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CASE REPORT

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Coronavirus disease 19 (COVID-19) and Cerebral venous sinus thrombosis (CVST): A case series and review of the literature

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Abstract

A large proportion of patients with coronavirus disease 19 (COVID-19) suffer from excessive coagulation activation and coagulopathy which predisposes them to a wide spectrum of thrombotic events including in situ pulmonary thrombosis, deep-vein thrombosis, and associated pulmonary embolism, as well as arterial thrombotic events. Cerebral venous sinus thrombosis (CVST) have also been reported but in a very small number of cases. This report aims to increase awareness about CVST as a potential neurological thromboembolic complication in patients with coronavirus disease. We report three COVID-19 patients presenting with CVTS. We also review all previously described cases and present an overview of their demographic, clinical, and diagnostic data. We describe three patients with concomitant coronavirus disease and CVST among 1000 hospitalized COVID-19 patients (2 males, 1female, and mean age of 37 years). One patient was previously healthy, while the two others had a history of chronic anemia and ulcerative colitis, respectively. CVST symptoms including seizure in two patients and headache in one patient occurred day to weeks after the onset of COVID-19 symptoms. Three months of anticoagulant therapy was given for all three patients with favorable outcomes. No neurological sequelae and no recurrence occurred within 6 months after hospital discharge. Our search identified 33 cases of COVID-19 complicated by CVST. The mean age was 45.3 years, there was a slight male predominance (60%), and more than half of cases were diagnosed in previously healthy individuals. All cases of CVT were clinically symptomatic and were observed in patients with a different spectrum of coronavirus disease severity. Headache was the most common complaint, reported by just less than half of patients. There was a high mortality rate (30.3%). CVT is a very rare, but potentially life-threatening complication in patients with COVID-19. It's mainly reported in relatively young individuals with no or little comorbid disease and can occur even in patients who do not display severe respiratory symptoms. Atypical

clinical presentations may pose a challenge to the early diagnosis and treatment. High suspicion is necessary as early diagnosis and prompt treatment with anticoagulation in all patients with COVID-19 and CVT could contain the mortality rate and improve neurological outcomes in these patients.

KEYWORDS

COVID-19, SARS-CoV-2, Cerebral venous sinus thrombosis-coagulopathy

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a universal health emergency due to a beta coronavirus called severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). It was initially viewed as primarily a respiratory disease but is now recognized as a complex multisystemic disorder with heterogeneous involvement including COVID-19-induced coagulopathy.[1] This coagulopathy predisposes to a wide spectrum of thrombotic events such as in situ pulmonary thrombosis, deep-vein thrombosis, and associated pulmonary embolism, as well as arterial thrombotic events (stroke, myocardial infarction, and limb artery thrombosis). Cerebral venous sinus thrombosis (CVST) have also been reported but in a very small number of cases.[2] CVST is a rare form of stroke (<1%), caused by occlusion of the dural venous sinuses and/or cerebral veins. In the current report, we present three cases with CVST as a potential complication for coronavirus disease 2019. We also review all previously described cases and present an overview of their demographic, clinical, and diagnostic data.

2 | METHOD

2.1 | A case series analysis

Within the period from March 2020 to July 2021, 1000 patients with SARS-CoV-2 infection were admitted to the COVID-19 medical care unit at our department. Of these, we identified 3 patients (Table 1) with concomitant CVST and SARS-CoV-2 infection, deriving an incidence of 3/1000 (0.003%) or 3 per 1000 SARS-CoV-2 cases.

2.2 | Literature search strategy

Bibliographic databases including MEDLINE, goggle scholar, and Science Direct were searched from December 1, 2019, before the first case of SARS-CoV-2 infection was reported, to July 15, 2021. The following keywords were used: "COVID-19", "SARS-CoV-2", "novel coronavirus", "Coronavirus", "severe acute respiratory syndrome coronavirus 2", "Cerebral venous thrombosis (CVT)",

TABLE 1 Characteristics of Three COVID-19 patients presenting with cerebral venous sinusthrombosis

