Thrombembolism after COVID 19 – our experience with 6 cases.

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Abstract

Background: The 2020 year was different. WHO announced a global pandemic and till now we have had over 2 million fatality rates? The SARS CoV-2 virus causes acute respiratory viral infection and is associated with a wide range of complications.

Aim: In this article, we are representing six patients with deep venous and arterial thrombosis after Covid-19 and their treatment.

Materials and Methods: The patients were treated successfully by the Department of Vascular Surgery and the Department of Burns, Plastic, Reconstructive and Aesthetic Surgery of the “St. George” University Hospital, Medical University Plovdiv, Bulgaria.

Results: Some of them were treated conservatively and others surgically. The localizations were upper and lower extremities and the hard palate. Amputation of the affected limb, soft tissue defects, and conservative treatment was required. The arterial thrombosis was more than venous ones. All the patients were stable at discharge.

Conclusion: After COVID-19 complications include Thrombotic events – Acute Limb Ischemia (ALI), Venous Thromboembolism (VTE), Pulmonary Embolism (PE), Disseminated Intravascular Coagulopathy (DIC) Syndrome. Thromboprophylaxis is very important. It depends on the severity of the infection, the underlying causes, and the course of treatment.

Keywords: COVID-19, complication, thrombosis, amputation, limb ischemia,

Introduction

In 2019, the World Health Organization (WHO) declared the Covid-19 pandemic (SARS-CoV-2). Over the last year, the whole world has undergone a significant change. Present data from the European Center for Disease Control and Prevention show that the mortality rate due to Covid-19 has reached 2 800 000. The infection usually presents with flu like features, however, in approximately 15% of the cases, it assumes a severe course with development of pneumonia and multi-organ failure. Another characteristic of the infection is

that complications are not uncommon in mild cases and are frequent in severe cases. A typical complication, which could result in lethal outcome or permanent disability is vascular occlusion. In most cases, venous thromboembolism occurs, alongside with development of arterial thrombosis, which worsens prognosis.

Materials and Results

In this report, six clinical cases of acute venous and arterial thrombosis after Covid-19 infection are presented. They received initial inpatient treatment at the Department of Vascular Surgery of “St. George” University Hospital, followed by management at the Department of Burns, Plastic, Reconstructive and Aesthetic Surgery.

Case 1

A 47-year - old male with type II diabetes mellitus (DMTII) and underlying cardiac failure was admitted with 15day symptoms of right lower limb ischemia. The patient had tested positive for COVID-19 on the PCR-test a month earlier. On physical examination, he had cyanosis of the right

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Figure 1-4. From Day 1 to Day 4, before and after surgery (Necrectomy and autoplasmic cutis libera)

foot, hardly palpable pulse in the common femoral artery on the right and absent pulsations distally. On ultrasound imaging, he had thrombosis of *a. iliaca externa*, *a. femoralis superficialis* and *a. poplitea dex.* Thrombendarterectomy (TEA) was performed of the occluded arteries. Post-surgery, the affected lower extremity regained pulsations and warmth. Following the surgical procedure, the patient was subject to repeated removal of necrotic tissue due to necrotic lesions in the anterolateral aspect of the right calf and foot. Soft tissue necrosis and exposed bone on the right calf necessitated daily necrectomies of bone and soft tissue followed by vacuum assisted closure (VAC) therapy and autoplasty of free cutis (ACL) of the right shin area. (Case 1, Figures 1-4) Additional treatment included low molecular weight heparin (LMWH), antibiotics and antidiabetic medication. On a follow-up examination the patient seemed stable with visible tissue regeneration in the operated area.

Case 2

A 53-year-old female with signs of ischemia of the left lower limb. Her comorbidities included arterial hypertension and ischemic heart disease. The patient reported pain, numbness and sensation of coldness in the affected area. She was treated as inpatient for COVID-19 infection before admission. On physical examination, she had no palpable pulse along the left ileo-femoral axis and pallor of the skin. Ultrasound diagnostic procedure revealed stenotic left iliac artery and obstruction of the left superficial femoral

artery. On CT angiography occlusion of the proximal left superficial femoral artery was visible (Case 2, Figure 5)

The patient was diagnosed with thrombosis of left iliac artery. TEA was performed followed by a lower left limb

Figure 5. CT- angiography.

Figures 6 and 7 – re-amputation, local flap and cutis libera autoplasic

amputation at the level of the lower third of the thigh. After infection of the amputation stump the patient underwent new amputation to the upper third of the thigh and VAC drainage.

Surgical treatment was applied, consisting of staged necrectomy, local flap and ACL (mesh-graft 1:1,5). (Case 2, Figures 6, 7) Medication included Clexane 0.6 ml s.c bid and antibiotics. The wound healed up and the patient was stable at discharge.

Case 3

A 41-year-old male patient with signs of ischemia of the right lower limb and complaints of coldness and pale blue coloration in the affected area.

His comorbidities included: DMTI, peripheral vascular disease, ischemic heart disease and a history of past myocardial infarction. The patient was diagnosed with COVID-19, 53 days before admission. On physical examination, he had no palpable pulse in the entire right iliac - femoral axis and necrosis of hard palate. (Figures 8, 9)

Ultrasound confirmed the thrombosis of the right iliac artery. TEA of *a. iliaca dex.* and *a. femoralis dextra* was performed. Post-surgery, the patient reported bleeding in the right inguinal area.

Revision of the suture of right femoral artery was performed, followed by thrombectomy. In the course of the surgical revision, *a. femoralis superficialis dex* was ligated due to excess bleeding. Unfortunately, after the procedure, gangrene developed in the area, necessitating amputation of the limb.

A week later, repeated amputation was performed due to deep vein thrombosis in *v. femoralis dex.* Regardless

of the administration of low molecular weight heparin (LMWH) and antibiotics, the patient state deteriorated and another thrombectomy was performed with ligation of the affected vein. VAC drainage and graft surgery followed for wound closure. Three months after discharge, severe infection resulted in fatal outcome in this case.

Figures 8 and 9 – Necrosis after thrombosis of hard palate

Case 4

Case 4 is that of a 62-year-old male treated for a SARS-CoV-2 infection on an outpatient basis. After discharge, he noticed a blue discoloration of fingers 2 and 3 on his left hand, accompanied by coldness and pain in his left arm. Physical examination was consistent with upper-limb ischemia with a sensory and motor deficit. (Figures 10, 11) Ultrasound examination revealed lack of blood flow in the axillar artery, brachial artery and the arteries of the wrist. TEA was performed on day 1 and 2 after admission. Despite initiating heparin infusion at a rate of 1000E/h, no pulse was noted in the wrist arteries. Thrombectomy was performed. A day later, no pulse was felt in a. radialis. