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Case Report

The Role of the Autopsy During the COVID-19 Pandemic in a Case of Sudden Death with Fatal Hemorrhage and Thrombosis Post chAdox1nCoV-19 VACCINE - A Case Review

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Abstract: This case report describes an elderly patient who experienced sudden death from fulminant pulmonary, gastrointestinal and nasal hemorrhage one day after receiving his second dose of the AstraZeneca ChAdox1nCoV-19 vaccine, during the SARS-CoV-2 pandemic. The patient was PCR negative for SARS-CoV-2, but had thrombocytopenia, erythroblastosis and markedly elevated D-Dimer levels. The clinical diagnoses considered included hypovolemic shock, Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), PCR negative SARS-CoV-2 infection, Vaccine-Associated Enhanced Disease (VAED), Vaccine-induced Covid-19 mimicry Syndrome and Adenovirus induced thrombocytopenia and thrombosis. The autopsy findings revealed diffuse pulmonary hemorrhage, thrombosis of the microvascular system of the lungs, myocardium and kidneys, together with metastatic foamy cell prostate carcinoma to the lung and bone marrow. Disseminated Intravascular coagulation (DIC) secondary to advanced prostate cancer remained a significant differential diagnosis. This case report highlights the complexity of diagnosing (VITT) and the importance of considering other potential causes of thrombocytopenia and thrombosis, including the presence of solid tumors, particularly in elderly patients. The autopsy provided crucial insights into the patient's condition.

Keywords: Sars-CoV-2; Spike Protein; AstraZeneca ChAdox1 nCoV-19 vaccine; Immune Thrombotic Thrombocytopenia Syndrome; Hypercoagulable states; Metastatic Prostate cancer; Micro thrombosis, Thrombocytopenia; Autopsy.

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1. Introduction

The SARS-CoV-2 pandemic began in December 2019 in Wuhan China, leading to widespread morbidity and mortality globally, causing a disease spectrum referred to as COVID-19 [1]. By the time of this case presentation, 187 million persons were infected and 4 million had died from COVID-19 [2]. The emergence of new variants, such as the Delta variant [3], increased the severity of the disease, even affecting those who had received a single dose of the AstraZeneca ChAdOx1 nCoV-19 vaccine. There were seemingly increased morbidity and mortality with each new variant of SARS-CoV-2.

Various emergency vaccines, including those from Oxford, AstraZeneca vaccine; Moderna vaccine; Sinopharm COVID_19; BioNTech; Pfizer vaccine; Janssen/Johnson and Johnson vaccine; and Gam-COVID-Vac [Sputnik V], were developed to provide immunity

against the SARS-CoV-2 [4]. However, these vaccines did not completely prevent infection but rather facilitated milder forms of COVID-19 in vaccinated individuals. Untoward effects accompanied vaccination. Pain at injection sites, fever, lethargy, Bell 's palsy, Guillain-Barré Syndrome, myocarditis, haemorrhages, and the Thrombotic Thrombocytopenic syndrome, were reported post SARS-CoV-2 vaccinations [5-9].

Severe breakthrough infections led to recommendations for booster vaccinations [10]. A Vaccine Breakthrough Infection is defined as the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected more than fourteen days after receiving all recommended doses of an FDA-authorized COVID-19 vaccine. Injectable COVID-19 vaccines produce circulating IgM and IgG antibodies but very little IgA antibodies at the entry points of SARS-CoV-2. A nasal vaccine generating protective IgA antibodies at the sites of entry in the upper airways around Waldeyer's ring [11, 12] would have been more effective. The case report describes a patient who received two doses of the AstraZeneca ChAdOx1 nCoV-19 vaccine and developed thrombocytopenia, fatal gastrointestinal, and pulmonary haemorrhage one day after the second dose. The patient was PCR negative for SARS-CoV-2. The clinical and pathological details of this case are discussed based on the available scientific information on COVID-19, following the autopsy.

2. Case Report

The patient, a 72-year-old individual, presented to the hospital with a one-week history of worsening shortness of breath, persistent cough, hemoptysis, chest pain, generalized weakness, and decreased appetite. The shortness of breath was experienced both at rest and on exertion, and the chest pain was central and non-radiating. The patient had no known chronic diseases except for lethargy over the past year. The patient had received the first dose of the AstraZeneca COVID-19 vaccine in April 2021 and the second dose in June 2021, one day before presenting at the hospital.

Upon examination, the patient exhibited mild icterus, cyanosis at the extremities, and pallor of the mucous membranes. Ecchymosis was noted on the right side of the neck, and the skin showed signs of dehydration. The patient had tachycardia [110/min], blood pressure of 140/68 mm Hg, respiration rate of 32/min, and a temperature of 36.8°C. The breathing was labored, with blood-stained nostrils, harsh breath sounds, and diminished air entry in the lower and mid-zones of both lungs. The abdomen was non-tender, with no palpable organs or masses, and bowel sounds were audible. The patient was alert and fully oriented, with mild objective weakness in all limbs and a negative Babinski reflex. Pulse oximetry while breathing room air showed an SPO_2 of 77%. Continuous intravenous crystalloids and oxygen via nasal cannula were administered, resulting in an improvement in SPO2 to 89-96%. Table 1 summarizes the laboratory results and reference ranges for complete blood count, renal function, and liver function tests.

Table 1. Showing laboratory results with reference range values for the complete blood count, Renal function and Liver function tests.

Test	Result	Reference Range
White Blood Cell Count	4.47×10^3 /μL	[4.00—10.00]
Red Blood Cell Count	3.07×10^6 /μL	[4.50—5.50]
Hemoglobin	8.70 g/dL	[13.0—17.0]
Hematocrit	27.30%	[40.0—50.0]
Mean Corpuscular Volume	88.90 fL	[83.0—101.0]
Mean Corpuscular Hemoglobin Concentration	31.90 g/dL	[31.50—34.50]
Platelet Count	20×10^3 /μL	[150.0—410.0]
Urea	62.0 mg/dL	[16.6—48.0]
Blood Urea Nitrogen	29.0 mg/dL	[8.0—23.0]

Creatinine	1.40 mg/dL	[0.70—1.20]
Sodium	133.0 mmol/L	[136.0—145.0]
Potassium	4.93 mmol/L	[3.40—4.50]
Chloride	98.70 mmol/L	[98.0—107.0]
Albumin	4.00 g/dL	[3.50—5.20]
Total Protein	7.20 g/dL	[6.40—8.30]
Alanine Aminotransferase	13.0 U/L	[0.0—41.0]
Aspartate Aminotransferase	54.0 U/L	[0.0—40.0]
Direct Bilirubin	0.54 mg/dL	[0.0—0.20]
Total Bilirubin	1.65 mg/dL	[0.0—1.20]
Gamma-Glutamyl Transferase	57.0 U/L	[0.0—60.0]
Alkaline Phosphatase	122.0 U/L	[40.0—129.0]
Calcium	9.40 mg/dL	[8.80—10.20]
Phosphorus	4.60 mg/dL	[2.50—4.50]
Magnesium	2.00 mg/dL	[1.60—2.40]
Prothrombin Time	14.70 s	[10.0—12.0]
Partial Thromboplastin Time	26.10 s	[28.0—32.0]
International Normalized Ratio	1.29	[1.50—2.50]
D-Dimer	2500 ng/mL	[200—500]