	Patient 1	Patient 2	Patient 3
Age (years)	45	48	22
Sex	Female	Male	Male
comorbidities	none	Pulmonary embolism Ulcerative colitis	None
Symptoms of covid-19 infection:	Dyspnea, cough and headache	fever, cough, and shortness of breath	None
COVID-19 severity	Moderate	Mild	Mild
Symptoms of CVT	Facial palsy	Seizure	Seizure
Days from COVID-19 symptoms	20 days	15 days	Same day
Location of CVT	Superior sagital sinus	Sigmoid and lateral sinuses	superior sagital sinus and frontal cortical veins
Prothrombotic work-up	Anemia Normal anti-dsDNA/ antiphospholipid antibodies	Anemia, raised CRP, raised WBC	Raised CRP Normal anti-dsDNA
Treatment	ACC	ACC -AED	ACC-AED
Outcome (death, alive)	Discharged	Discharged	Discharged

Abbreviations: ACC, anticoagulation; AED, anti-epileptic drug; COVID-19, coronavirus disease 2019; CVT, cerebral venous thrombosis;

"Cerebral venous sinus thrombosis", "Venous thrombotic events (VTE)", and "Stroke in young". Lists references of all included studies were also inspected to extract additional eligible studies. Only studies with case descriptions were included.

3 | RESULTS

3.1 | Case 1

A non-smoker healthy 45-year-old woman tested positive for SARS-CoV-2was admitted to the ward with a 20-day history of cough, shortness of breath and persistent headache despite Step 2 analgesics. No clinical abnormalities were identified at her initial physical examination. Notable microcytic anemia with hemoglobin of 5.6 g/dL (determined to be due to iron deficiency) on admission was the only identified abnormality by laboratory tests. Chest CT-scan showed peripheral unilateral ground-glass opacities in the upper and lower right lobes with low CT-extent (less than 10% of parenchymal involvement). The patient received low molecular weight heparins (LMWH) for thromboprophylaxis (enoxaparin 40 mg daily).On the 2nd day of her admission, she developed facial nerve palsy. Cerebral CT angiography revealed a floating thrombus of the superior sagittal sinus. As the time of onset was unknown, acute reperfusion therapies with thrombolysis could not be expected to be any more effective. Thus, LMWH therapy at curative dose was started, then switched to oral anticoagulation with warfarin, which led to complete regression of facial palsy within 10 days. Biological tests revealed negative results for common acquired and inherited thrombophilic conditions. The patient was discharged home on warfarin for 3 months.

3.2 | Case 2

A non-smoker 48-year-old man presented with 5 days of cough, shortness of breath, and fever. He had a history of venous thromboembolism in 2010, and ulcerative colitis treated with long-term corticosteroid therapy. He was hospitalized in a ward for 10 days after being tested positive for SARS-CoV-2 via nasopharyngeal swab RT-PCR. Two weeks after discharge, he was readmitted because of a generalized seizure. Vital signs on admission included a blood pressure of 110/70 mmHg, pulse rate of 100 beats/minute, respiratory rate of 16 cycles/minute, SpO2 of 97% on room air, and body temperature of 37.5 degrees Celsius. The neurological examination was unremarkable. Laboratory tests showed elevated levels of CRP (113 mg/L), increased white cell count with 10% lymphocytes, normocytic normochromic anemia (hemoglobin of 8.6 g/dl), while levels of serum creatine kinase (CK) and lactate dehydrogenase (LDH) were normal. Chest CT angiogram showed focal ground-glass opacities in the right upper lobe affecting less than 10% of the lung parenchyma. Bilateral pulmonary embolism with signs of pulmonary arterial hypertension was also identified. A Cerebral CT angiogram revealed cerebral venous thrombosis of the lateral sinus. Next to anticonvulsive therapy, the patient was started on therapeutic anticoagulation with LMWH (enoxaparin) followed by oral anticoagulation (Warfarin). His neurologic status remained stable over his hospital course. He was discharged home on oral anticoagulation after 20 days. At a 5-month follow-up, the patient was entirely asymptomatic and had no seizure recurrence.

