Case Report

COVID-19 vaccine: Culprit or innocent bystander in a rare adverse gastro-intestinal surgical event? A case report with review of literature

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Abstract

Corona virus disease (COVID-19) initially appeared to be an exclusively respiratory ailment. While that is true in a vast majority of the cases, its evolution and later evidence have shown that it can afflict virtually any organ system in the human body after first gaining entry through the respiratory tract. The COVID-19 vaccines were one of the turning points in the campaign to control the COVID-19 pandemic. However, after their extensive use all over the world, it has emerged that they can cause some dangerous collateral damage. We, herein, report the case of a 58-year-old woman who presented to us with signs and symptoms of acute intestinal obstruction 4 months after receiving her first dose of Covishield® vaccination for COVID-19. Her blood tests showed a high D-dimer and normal platelet count. She was previously admitted to the hospital with an acute abdomen 3 months back. A contrast-enhanced computed tomography (CECT) scan of the abdomen done then had revealed thrombi in the aorta and inferior mesenteric and splenic arteries. She was started on low-molecular-weight heparin and discharged on tablet Warfarin after clinical improvement. CECT abdomen done during her present admission revealed a proximal small bowel stricture with dilated proximal and collapsed distal loops. She underwent a laparoscopic jejuno-ileal resection anastomosis. During the post-operative period, a repeat CECT abdomen done to evaluate multiple episodes of vomiting revealed pulmonary embolism in the lower chest cuts. A venous Doppler revealed extensive deep venous thrombosis of the left lower limb. A thrombophilia profile diagnosed anti-phospholipid antibody syndrome, an exacerbation of which was likely precipitated by the COVID-19 vaccine.

Keywords: Anti-phospholipid antibody syndrome, COVID-19, deep vein thrombosis, pulmonary embolism, resection, and anastomosis

Introduction

Corona virus disease (COVID-19) is a serious respiratory disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Although the majority of COVID-19 patients experience relatively mild disease, some experience critical illness associated with high rates of vascular events that often prove fatal.[1] As of May 15, 2023, a total of 13,352,935,288 vaccine doses had been administered all over the world. Out of these, 2,206,675,383 vaccine doses were administered in India.[2] A total of 1,749,413,882 Covishield® doses were administered, and 5,055,562 vaccine-related adverse events were reported in Vigibase.[2,3] Out of these, 1771 recipients developed venous thrombosis, 367 had arterial thrombosis, and 355 developed antiphospholipid antibody syndrome, according to Vigibase data, as of May 21, 2023.[3]

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Case History

A 58-year-old obese post-menopausal woman presented to the emergency ward with complaints of severe abdominal pain, multiple episodes of vomiting, abdominal distension, and constipation. She was a homemaker and was a known case of rheumatoid arthritis on treatment. She did not have any addictions. She was admitted 3 months back with the complaint of acute abdominal pain and was treated conservatively. At that time, she gave a history of getting administered with the first dose of the COVID-19 vaccine Covishield®, 1 month prior to that previous presentation. During that previous admission, a contrast-enhanced computed tomography (CECT) scan of the abdomen had revealed thrombi in the aorta and inferior mesenteric and splenic arteries. A specialist in hematology was called in, and he opined that the multi-major vessel thrombosis could be COVID vaccine-induced. She was subsequently started on anti-coagulant therapy (Injection Enoxaparin initially, which was switched over to oral tablet Warfarin). Upon clinical improvement, she was discharged from the hospital with advice for regular follow-ups, repeat imaging, and monitoring of Warfarin therapy with serial prothrombin time and international normalized ratio (PT/INR) values so as to maintain INR between 2 and 3. During the present presentation, on examination, the abdomen was distended but soft with hyperperistaltic bowel sounds. A per rectal examination revealed an empty rectum. A plain X-ray of the abdomen showed distended small bowel loops. A magnetic resonance imaging (MRI) enterography which was done on the advice of her family physician, just prior to presentation to us, revealed a strictured jejunum with dilated proximal jejunal loops [Figure 1a and b]. Thus, she was diagnosed to have small bowel obstruction. She was put on a trial of conservative management (nil per oral, antibiotics, intra-venous fluid support) over the first 3 days of her admission. Failing this, she, along with her family, was counseled for surgery. At laparoscopy, she was found to have a strictured stretch of the jejunum about 25 cm from the duodeno-jejunal flexure [Figure 1c]. The proximal jejunum was dilated, while the small bowel distal to the strictured stretch was found to be of normal caliber. The rest of the abdomen was normal. She underwent a totally laparoscopic segmental resection of the strictured stretch, followed by a stapled cum sutured end-to-end anastomosis [Figures 1d, 2a-d, 3a-d]. The small intestinal segmental resection specimen showed the proximal dilated bowel, the strictured stretch and the distal normal caliber bowel [Fig 4 a and b]. She had a smooth initial post-operative recovery. She was kept nil by mouth for 4 days. After she passed flatus, she was started on clear liquids, which she tolerated. On post-operative day (POD) 6, she was started on thick liquids and then, subsequently, on soft diet by POD 8. Her naso-gastric tube was removed on POD 4, abdominal drain on POD 6, and per-urethral catheter on POD 7. By POD 9, she started having nausea with multiple episodes of vomiting, while continuing to pass flatus. A repeat CECT abdomen was then done. It showed a smooth passage of contrast across the anastomosis without a leak. It also reported pulmonary embolism in the visualized part of the lower thorax. Subsequently, a CT pulmonary angiography and bilateral lower limb venous Doppler were performed. These confirmed the bilateral pulmonary embolism along with left lower limb deep venous thrombosis. After this, she was referred to a specialist cardiologist, chest physician, and hematologist. A 2D-echogram revealed mild left ventricular hypertrophy, a left ventricular ejection fraction of 50%, and no significant pulmonary hypertension. Injection Enoxaparin 0.6 ml subcutaneous twice daily was started. This was then replaced with tablet Xarelto (Rivaroxaban) 15 mg BD after 2 days as per the pulmonologist's opinion. The hematologist suspected an exacerbation of anti-phospholipid antibody (APLA) syndrome as the lupus anti-coagulant test