The blood film of the patient showed polychromasia with increased reticulocytes and diminished platelets. Unfortunately, the PF4 "HIT" (Heparin-Induced Thrombocytopenia) ELISA test was unavailable. A nasopharyngeal swab test for SARS-CoV-2, performed on admission using the Xpert Xpress SARS-CoV-2 real-time RT-PCR test assay, returned negative results. Imaging studies revealed significant findings. The chest X-ray showed bilateral pulmonary infiltrates with consolidation, while the CT chest scan demonstrated bilateral patchy and diffused alveolar infiltrates, particularly in the lower lobes, along with bilateral atelectasis in the basal region.

Tragically, immediately following the CT scan, the patient suffered a cardiopulmonary arrest and could not be resuscitated despite several attempts. The clinical diagnoses considered were PCR-negative COVID-19 with pulmonary embolism, dehydration, and Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT).

2.1 Autopsy Findings

The autopsy, performed three days after the patient's demise, revealed several significant findings regarding the patient's condition. The body exhibited pallor, mild icterus, cyanosis of the extremities, and ecchymosis on the right side of the neck. Lividity was present on the back. The brain was edematous, weighing 1520 g, with no evidence of sagittal sinus thrombosis, cerebral hemorrhage, or infarction. Both lungs were markedly heavy; left: 1480 g (reference: 583 ± 216 g), right: 1640 g (reference: 663 ± 239 g). They were consolidated and displayed a dark hemorrhagic-red appearance. Multiple small white nodules were observed on both pleural surfaces. Pulmonary embolism was identified in peripheral vessels, but no bronchogenic tumor was found. The paratracheal and bronchial lymph nodes were not enlarged.

The heart had an unremarkable epicardial surface, with all three coronary arteries patent and free from atheromatous plaques. The heart weighed 420 g (reference: 365 ± 71 g) and showed a focal area of acute myocardial infarction or injury on the posterior wall of the left ventricle. The left ventricular wall measured 10 mm in thickness (reference:

10.5–12.5 mm). The mitral valve circumference measured 130 mm (reference: 92–98 mm); the aortic valve, 80 mm (reference: 81–85 mm); the tricuspid valve, 110 mm (reference: 114–118 mm); and the pulmonary valve, 80 mm (reference: 72–75 mm). The right ventricular wall measured 2 mm (reference: 3.5–4.0 mm).

The spleen was enlarged and congested, weighing 300 g (reference: 156 ± 87 g). The liver weighed 2040 g (reference: 1677 ± 396 g) and appeared pale. Approximately 400 mL of blood was found in the stomach, with no evidence of peptic or gastric ulcers or neoplasms. Blood was also present in both the small and large intestines, without any detectable tumors. The kidneys were pale and edematous, weighing 160 g (left; reference: 160 ± 41 g) and 120 g (right; reference: 162 ± 39 g). No renal tumors were observed. Both adrenal glands weighed approximately 15 g each (reference: 8.3–16.7 g) and appeared structurally unremarkable. Reference ranges for organ weights were based on adult autopsy standards [13].

The provisional diagnosis included hypovolemic shock secondary to gastrointestinal and pulmonary hemorrhages due to thrombocytopenia, pulmonary embolism, and metastatic lung cancer. Acute myocardial infarction with left ventricular failure was also identified. Considering the recent administration of the AstraZeneca ChAdOx1 nCoV-19 vaccine, vaccine-induced immune thrombocytopenia with hemorrhage and microthrombosis was considered.

2.2 Histology

The pathology of the lung revealed changes like those observed in COVID-19. There was thrombosis in the microvascular circulations of the pulmonary and bronchial tree, with thrombus formation originating within the micro vessel's walls, between the endothelial cells and the basement, rather than within their lumens. Fibrin microthrombi were present within alveolar capillaries, and the interstitium was widened with fibrin deposits. Fibrin was also seen in alveoli in focal areas (Figure 1). There was pulmonary thromboembolism of large and medium sized pulmonary vessels. Of note, there were thrombosis within the Vasa externa and interna of the large and medium sized pulmonary vessels (Figure 2).

Fibrin deposits were also present in the adventitia of the large and medium sized pulmonary vessels, and peribronchiolar region. There was no proliferation of alveolar type 1 or type 2 pneumocytes. Areas of secondary atelectasis and emphysematous changes were also present. There was also diffuse alveolar hemorrhage, and metastatic foamy cell prostate carcinoma on the pleura and in small pulmonary vessels and alveoli (Figure 3). There were no inflammatory cellular infiltrates within alveoli.

The pathology of the myocardium revealed changes consistent with Covid-19 pathology. Thrombosis was observed in microvascular circulation, originating within the walls of the vessels between the endothelial cells and the basement membrane. At the posterior wall of the left ventricle, where gross myocardial infarction/injury was seen at autopsy, there was rupture of vessels of the thrombosed microvascular circulation and accumulation of fibrin among the myocardial fibres.

Notably there were no changes typically associated with acute myocardial infarction such as waviness of cardiac myocytes, contraction band necrosis or acute inflammatory cell infiltrate. These were indicative of the COVID-19 pathology seen in the areas represented macroscopically as myocardial infarction/injury (Figure 4).

Microscopic examination of the kidneys revealed microthrombosis within the renal interstitial vessels. The spleen showed evidence of haemorrhage, congestion of the sinusoids, and areas of extramedullary haematopoiesis. In the liver, sinusoidal congestion and extramedullary haematopoiesis were also observed (Figure 5). Additionally, small clusters of prostatic carcinoma cells were identified within the hepatic sinusoids. Examination of the gastrointestinal tract revealed diffuse haemorrhage throughout all levels of the system.

Figure 1. H&E x200 showing alveolar capillary thrombosis (A), alveolar haemorrhage (B).