3.3 | Case 3

A non-smoker healthy 22-year-old man was admitted to the ward with a first generalized tonic–clonic seizure. On admission, physical and neurological examinations revealed nothing particular. Serum CRP level was increased at 84 mg/L, otherwise results of laboratory tests were within normal limits. Meningitis was excluded as cerebrospinal fluid analysis from lumbar puncture showed no abnormalities. Brain CT-scan and Magnetic resonance imaging (MRI) were performed and identified CVT of the superior sagittal sinus and the frontal cortical veins complicated by hemorrhage. Nasal swab polymerase chain reaction (PCR) was positive for COVID-19.The patient was started on intravenous adjusted-dose unfractionated heparin and transitioned to enoxaparin, then to oral anticoagulation (Warfarin). He remained clinically stable during hospitalization, and he was discharged home on warfarin on 15th hospital day. Screening tests for a thrombophilic state were within normal amounts. Brain MRI performed 1 month after hospital discharge showed complete resolution of the venous thrombosis.

3.4 | Review of the literature results

The information from the literature review is summarized in Table 2. A total of 24 descriptive studies and case reports involving 33 patients with CVT, and Coronavirus disease were pooled in our final analysis. The mean age was 45.3 years, one patient was 2-year-old, and patients under 40 make up nearly half of reported cases ($n = 14$; 42.42%). There was a slight male predominance (60%), and more than half of cases were diagnosed in previously healthy individuals ($n = 17$; 51%). CVT was observed in

TABLE 2 Characteristics of previously described cases of cerebral venous sinus thrombosis in COVID-19 patients included in the review

Study	Country	Patients	Age	Comorbidity	COVID-19 severity	Neurological symptoms	Day from COVID-19 symptoms	Location of CVT	Prothrombotic work-up	Treatment	outcome
Cavalcanti[25]	US	M	38	Mild ASD	Critical	AMS	10	Distal superior sagittal sinus	Raised D-dimer	EVT ACC	Death
		F	41		Mild	AMS aphasia					
		M	23		Critical	GCS drop	7	Distal straight sinus		EVD ACC	Death
Klein[26]		F	29		Mild	Post-ictal AMS Aphasia Facial palsy Seizure	>7	Distal L transverse and sigmoid sinus	Raised CRP, D-dimer, LDH, anti-CL IgM Low ferritin	ACC AED	Alive
Garaci[27]	Italy	F	44		Severe	AMS Aphasia Headache R hemiparesis	14	Vein of Galen, L internal cerebral vein, straight sinus	Raised D-dimer Normal anti-CL, anti-B2gp1, anti-dsDNA IgM	ACC	
Malentacchi[5]		M	81	Prostate CA	Critical	AMS GCS drop		R sigmoid sinus	Raised CRP, D-dimer, LDH Normal fibrinogen	ACC	Death
Hughes[2]	UK	M	59	Obesity HTN DM	Moderate	Aphasia Dysarthria R hemiparesis R hypoesthesia	4	R transverse and sigmoid sinuses	Raised fibrinogen, CRP, ESR	ACC	Alive
Dahl-Cruz[28]	Spain	M	58		Moderate	Ataxia R hemiparesis R hypoesthesia	7	Superior sagittal and R transverse sinus	Raised CRP, D-dimer	ACC AED	Discharged
Poillon[4]	France	F	62	Obesity	Moderate	Blurry vision GCS drop Headache R hemiparesis	15	Vein of Galen, internal cerebral vein, straight sinus, L-transverse sinus	Raised D-dimer		
		F	54	Breast CA	Moderate	Headache	14	L transverse sinus	Raised CRP, D-dimer Normal LDH		
Hemasian[29]	Iran	M	65		Mild	GCS drop Seizure		R transverse and sigmoid sinuses	Raised LDH Normal CRP, ESR	ACC AED	Discharged
Li[30]	China	M	32		Severe		15			ACC	Discharged
Tu[1]	SG	M	30		Mild	Headache	1	L transverse and sigmoid Sinuses	Normal CRP, D-dimer, anti-CL IgM and IgG	ACC	Discharged
		M	30		Mild	Seizure		L transverse and sigmoid sinuses, extending into the internal jugular vein	Raised CRP, D-dimer, homocysteine, LAC, low protein C activity Normal protein S, anti-CL, anti-b2gp1 IgM and IgG	ACC AED	Death
Rehan Asif[31]	UK	M	18	NO		Headache, photophobia	15		Normal CRP, D-dimer, fibrinogen	ACC	Discharged
Baudar[6]	Brussels	F	33	Oral contraception	Moderate	Headache, seizure	21	Left parietal cortical CVT	Raised Fibrinogen and D-dimer	ACC	Discharged
Felix Nwajei[9]	Boston	F	68	NO		Nausea, vomiting, generalized weakness, and headache	15	Posterior superior sagittal sinus and torcula, straight sinus, the vein of Galen, inferior sagittal sinus	Increased inflammatory markers	ACC	Discharged
		F	79	HTN		Headaches	3	The right transverse sinus		ACC	Discharged
		F	25	Evans Syndrome, idiopathic thrombocytopenic purpura on avatrombopag, von-Willebrand Disease		Headache, blurry vision, tingling of the right upper extremity	120	Superior sagittal sinus		ACC	Discharged