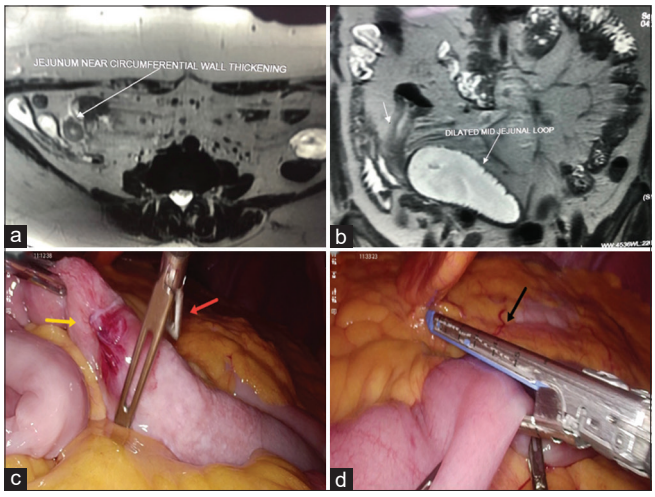

Figure 1: a and b: MRI enterography pictures. a) Strictured proximal small bowel; b) dilated jejunal loop proximal to stricture; c and d: Op. pictures. c) Strictured proximal small bowel segment (yellow arrow) being palpated via tactile feedback by a soft grasper (red arrow); d) proximal small bowel being transected using a linear cutter (black arrow)

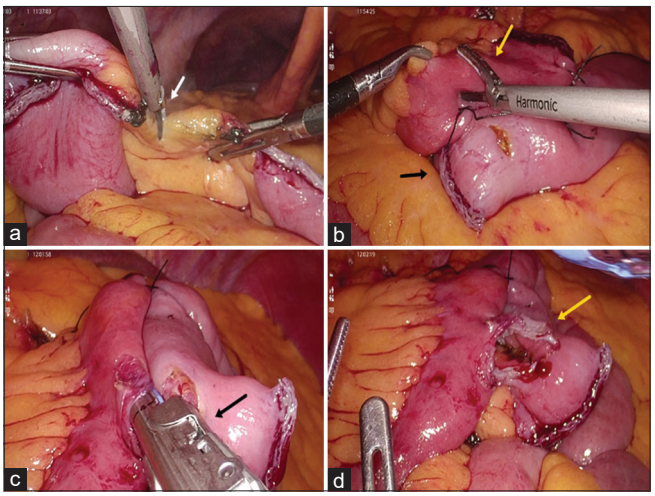

Figure 2: Op. pictures. a) Division of the mesentery using the harmonic scalpel (white arrow) after proximal and distal bowel transaction; b) enterotomies being made with harmonic scalpel (yellow arrow); also seen is the transection staple line (black arrow); c) linear cutter inserted through the enterotomies prior to firing and creation of stapled anastomosis; d) stapled anastomosis created (yellow arrow)