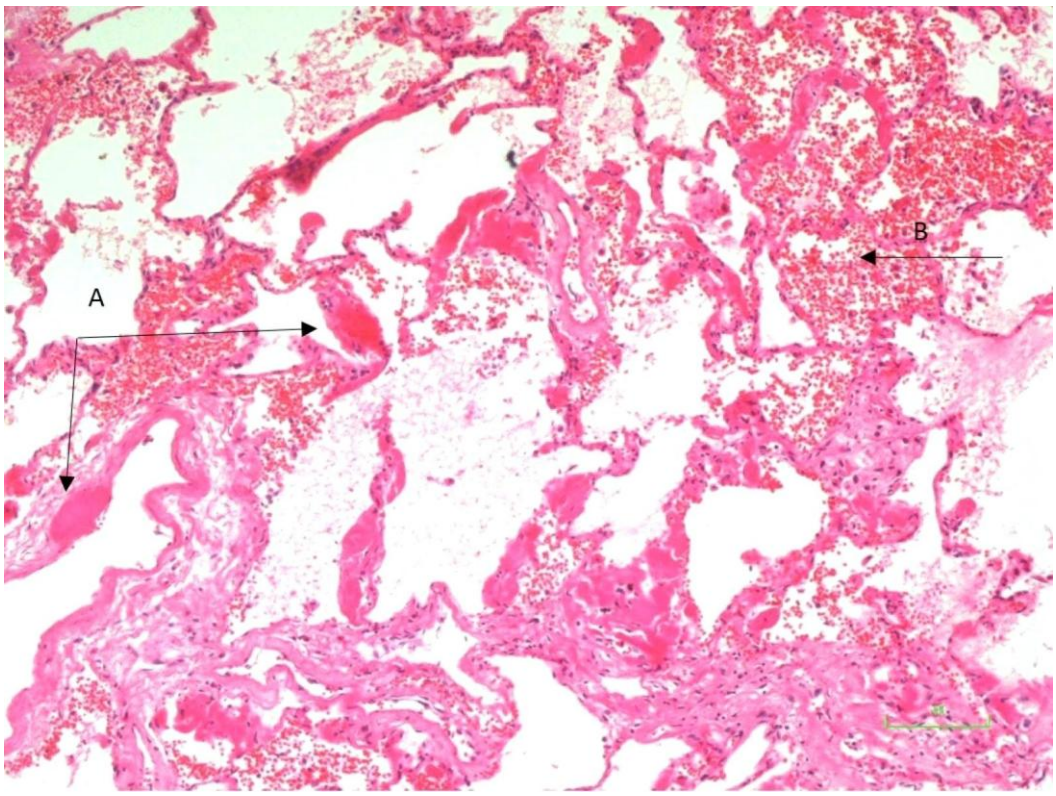


Figure 2. H&E x200 shows tumour emboli in small pulmonary artery [A] and thrombus of vasa interna [B] and externa [C] together with alveolar and capillary metastatic carcinoma [D].

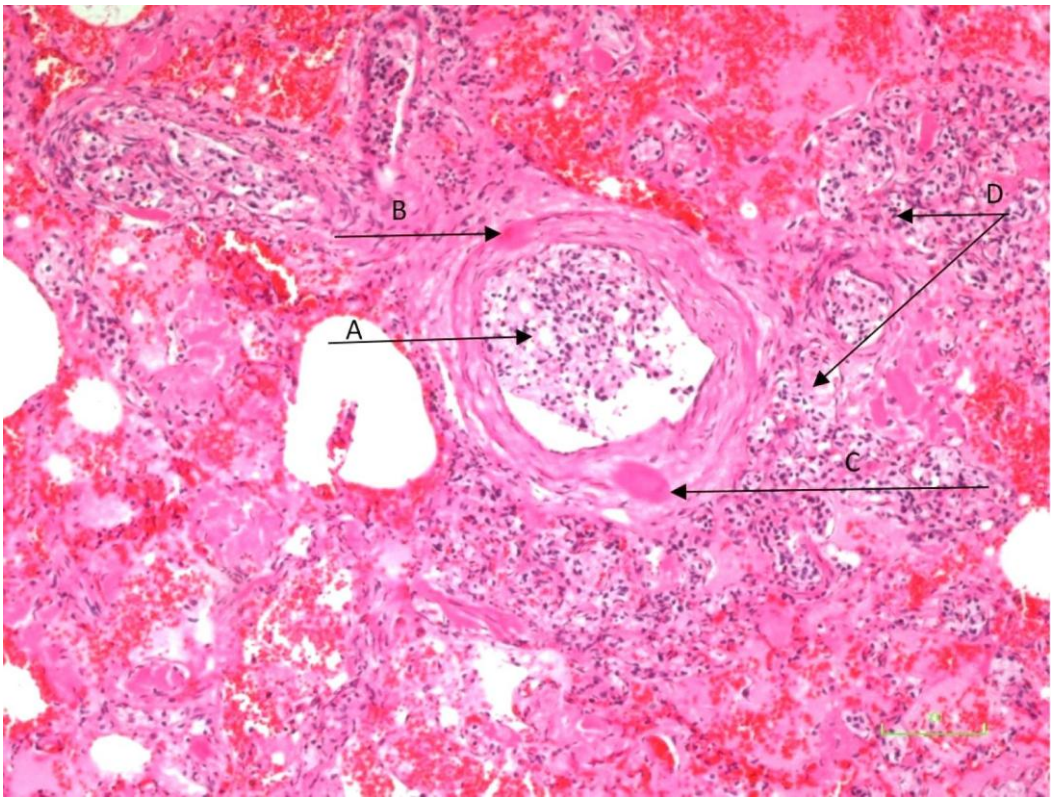


Figure 3. H&E x 200 shows fibrin thrombosis of alveolar capillary (A), alveolar haemorrhage (B) and metastatic cancer in alveoli (C) and alveolar capillaries (D).