TABLE 2 (Continued)

Study	Country	Patients	Age	Comorbidity	COVID-19 severity	Neurological symptoms	Day from COVID-19 symptoms	Location of CVT	Prothrombotic work-up	Treatment	outcome
Chougar[32]	Paris	M	72	NO	Mild	Sudden left hemiparesis, AMS	Few days	The internal cerebral veins and the vein of Galen		ACC	Death
Katarina Dakay[3]	US	M	17	Obesity		Headache, blurry vision	About the same time	The left transverse and sigmoid sinuses extending to the left Internal jugular din and straight sinus;	Elevated D-dimer	ACC	Discharged
		F	72	Breast cancer	Severe	Dysarthria, left hand weakness as well as dyspnea	3	Right sigmoid sinus and jugular bulb	Elevated C-reactive protein	Not anticoagulated due to change in goals of care	Death
		M	26	NO	Mild	Left arm and leg severe hemiparesis and mild sensory loss	15	Hemorrhage in the right parasagittal region	Normal	Not anti coagulated due to size of hemorrhage	Discharged
Paul Bolaji[33]	UK	M	63	NO	Mild	Left-sided weakness and inability to stand	2	Extensive venous sinus thrombosis with bilateral venous cortical infarcts and acute cortical hemorrhage	Eleveted D-dimers	ACC	Discharged
Safwat Abouhashem[34]	Egypt	M	22	NO		Seizure	3	Left transverse sigmoid sinus		ACC	Death
		M	28	NO	Mild	Headache, AMS		Venous sinus thrombosis		ACC	Death
Ameeka Thompson[24]	UK	M	50	ND	Severe	AMS	The same time	Superior sagittal sinus, left transverse sinus and left sigmoid sinus	Normal fibrinogen Positif anti-cardiolipin antibodies	ACC	Discharged
Yohsuke Sugiyama[35]	Japan	M	56			Headache and vomiting	12	Confluences of sinus to left transvers sinus	Raised D-dimers	ACC	Discharged
Lai Chee Chow[7]	Malaysia	F	72	Polycythemia vera	Severe	AMS, right-sided body weakness	40	Straight sinus, vein of Galen, and bilateral internal cerebral veins		ACC AED	Discharge
Haroon[36]	Quatar	M	30	ND	Mild	Headache mild left arm weakness	4	Superior sagittal sinus	Raised CRP D-dimers	ACC	Discharged
Kananeh[37]	USA	M	54	HTN	Critical	Headache, AMS		Straight sinus	Elevated D-dimer and inflammatory markers	ACC EVD	DEATH
Fabian Roy-Gash[38]	France	F	63	ND		Aphasia and right hemiplegia	Before	CVT and hemorrage	Hyperfibrinogenemia high ferritin levels	ACC AED	Death
Farida Essajee[8]	South Africa	F	2	Tuberculous meningitis		Left-sided weakness and lethargy	Before	Superior sagittal sinus and the transverse sinuses	Raised CRP, D-dimers, fibrinogen, ferritin	Antituberculous treatment prednisone Aspirin	Discherged

Abbreviations: ACC, anticoagulation; AED, anti-epileptic drug; AMS, altered mental status; ASD, autism spectrum disorder; CA, cancer; COVID-19, coronavirus disease 2019; CVT, cerebral venous thrombosis; DM, diabetes mellitus; EVD, external ventricular drain; EVT, endovascular thrombectomy; F, female; GCS, Glasgow coma scale; LAC, lupus anticoagulant; M, male; US, United States; UK, United Kingdom.