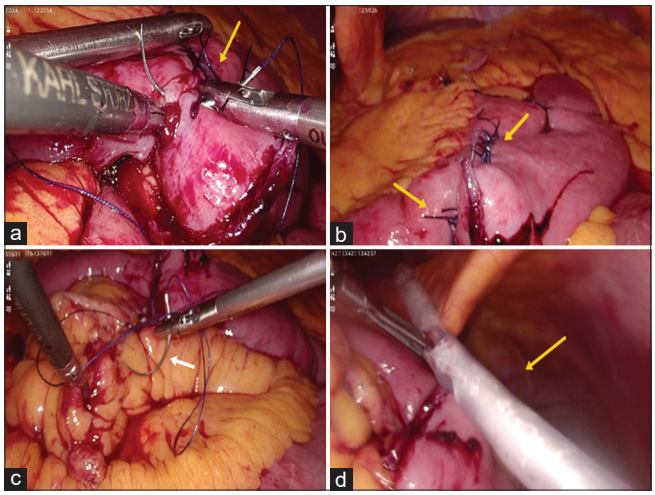

Figure 3: Op. pictures. a) Suture closure of the enterotomy (yellow arrow) in progress; b) stapled cum sutured anastomosis (yellow arrows); c) suture closure of mesenteric defect (white arrow); d) tube drain left in situ (yellow arrow)

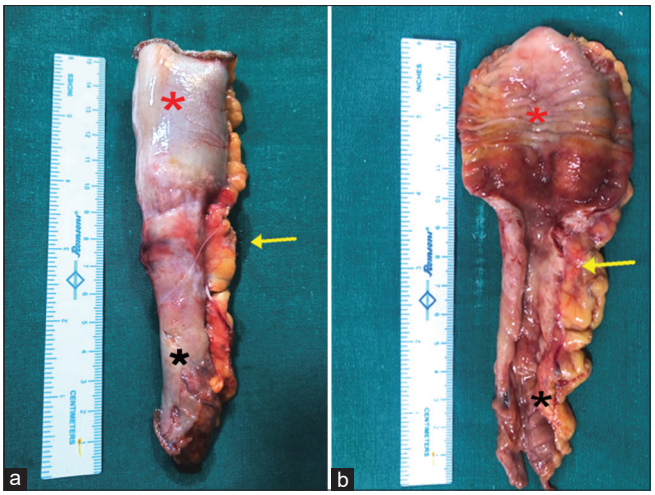

Figure 4: a and b: Operative specimen. a) Resected specimen with the strictured stretch (yellow arrow), proximal dilated jejunum (red asterisk), and distal collapsed jejunum of normal caliber (black asterisk); b) the cut open operative specimen

was positive (DRVVT). Anti-phospholipid antibodies (IgG and IgM) were absent. He advised to confirm the diagnosis after repeat testing for anti-phospholipid antibodies after 3 months and once the patient was off anti-coagulation. Protein C and S levels were unreliable to achieve diagnosis as they were sent in the acute stage of thrombosis (increased levels of activated protein C, i.e. >199.0, decreased levels of protein C, protein S activity, and antithrombin 3). Immunological work-up revealed the presence of anti-neutrophil cytoplasmic antibody (p-ANCA). He advised the patient to be on lifelong anti-coagulation with Warfarin and to target keeping INR between 3 and 4. The patient was discharged from the hospital on POD 12. On her POD 15 out-patient department follow-up visit, all her operative wounds had healed well. Her histopathology evaluation (HPE) report showed features of fibro-inflammatory stricture. The HPE report also mentioned that in view of history of mesenteric vascular thrombosis with possible embolism, the histological picture was consistent with late sequelae of transmural ischemic insult, that is, ischemic ileitis. This raised a suspicion that the surgical problem she faced was probably due to micro-vessel end arterial thrombo-embolism precipitated by aggravation of APLA syndrome, possibly due to the first dose of COVID-19 vaccine which she had received prior to her earlier admission, although her CECT abdomen did not reveal any thrombus in the superior mesenteric artery, which is the main vessel supplying the afflicted territory.

At the time of writing this paper, a telephonic interview was conducted with the patient 19 months after her surgery. She continues to be asymptomatic ever since and continues to be on Warfarin therapy along with medications for her rheumatoid arthritis.

Discussion

In 2020, in an international effort to tackle the COVID-19 pandemic, many countries have developed vaccines against SARS-CoV-2. One such vaccine is the ChAdOx1-S/nCoV-19 vaccine, which is a recombinant, replication-deficient chimpanzee adenoviral vector vaccine developed by Oxford-Astra Zeneca and is being locally manufactured in India by the Serum Institute of India, with the brand name being Covishield®.[4] The vaccine expresses the SARS-CoV-2 spike protein gene, which instructs the host cells to produce the protein of the S-antigen, unique to SARS-CoV-2, allowing the body to generate an immune response and to retain that information in memory immune cells.[5] However, toward the end of February 2021, adverse events related to vaccination were seen to emerge. A significant number of venous thromboses in unusual sites (cerebral venous-sinus thrombosis and splanchnic vein thrombosis) in combination with thrombocytopenia were observed in individuals who received the Astra Zeneca (AZ) vaccine.[6] Investigators found that these thrombotic thrombocytopenic syndromes shared striking similarities with severe heparin-induced thrombocytopenia (HIT), a well-known hyper-coagulable disorder caused by platelet-activating antibodies that recognize multi-molecular complexes like those formed by platelet factor 4 (PF-4) and anionic heparin, triggering prothrombotic events. Greinacher *et al.*[7] have concluded in their study that vaccination with ChAdOx1nCov-19 can result in the rare development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics auto-immune heparin-induced thrombocytopenia, and have named this novel entity vaccine-induced immune thrombotic thrombocytopenia (VITT) to avoid confusion with heparin-induced thrombocytopenia. The definition of VITT is the presence of venous or arterial thrombosis, thrombocytopenia, and auto-antibodies (anti-PF4–polyanion or anti-PF4–heparin antibodies) within 5–30 days of vaccination with either Astra Zeneca or Janssen/Johnson & Johnson COVID-19 vaccines.[8] In fact, VITT shares many similarities with HIT as both disorders are facilitated by PF4 auto-antibodies, leading to platelet activation