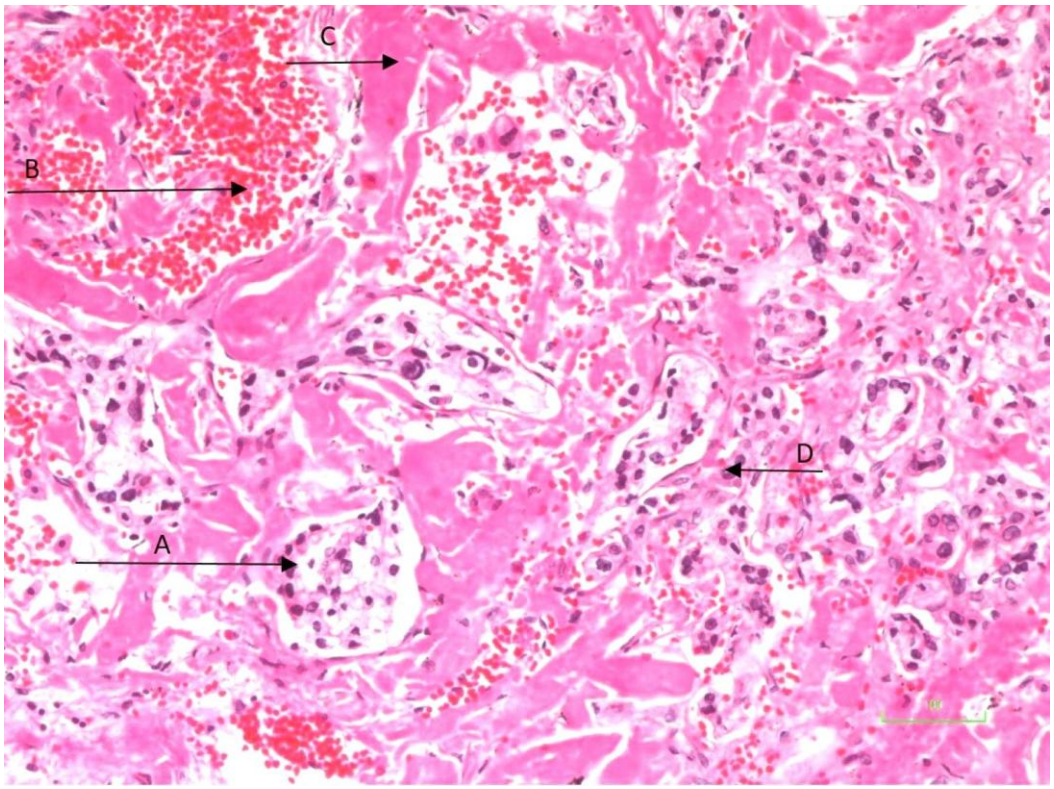
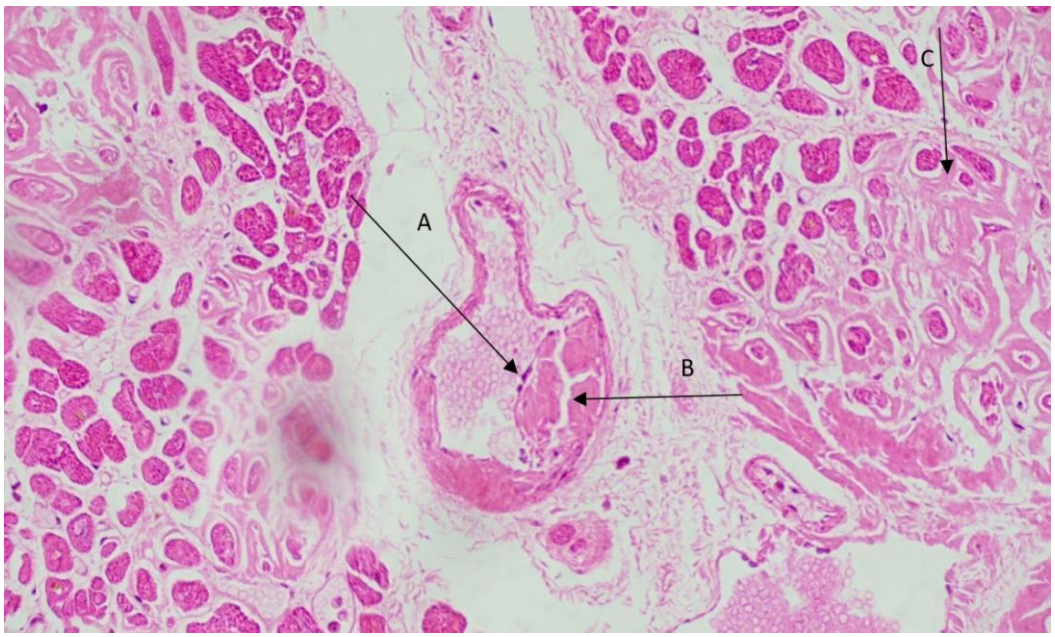


Figure 4. H&E x 200 microscopy in the posterior wall of the left ventricle of gross myocardial infarction/injury see at autopsy showing myocardium venule endothelial cells (A), thrombus in its wall (B) between endothelial cells and the basement membrane, and fibrin in the myocardial interstitium encasing myocardial fibres (C).



Sections from the rib showed almost complete replacement of the bone marrow by foamy cell prostatic adenocarcinoma, with a few isolated foci of normoblasts. Megakaryocytes were not identified. Immunohistochemical staining for prostatic carcinoma was

positive for prostate-specific antigen (PSA) (Figures 6 and 7). Examination of the brain revealed no evidence of cerebral venous sinus thrombosis; however, cerebral oedema and congestion were present, along with focal areas of hemorrhage.

Figure 5. H&E x200 showing liver with extramedullary haematopoiesis (A).

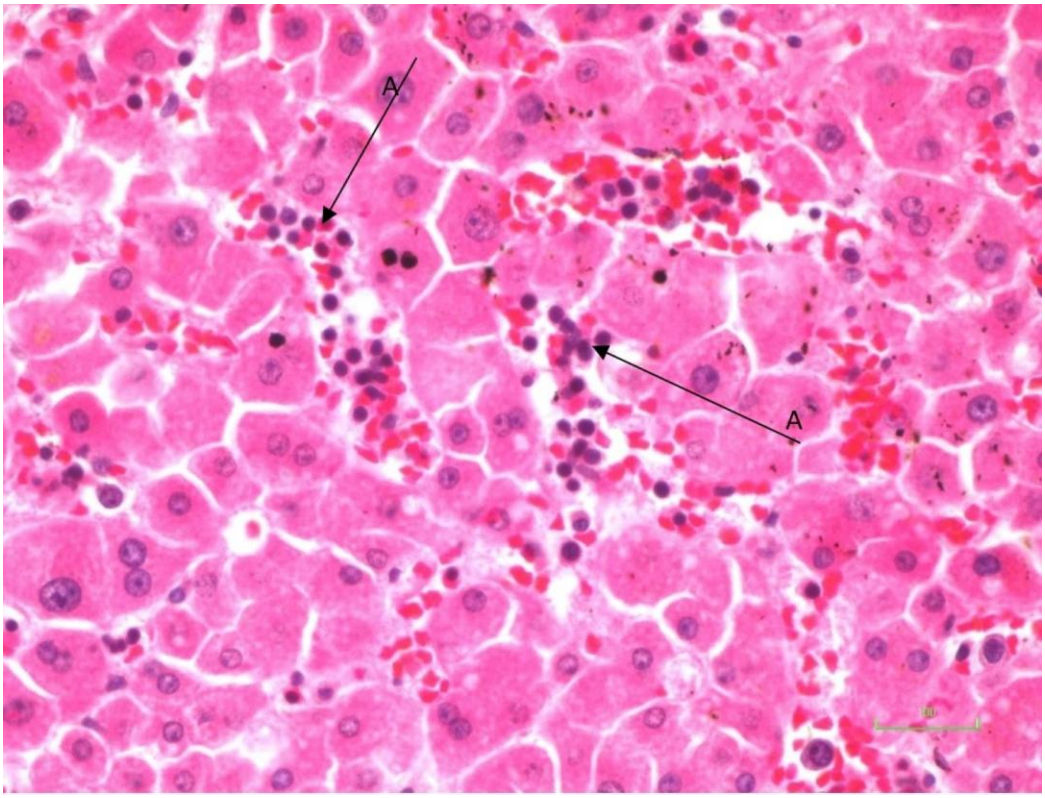


Figure 6. H&E x200 showing bone marrow replacement with metastatic cancer (A).