patients with a different spectrum of Coronavirus Disease severity, ranging from mild (n = 41.66%), to moderate (n = 20.8%), and severe (n = 37.5%) disease. In most cases (n = 31, 93%), clinical manifestations of CVT developed with or after (1 day–16 weeks) the emergence of respiratory or systemic symptoms of Coronavirus disease. However, in 2 cases, CVT occurred few days before. All cases of CVT were clinically symptomatic. Headache was the most common complaint, reported by just less than half of patients (n = 14, 42.4%), and was the only symptom of CVT in 3 cases. Altered mental status and hemiparesis were identified in 30.3% (n = 10) and 24.2% (n = 8) of cases, respectively, while aphasia and epileptic seizures were present both in 21.2% (n = 7) of cases. The most frequently involved sinuses were the transverse sinus (39.3%), and the sigmoid sinus (27.2%), followed by the superior sagittal sinus and the straight sinus, both involved in 21% of cases, and in nearly one-third of all affected patients (n = 33%), multiple venous sinuses were involved. The most commonly reported laboratory abnormalities were elevated serum CRP and D-dimer levels in 30.3% and 45.4% of cases, respectively.

Some risk factors for CVT have been identified in six among the 33 affected patients, including solid tumors,[3–5] long-term oral contraception[6]; polycythemia vera,[7] concomitant tuberculous meningitis in a 2-year-old child,[8] Evans Syndrome, idiopathic thrombocytopenic purpura, and von-Willebrand Disease.[9] Regarding therapeutic management, anticoagulant therapy was administered to the majority of patients (n = 27, 81.8%), endovascular reperfusion therapy was performed in 2 patients only, while antiplatelet therapy was prescribed to the pediatric patient.[8] Elsewhere, 6 patients received anticonvulsive medication, and one patient had external ventricular drainage inserted due to cerebral venous infarction with hemorrhagic transformation. Out of the 33 affected patients, 10 of them died. This gives a mortality rate of 30.3%.

4 | DISCUSSION

We report unusual presentations of COVID-19 disease with CVT in three young patients, all of whom survived with favorable neurologic outcomes. Our cases corroborate the current and growing body of literature describing COVID-19 disease as a coagulopathy that can involve both arterial and venous systems. Several laboratory tests have been consistent with hypercoagulable state in COVID-19 such as increased plasma levels of fibrinogen, D-Dimère and factor VIII as well as the presence of circulating antiphospholipid antibodies (aPL).[10]Systemic inflammatory response syndrome was suggested as a major contributor to COVID-19-associated coagulopathy, but virus-induced angiitis might also be involved.[11,12] In our cases, 2 prothrombotic risk factors were present including anemia in case 1, and ulcerative colitis in case 2; however, COVID-19 have probably contributed as a precipitating factor.

Clinical manifestations of the COVID-19-related coagulopathy include deep-vein thrombosis, pulmonary embolism, catheter-associated thrombosis, myocardial infarction, limb ischemia, while cerebrovascular thrombosis is uncommonly reported. In our cases, CVT occurred with no other clinical signs of systemic coagulopathy. The incidence of CVT in COVID-19 patients remains unknown and varied widely across studies (Table 2): 0.001% among all patients diagnosed with COVID-19 in Singapore,[13] 0.02% to 1% in multicenter cohorts of hospitalized patients with COVID-19,[14] and 0.06% among hospitalized patients with SARS-CoV-2 infection referred for neurological assessment.[15] In a systemic review by Baldini and al.,[16] the estimated frequency of CVT among patients hospitalized for SARS-CoV-2 infection was 0.08% and CVT accounted for 4.2% of all cerebrovascular disorders in individuals with COVID-19. In another systemic review, the incidence of CVT in COVID-19 patients was estimated to be approximately 3 times higher than previously published population incidence (4.5 per 100,000 vs. 1.6 per 100,000). These results underline the relatively high incidence of CVT in SARS-CoV-2 patients when compared with an expected rate of only 5 to 20 per million per year in the general population. Many reports indicate that elderly patients with COVID-19 are more likely to progress to severe disease and have worse outcomes compared with young and middle-aged. Surprising, COVID-19-related CVT are mainly reported in relatively young individuals with no or little comorbid disease. In our literature review, the mean age of patients was 45.3 years.