and consumption.[9] The epidemiological data illustrated that over 85% of VITT cases occurred in women under 60 years of age, despite higher rates of vaccination among the elderly.[10] While its exact pathogenesis has not been established yet, a recent study demonstrated that ChAdOx1 COVID-19 vaccine induces higher rates of inflammation and platelet activation compared to other COVID-19 vaccines.[11] Therefore, the findings supported the assumption that VITT is most likely to be an auto-immune phenomenon.[12] Previous studies have revealed that SARS-CoV-2 infection could trigger auto-immunity.[13] But, the purported association between COVID-19 vaccine/s and auto-immune phenomena needs further investigative research to firmly establish it.[14] In our patient, VITT was ruled out since her serial platelet counts were within normal limits (she never had thrombocytopenia). The cross-reaction between SARS-CoV-2 proteins and a variety of tissue antigens could lead to auto-immunity against connective tissue and the cardiovascular, gastro-intestinal, and nervous systems.[15] Vojdani and Kharrazian[16] reported that AZ vaccination induced a more pronounced increase in several inflammatory and platelet activation markers compared to mRNA vaccination and that post-vaccination thrombin generation was higher following AZ vaccination compared to mRNA vaccination. Infections act as environmental triggers to cause auto-immune diseases triggered by vaccines, while microbial antigens can elicit cross-reactive immune responses against self-antigens.[14] The immune cross-reactivity triggered by the similarity between certain vaccine components and specific human proteins could render the immune system against pathogenic antigens to attack similar self-proteins in susceptible populations and lead to auto-immune diseases, a process known as molecular mimicry.[17] Vaccination can, therefore, probably induce the formation of antibodies against platelet antigens or auto-antibodies against the phospholipid antigen as part of the inflammatory reaction and immune stimulation. Our case was one such presentation, wherein she received a dose of Covisheild®/ChAdOx1nCov-19 vaccine 1 month prior to her initial presentation. In an effort to find the cause, she was noted to probably have an auto-immune condition, APLA syndrome, which could have been exacerbated by the vaccine she received earlier. This in turn probably caused her progressing thromboses involving the aorta and inferior mesenteric and splenic arteries initially, followed by pulmonary embolism, deep venous thrombosis, and possible small bowel end-arterial thrombosis later.

After review of the literature from a recent few years, it is noted that COVID disease and COVID vaccinations have increased the thrombotic/thromboembolic events. The organ system involved varies significantly in the general population. Patients developed one or more thrombotic events, either venous or arterial, mainly cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis, pulmonary embolism, deep vein thrombosis (DVT), and ischemic stroke.[18] The most common thromboembolic complications are pulmonary embolism, deep vein thrombosis, and rarely mesenteric ischemia. Following prompt diagnosis, patients with mesenteric ischemia should be treated with fluid resuscitation and surgical resection of necrotic bowel with restoration of blood flow to the ischemic intestine.

List of abbreviations

Abbreviation	Definition
COVID-19	Corona Virus Disease
CECT	Contrast-Enhanced Computed Tomography
APLA	Anti-Phospholipid Antibody Syndrome
SARS-CoV2	Severe Acute Respiratory Syndrome – Coronavirus 2
PT/INR	Prothrombin Time/International Normalized Ratio
MRI	Magnetic Resonance Imaging
POD	Post-Operative Day
DRVVT	Diluted Russell Viper Venom Time
p-ANCA	Perinuclear Anti-Neutrophil Cytoplasmic Antibodies
AZ	Astra Zeneca
HIT	Heparin Induced Thrombocytopenia
PF4	Platelet Factor 4
VITT	Vaccine-Induced Immune Thombotic Thrombocytopenia
mRNA	Messenger Ribonucleic Acid
CVST	Cerebral venous sinus thrombosis
DVT	Deep Venous Thrombosis

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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