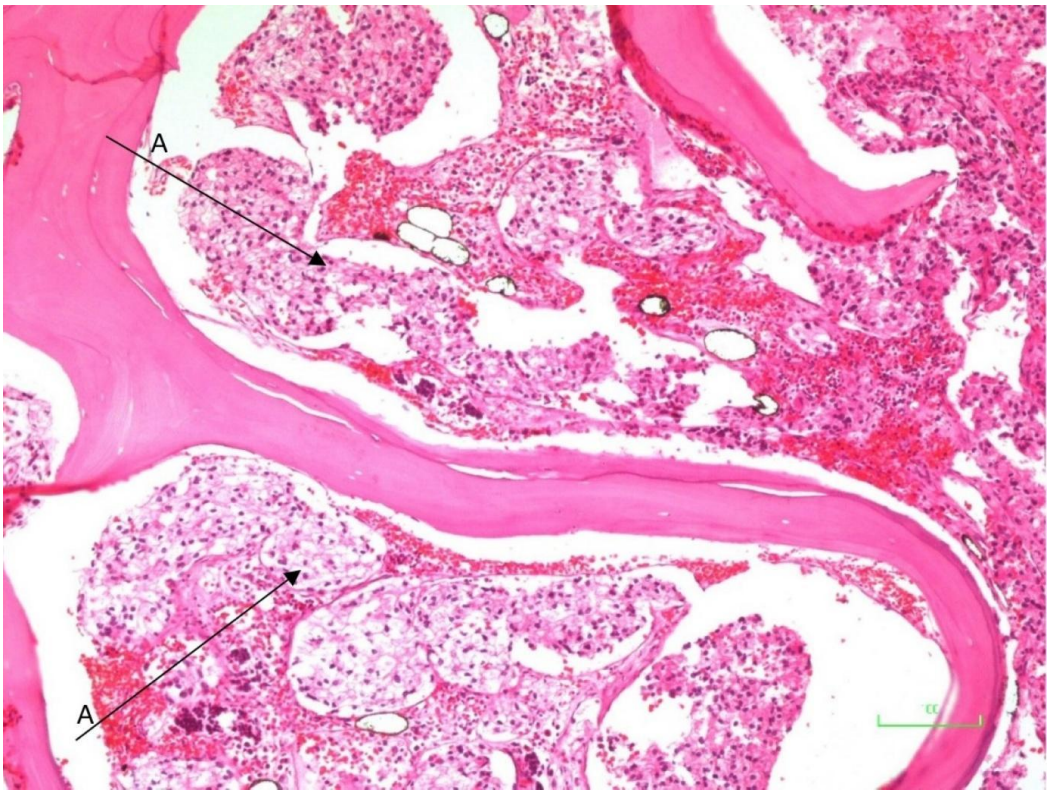
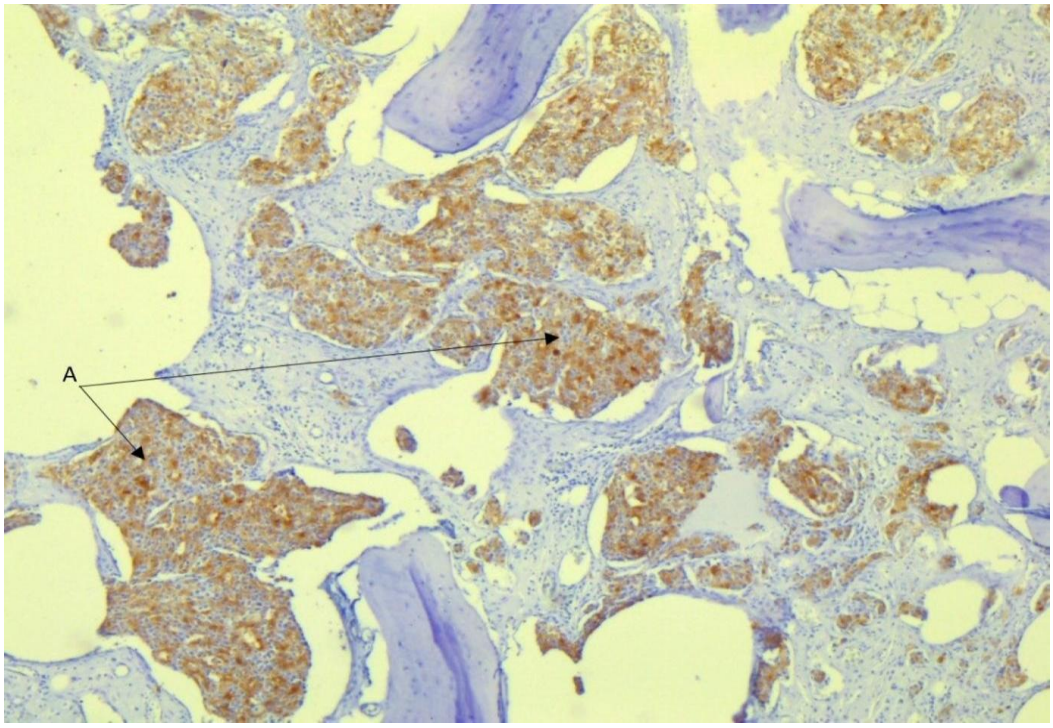


Figure 7. PSA x 200 showing cancer in bone marrow staining positive for Prostate Specific antigen (A).



3. Discussion

The autopsy findings identify significant pathological changes in the patient's lungs. The presence of fibrin deposits in the adventitia of large and medium-sized pulmonary vessels, as well as in the peribronchiolar region, suggests extensive vascular involvement. The absence of proliferation of alveolar type 1 or type 2 pneumocytes indicates that there was no regenerative response in the alveolar epithelium. Additionally, the areas of secondary atelectasis and emphysematous changes point to compromised lung function. The diffuse alveolar haemorrhages and metastatic foamy cell prostate carcinoma found on the pleura and in small pulmonary vessels and alveoli further highlight the severity of the patient's condition. The lack of inflammatory cellular infiltrate within the alveoli suggests that the haemorrhages and metastatic deposits were not accompanied by an inflammatory response.

Several other important issues common to SARS-CoV-2, COVID-19, the Adenovirus-vectored vaccine, and advanced prostate cancer were highlighted in this case. The combination of COVID-19 pulmonary and cardiac pathology, acute pulmonary and gastrointestinal haemorrhage, and metastatic prostate cancer to the lung and bone marrow, all in relation to the administration two doses of the AstraZeneca ChAdOx1 nCoV-19 vaccine, presented a unique and challenging scenario of a complex interplay of various medical conditions. The differential diagnoses associated with this case are presented.

