due to cramps and was started on spironolactone. Further improvement of her symptoms was observed.

Discussion

To our knowledge, this is the first case reported in the literature of protein-losing enteropathy likely triggered by COVID-19 vaccination, shedding light on an alternative mechanism that could provoke this condition in a patient with Fontan circulation.

Viral infection leads to acute inflammatory response and increased permeability of the intestinal mucosa, one of the possible triggers for development of protein-losing enteropathy.[3] There are several case reports of COVID-19 infection in adults with Fontan circulation in the literature but none leading to protein-losing enteropathy development.[6] Although the prognosis seems to be favourable in these patients, complications have been documented with thrombotic complications being the most common.[7]

The spike protein resulting from COVID-19 vaccination attaches to the cell surface as it would to the viral surface, rather than assembling into new viral particles. Due to genetic modification, spike protein enhances the immune response and prevents its binding to angiotensin-converting enzyme 2 receptors. The short-term cardiovascular safety of the COVID-19 vaccine has been confirmed; however, it was shown that the vaccine may cause a prominent increase in inflammatory markers, especially after the second dose and a transient deterioration of endothelial function at 24 hours with subsequent return towards baseline at 48 hours.[8]

In our case, protein-losing enteropathy in patient with Fontan circulation developed 10 days after COVID-19 booster dose. This

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is, to our knowledge, the first case report of such temporal consecutiveness. We believe adverse effects after COVID-19 vaccination are rare and therefore do not outweigh its benefits. However, clinicians caring for these high-risk patients should be aware of all possible adverse events associated with COVID-19 vaccination to develop a personalised therapeutic approach.

Protein-losing enteropathy is a condition with a highly variable clinical picture and an unpredictable course, with a reported 5-year survival rate of 88% after diagnosis.[9] Chronic protein loss leads to multi-organ involvement with harmful systemic consequences, including abnormal wound healing, dysfunctional coagulation cascade leading to both increased thrombotic and bleeding risk, reduced bone density due to hypocalcaemia, and low immunoglobulin levels increasing the risk of infections.[10,11]

Protein-losing enteropathy is confirmed by the presence of hypoalbuminemia and elevated apha-1 antitrypsin in spot stool sample or abnormal clearance of alpha-1 antitrypsin in 24 hours.[2,12] Other possible causes of protein loss must be ruled out.

Upon its diagnosis, it is crucial to identify potentially reversible causes with echocardiogram, cardiac magnetic resonance, cardiac computed tomography scan, or cardiac catheterisation, which is essential to invasively evaluate the haemodynamic of the Fontan circulation (i.e. systemic venous pressure, pulmonary artery pressure, cardiac output, and ventricular end-diastolic pressure) and can also be therapeutic. A small change in gradients; even a gradient of 1 – 2 mmHg could be considered significant in the context of a Fontan circulation. Arrhythmias should be ruled-out by electrocardiogram or Holter monitoring. In the current era, the role of lymphatic circulation in patients with a Fontan operation is becoming predominant. Lymphatic abnormalities may be identified by T2-weighted MRI liver lymphangiography, leading to invasive treatment for protein-losing enteropathy.[13]

Overall, we aimed to highlight an uncommon consequence likely arising from the COVID-19 vaccine. Multicentric studies are warranted in the future to provide high-quality evidence on underlying mechanisms and treatment strategies for protein-losing enteropathy.

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Competing interests. The authors declare none.

Ethical standards. This article does not contain any studies with human participants or animals performed by any of the authors.

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