CVT can be the initial clinical manifestation of the infection, but the majority of CVTs develop within a median of 7 days after onset of COVID-19 symptoms, with a wide range of a few days up to several weeks,[16] as was the case in our patients. This suggests that patients who have recovered from SARS-CoV-2 might continue to have a hypercoagulable state and be at increased risk for venous and arterial thrombosis for a long period after recovery.[17]

Neurological symptoms of COVID-19 related CVT are quite common, including mainly headache in 5.6% to 70.3% and encephalopathy in 7.5% to 84.3%. Seizure may also be a common presenting symptom, even in those without prior history of epilepsy.[18] These non-specific neurological symptoms may obscure the early presenting findings of CVST, particularly in critical illness where toxic-metabolic derangement is common which makes the diagnosis of CVST in COVID-19 patients particularly challenging.[19] As a result, we suggest that any neurologic symptom in patients with COVID-19 such as headache,

mental status deterioration, or seizure, should lead us to suspect CVT even in the absence of focal neurological deficits. Women with COVID-19 seem to be at higher risk for CVST, as this is the case in non-COVID-19 patient populations[20] and tend to seek care sooner than men.[21] However, as women are known to have a higher frequency and intensity of COVID-19-related headaches, and suffer more often from migraines than men, they are more likely to be misdiagnosed when they are having a COVID-19-related CVT.[9]

Our literature review showed that CVT in COVID-19 patients is associated with a higher mortality rate as compared with CVT in non-COVID-19 patients (30% vs 15%, respectively). It remains unclear whether this increased mortality in patients with COVID-19 and CVT is related to the neurological involvement or the severity of COVID-19 disease, as reports considered in this review of the literature did not provide enough details about the underlying causes of death. However, CVT seems more likely to be involved as most deaths occurred in patients with mildrespiratory symptoms.

Anticoagulation with unfractionated heparin (UFH) or (LMWH) combined with aggressive hydration is the main stay for the treatment of patients with acute CVT,[22] while endovascular thrombolysis and mechanical thrombectomy are reserved for very selected cases.[23] Early initiation of anticoagulation in COVID-19 patients with suspected CVT or predisposed to developing CVT is thought to be helpful to decrease further propagation of clot and pulmonary embolism and reduce the mortality rate. Although, there is still a general lack of scientific evidence of the effectiveness of anticoagulation in COVID-19 patients, as hemorrhagic complications have also been reported, including acute hemorrhagic necrotizing encephalopathy and increased rates of intracerebral hemorrhage in patients on therapeutic anticoagulation for systemic VTE.[9] In addition, there is no yet universal consensus regarding the timing, dosage, choice, and duration of anticoagulation in patients with COVID-19 and CVT.[24] Our patients had received initial therapy with LMWH and then switched to oral anticoagulation with warfarin for a total duration of 3 months. All of them survived with favorable neurologic outcomes.

5 | CONCLUSION

CVT is a very rare, but potentially life-threatening complication in patients with COVID-19. It's mainly reported in relatively young individuals with no or little comorbid disease and can occur even in patients who do not display severe respiratory symptoms. Atypical clinical presentations may pose a challenge to the early diagnosis and treatment. Thus, high suspicion is necessary and CVT should be kept in as a differential diagnosis when patients with COVID-19 present with headache, encephalopathy, seizure, or focal neurologic deficit. Early diagnosis and prompt treatment with anticoagulation in all patients with COVID-19 and CVT could contain the mortality rate and improve neurological outcomes in these patients.

AUTHOR CONTRIBUTIONS

This work was carried out in collaboration among all authors. Authors Kallel Nesrin, Saidani Amal, and Maddeh Sabrine have made substantial contributions to acquisition and interpretation of data. Kotti Amina, Gargouri Rahma, and Moussa Nadia have been involved in drafting the manuscript. Msaad Sameh and Feki Walid had given final approval of the version to be published. All authors read and approved the final manuscript. All authors had contributed to the reduction of this article.

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CONFLICT OF INTEREST

The authors do not have any conflict of interest.

ETHICAL APPROVAL

Ethical approval has been collected and preserved by the authors.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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