3.1 Metastatic Prostate Cancer, Hypercoagulable States, Thrombotic Thrombocytopenic Purpura, Tumor-Induced Immune Thrombocytopenia (VITT), Pulmonary Tumor Thrombotic Microangiopathy, and Disseminated Intravascular Coagulation (DIC)

The patient had metastatic prostate cancer that infiltrated the bone marrow, leading to anemia and thrombocytopenia. This infiltration caused extramedullary hematopoiesis in the liver and spleen as a compensatory mechanism [14]. The metastatic prostate cancer to bone marrow was gradual and would have been infiltrating over a protracted period, producing anemia, and thrombocytopenia and the patient's year-long lethargy [15,16]. Barisas et al. [17] in their study of "Extramedullary hematopoiesis in cancer" discovered

factors stimulating the development of myeloid cells that suppress the immune system and aid tumor growth. This suggests potential new approaches to cancer.

Prostate cancer is the second most common cancer occurring in the male population worldwide [18]. There is a high prevalence of prostate cancer among Tobagonians in the West Indies [19, 20]. The growth is insidious and is often diagnosed at an advanced stage with the use of the serum PSA or at autopsy as with the case in discussion. Hypercoagulable states exist in patients afflicted with cancers which can result in life-threatening pulmonary thromboembolism. Thrombotic Thrombocytopenia Purpura (TTP) is one of the manifestations of this hypercoagulable state. Metastatic prostate cancer to bone marrow mimicking Thrombotic Thrombocytopenia Purpura (TTP) has been reported in the literature. The case in discussion is very much like that reported by Griffin and Jaglal [21] in which metastatic prostate cancer presented as TTP.

The peripheral blood film showed erythroblastosis, and diminished platelets which pointed to bone marrow stress. The immunocytochemistry on the bone marrow metastases revealed prostate cancer as the primary tumor. This patient had advanced prostate cancer and had the AstraZeneca vaccination. His metastases to bone marrow, which was discovered at autopsy, was a major factor contributing to his thrombocytopenia and the subsequent bleeding diathesis.

Immune thrombocytopenia has been associated with solid tumors like prostate carcinoma [22] which responds to corticosteroid therapy. Clinicians should be aware of anemia and decreasing platelet counts as early signs of immune-related thrombocytopenia in patients with solid tumors [23]. In such patients with tumors induced immune thrombocytopenia, the risk of bleeding, arterial thromboembolism, or venous thrombosis is increased. Therefore, in elderly patients receiving the AstraZeneca COVID-19 Vaccine who present with thrombocytopenia, it is crucial to seek and exclude solid tumors along with known causes of thrombocytopenia before diagnosing Vaccine Induced Immune Thrombotic Thrombocytopenia [24-26].

The patient also had metastatic prostate cancer in the lungs, leading to Pulmonary Tumor Thrombotic Microangiopathy (PTTM) [27, 28], which is associated with hypoxemia, acute pulmonary decompensation, and pulmonary hypertension. The syndrome is rapidly fatal and offers challenges in antemortem diagnosis, especially within the context of COVID-19 pulmonary pathology [29,30]. Disseminated intravascular coagulation, often linked to metastatic carcinomas, may also explain the microvascular thrombosis, thrombocytopenia, and hemorrhage observed in the lung microscopy of the patient in discussion [31].

COVID-19 can indeed present with a variety of pathologies, and this complexity is often heightened in elderly patients who may have multiple underlying health conditions. Clinicians need to be vigilant and consider the possibility of coexisting pathologies when diagnosing and treating elderly patients with COVID-19. This approach can help ensure comprehensive care and better outcomes for this vulnerable population.

3.2 SARS-CoV-2 spike protein. ChAdOx1nCoV-19 vaccine spike protein. Vaccine Induced Immune Thrombotic Thrombocytopenia

The Sars-CoV-2 virus responsible for COVID-19 causes its pathogenesis upon entry into the host upper airway by its spike protein (S protein) interaction with ACE2 receptor sites on target cells [32]. Viral replication in the upper airway epithelium, viremia, and cytokines produced and released into the circulation during spike protein/ACE2 interaction, trigger endothelial cell dysfunction. This dysfunction causes microvascular leakiness, with plasma interacting with subluminal pericytes, generating systemic thrombosis of the microvascular systems, which is the hallmark of COVID-19 [33, 34].

Vaccines against SARS-CoV-2 were therefore designed to produce native S protein (spike protein) as the main agent, to induce immunity against the SARS-CoV-2 [35]. The AstraZeneca coronavirus vaccine known as ChAdOx1 nCoV-19 is a vaccine developed against SARS-CoV-2 by the University of Oxford partnered with the British-Swedish company AstraZeneca. The Oxford-AstraZeneca team used a modified version of a chimpanzee adenovirus, known as ChAdOx1 and modified its genetic DNA material to produce the spike protein of SARS-CoV-2. This modified adenovirus when injected into the human host produces spike proteins of SARS-CoV-2 against which immunity is produced. [36,37].

A large clinical trial showed the vaccine offered strong protection with an overall efficacy of 70·4% after two doses and protection of 64·1% after at least one standard dose, against symptomatic disease, with no safety concerns. However, little protection is provided against viral replication and shedding in the upper airways due to the lack of a vibrant local IgA immune response, indicating a risk of transmission of virus from vaccinated individuals [37,38]. There have been untoward effects both mild and severe that have been reported after administration of this vaccine. Pain at the injection site, tiredness, headache, muscle pain, fever and chills are mild temporary side effects which last for one to two days post vaccination. Thrombocytopenia with bleeding symptoms following Pfizer and Moderna SARS-CoV-2 vaccination have been reported [39]. Thrombosis with Thrombocytopenia Syndrome (TTS) or (VITT) a most severe side effect has been reported following the administration of ChAdOx1 nCoV-19 vaccine. This syndrome classically occurs around 42 days post COVID AstraZeneca vaccination and produces arterial or venous thrombosis often cerebral or abdominal, thrombocytopenia and a positive PF-4 "HIT" [heparin-induced thrombocytopenia] ELISA. The incidence of this complication is rare and serious outcomes including death may occur [40-42].

Severe headaches, visual changes, abdominal pain, nausea and vomiting, back pain, dyspnea, leg pain and/or swelling, petechiae, easy bruising or bleeding may herald Thrombosis with Thrombocytopenia Syndrome post vaccination. The patient in discussion presented with some clinical features like those of Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination, with a one-week history of shortness of breath, cough, chest pain, generalized weakness, decreased appetite, hemoptysis, nasal bleeding, ecchymosis on the side of his neck, and an elevated D-Dimer. These clinical features together with thrombocytopenia and massive pulmonary and gastrointestinal hemorrhage occurring 65 days post AstraZeneca ChAdOx1 nCov-19 first dose vaccination, provided clinical suspicion of the vaccine-related Thrombotic Thrombocytopenia Syndrome, although the PF4 "HIT" ELISA test for VITT was not done because of its unavailability. Moderate to severe thrombocytopenia and thrombotic complications at unusual sites beginning 1 to 2 weeks after vaccination against SARS-CoV-2 with ChAdOx1 nCov-19, suggest a disorder that resembles severe heparin-induced thrombocytopenia [43]. This prothrombotic disorder occurs because of platelet activating antibodies against platelet factor 4 (PF4).

The main post-vaccination features of the VITT are the occurrence of venous thrombosis in unusual sites (cerebral and abdominal) and the concomitant presence of bleeding symptoms associated with severe thrombocytopenia, often accompanied by laboratory signs of consumptive coagulopathy with low plasma fibrinogen and hugely increased levels of D-dimer. Pomara et al. [44] in their manuscript "Postmortem Findings in vaccine induced thrombotic thrombocytopenia" showed that vascular thrombotic occlusions occurred not only in the brain and gut but also in the microcirculation of multiple organs including the lungs, heart, liver kidney and limbs, which was like those observed in the case in discussion. Kowarz et al. [45] have proposed an immune-based patho-mechanism for vaccine induced immune thrombotic thrombocytopenia following vaccination with adenoviral vector-based vaccines. Based on their study, thrombosis may occur in any site in the human body where ACE2 receptors are expressed, following vaccination with adenoviral vector-based vaccines.

While Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination (VITT) was considered in the diagnosis in the case in discussion, the findings of metastatic prostate cancer to the lung and bone marrow at autopsy were significant. These findings provided an explanation for the thrombocytopenia and thrombosis of the microcirculation of the lung observed in the patient. The autopsy in this case served as a major diagnostic tool, shedding light on the underlying cause of the patient's symptoms.

3.3 Adenovirus-Vectored vaccine, spike protein, thrombosis and thrombocytopenia

There are many emerging observations and theories concerning adenovirus-vectored vaccine, its spike protein and post vaccination adverse events. The Adenovirus-vectored vaccine's spike protein is designed to invoke immunity against SARS-CoV-2 [36, 37]. Recombinant spike protein has been identified in the blood of vaccinated individuals, suggesting that the vaccine's spike protein can be released into the blood circulation and cause transient adverse effects. Theoretically it may also cause pathology like that of SARS-CoV-2, known as the "spike effect" [46-48]. This includes the possibility of microvascular thrombosis due to the spike protein interacting with ACE2 cells.

Zhang et al. [49] postulated after their study that SARS-CoV-2 binds to ACE2 receptor sites on platelets to enhance thrombosis in COVID-19. It is likely then that SARS-CoV-2 or its spike protein can directly interact with platelets and activate them, possibly being the primary mechanism for thrombotic complications in moderate to severe COVID-19 or in VITT. Chamling et al. [50] in their article described three patients with myocarditis/ myocardial injury post Covid-19 vaccination., using Cardiovascular Magnetic Resonance and other modalities. None of these patients were COVID-19 positive. The distribution of the myocarditis/myocardial injury observed was “non-ischaemic”, and like the pattern seen in ‘The Cardiac pathophysiology of Covid-19’ which is characterized by thrombosis of the microvascular circulation of the myocardium [34] [Figure 4]. A possible mechanism for this myocardial injury seen in COVID-19, is due to interaction between the SARS-CoV-2 Spike protein and cardiac ACE2 receptors on microvascular pericytes [51] leading to thrombosis of the myocardial microvascular system producing “non-ischemic type injury” to myocytes.

Brogna et al. [52] have been able to detect recombinant spike protein in the blood of individuals vaccinated against SARS-CoV-2. Devaux et al. [53] postulated that after Covid-19 vaccination a significant quantity of Vaccine Spike protein could transiently be released into the blood circulation and thereby leads to transient adverse effects of the vaccine by a mechanism of molecular mimicry [48]. Kowarz et al. [45] in their research provided evidence for the occurrence of splice reactions in adenovirus-based vaccines resulting in secretion of truncated Spike variants providing a potential mechanism underlying thromboembolic events that have been reported following adenovirus-based vaccination. Based on their splicing data, membrane-anchored and secreted soluble Spike protein variants are produced after vaccination. Secreted Spike protein variants are disseminated throughout the vascular system and may concentrate at endothelial cells expressing the ACE2 at their surface. These ACE2-bound Spike will then become a target of anti-Spike antibodies, generated after vaccination with the potential to result in antibody-dependent cell-mediated cytotoxicity and complement dependent cytotoxicity - and/or CDC-mediated inflammatory reactions both of which could serve as starting points for thrombus formation. By these means thromboses may occur in any site of the human body where ACE2 is expressed.

It is possible that the myocarditis/myocardial injury that Charmling et al [50] and the micro thrombosis observed by Pomara et al. [44] in their postmortem findings in vaccine-induced thrombotic thrombocytopenia observed in their patients post Covid-19 vaccination, was due a “Vaccine-induced Covid-19 mimicry syndrome “as postulated by Kowarzet al. [45]. Theory and evidence work together to understand scientific discoveries: evidence from observations and experiments provides the foundation, while theories offer comprehensive explanations that are repeatedly tested and modified based on new

evidence. This process is dynamic, as evidence can support, contradict, or lead to the refinement of theories, ensuring scientific knowledge is both reliable and self-correcting.

Continuing research and surveillance are essential for understanding the underlying mechanisms of these adverse events post Covid-19 vaccination and developing strategies to minimize their occurrence [54]. The question remains unanswered as to what role, if any, did the two doses of ChAdox1nCoV-19 vaccine played in the thrombosis of the microvascular system of the patient in discussion. This theory of the pathophysiology in Vaccine-induced COVID-19 mimicry syndrome does not in any way invalidate the usefulness of the AstraZeneca vaccine in COVID19, for the vaccine has saved many more lives than cause adverse side effects. These mechanisms highlight the complexity of vaccine-induced thrombosis and the need for ongoing research to fully understand and mitigate these adverse events [55].

Thrombocytopenia has been consistently reported following the administration of adenoviral gene transfer vector [56-58]. Adenovirus triggers platelet activation and promotes blood clotting [59]. In laboratory animals, intravenous administration of recombinant Adenoviruses causes thrombocytopenia, anemia and erythroblastosis in laboratory animals [60]. Thrombocytopenia, anemia, extramedullary hematopoiesis and erythroblastosis were noted in our patients. It is postulated that von Willebrand Factor (VWF0 and P-selectin are critically involved in a complex platelet-leukocyte-endothelial interplay, resulting in platelet activation and accelerated platelet clearance by the reticuloendothelial system, resulting in thrombocytopenia, following adenovirus administration [58].

The ChAdOx1 nCoV-19 vaccine (AZD1222) contains the replication-deficient simian adenoviral vector ChAdOx1 [61]. Administration of adenovirus-vectored vaccines has been associated with rare but significant hematologic effects, including thrombocytopenia and thrombosis. In this case, the ChAdOx1 vector may have contributed to the patient's thrombocytopenia, thrombosis, and erythroblastosis. Further research is warranted to investigate potential associations between adenoviral-vectored vaccines and hematologic abnormalities such as thrombocytopenia, erythroblastosis, and anemia.

3.4 False negative PCR Xpert Xpress test for SARS-CoV-2

Although the patient in discussion had a negative COVID-19 nasopharyngeal swab PCR Xpert Xpress test, the clinical picture on presentation and the pulmonary, renal and cardiac thrombotic microangiopathy seen at autopsy strongly suggested that the patient had COVID-19. The thrombosis of the microvascular systems with thrombosis originating between the endothelial cells and the basement membrane and not from within the vascular lumen is the hallmark of Covid-19 which was demonstrated in the pathological findings in the patient in discussion [62]. False negative reverse transcriptase chain reaction test results, in the presence of strong clinical, radiological, and pathological evidence of COVID-19 have been reported. This may occur because of poor sampling, viral load, and the sensitivity of the PCR test [63-67].

The diagnosis of COVID-19 can be made with great accuracy with the use of CT scanning. The CT scan, if used with the clinical presentation and SARS-CoV-2 serological testing, is most accurate and eliminates false positivity in those COVID-19 cases that are PCR negative [68]. It therefore begs the question whether the patient in discussion had PCR Negative COVID-19.

3.5 Coexistence of other viral infections during the SARS-CoV-2 pandemic

The PCR Xpert Xpress Sars-CoV-2 molecular rapid test has a specificity and sensitivity of 100%, hence its use in diagnosing COVID-19, and is not sensitive to other Corona viruses. [69,70] However it is interesting to note that Corona Virus 229E has been associated with thrombotic microangiopathy in the lungs, kidneys and other organs, during the COVID-19 pandemic. This raises the possibility that another coronavirus or virus might

have been responsible for the micro thrombosis in the patient who tested negative using the PCR Xpert Xpress Sars-CoV-2 test [71, 72].

The patient had the first vaccination against COVID-19 in April 2021 and his second dose of the AstraZeneca vaccine 65 days afterwards in June 2021. He presented to the hospital one day after his second dose of the vaccine and died on the day of presentation. The patient's clinical presentation suggested a possible COVID-19 infection contracted in June 2021, about seven to ten days before hospital admission. What role, if any, did the AstraZeneca ChAdox1 vaccine play in pulmonary, renal and cardiac micro thrombosis in the case in discussion remains unanswered. This highlights the complexity of diagnosing conditions in the context of COVID-19 pandemic and vaccination, where symptoms can overlap and confound the clinical picture.

3.6 Breakthrough infections amongst vaccinated patient during COVID-19

During the presentation of the patient in 2021, a second wave of COVID-19 affected citizens of Trinidad and Tobago with a SARS-CoV-2 strain with a greater pathogenicity than the strain of SARS-CoV-2 which occurred in 2020 [73,74]. It was most likely the Delta variant of SARS-CoV-2 which presented greater morbidity and mortality globally than [75]. It is possible that, for the patient in discussion, the first dose vaccination against SARS-CoV-2 offered no protection against the Delta variant, although it was stated that, "In exploratory analyses, a single standard dose of ChAdOx1 nCoV-19 had an efficacy of 76·0% against symptomatic COVD-19 in the first 90 days," [76].

It is possible that the patient has a breakthrough infection. Studies show that in individuals who were not previously infected with SARS-CoV-2, a single dose of either Pfizer or AstraZeneca vaccines barely induced neutralizing antibodies against variant Delta. A single dose of Pfizer or AstraZeneca was either poor or not at all, efficient against Beta and Delta variants [3,77]. This was of serious concern for individuals who only had their first dose of ChAdOx1 nCoV-19 vaccine and were awaiting their second dose. These individuals remained relatively unprotected and defenseless against the Delta Variant until they received their second dose. Further studies are needed to assess the efficacy of the AstraZeneca COVID-19 Vaccine against the new variants of SARS-CoV-2.

The true incidence of breakthrough infection and its pathophysiology continued to be the subject of much discussion, especially since the pandemic with the Delta variant. In one study reported by Gopinath et al. [78], Delta variants accounted for the largest number of BTIs [96%], followed by Alpha [0.94%]. BTIs were associated with low levels of neutralizing antibodies, high viral load [78]. Breakthrough infection induces different immune responses depending on prior history of vaccination and infection [79]. Spike protein of the SARS-CoV2 is responsible for the disease Covid-19. It is also implicated in the sequelae of Covid-19, namely the long syndrome [80-84].

3.7 Is there a relationship between spike protein and breakthrough infection?

Booster doses of AstraZeneca Sars-CoV-2 vaccine containing multiple variant spike proteins were recommended to improve the efficacy of the adenovirus vector vaccines [85, 86], to reduce the occurrence of breakthrough infection. A recent study conducted by Tarek et al. [87]. demonstrated that breakthrough infection effectively enhances the overall T cell response to S protein in SARSCoV2 variants, and supplement the value of vaccination to build protective wall based on adaptive response. This study reiterates the value of continuing research and surveillance as essential tools for understanding the underlying mechanisms of Covid-19 and its vaccines.

3.8 Vaccine-Associated Enhanced Diseases (VAED)

The patient might have had Vaccine-Associated Enhanced Diseases (VAED) which is a modified presentation of clinical infections affecting individuals exposed to a wild-

type pathogen after having received a prior vaccination for the same pathogen. The patient in discussion might have had Vaccine Associated Enhanced Respiratory Disease because of the severity of the respiratory symptoms and the pathological findings which involved predominantly the lower respiratory tract [88, 89]. Vaccine-Associated Enhanced Respiratory Disease is one of the potential adverse events that can occur following immunization against SARS-CoV-2 and subsequently contracting a wild variant of SARS-CoV-2 [90].

4. Conclusion

Autopsies have played a crucial role during the COVID-19 pandemic by serving as a major diagnostic tool. They have helped shed light on the underlying causes of patients' symptoms and deaths. For instance, in the case of the patient in discussion, the autopsy revealed metastatic prostate cancer to the lung and bone marrow, which provided explanations for the thrombocytopenia, fulminant pulmonary hemorrhage, pulmonary micro thrombosis, and the hypercoagulable states associated with advanced prostate cancer.

Autopsies have been essential in understanding the full extent of diseases, especially in complex cases like the one presented. They have helped differentiate between COVID-19-related complications and other underlying conditions such as Vaccine-Associated Enhanced Respiratory Disease and Pulmonary Tumour Thrombotic Microangiopathy, which present diagnostic challenges due to their similarities with severe COVID-19. This differentiation is vital for accurate diagnosis and treatment planning. Moreover, autopsies have highlighted the importance of investigating other potential causes of symptoms, such as thrombocytopenia, before attributing them solely to COVID-19 or its vaccines. This comprehensive approach ensures that patients receive appropriate care and that the medical community gains a better understanding of the disease and its complications. It is unfortunate however, that the great majority of patients who succumbed to Covid-19 did not receive the benefits of an autopsy and most were labelled as having died from the complications of COVID-19 or adverse effects of COVID-19 vaccines.

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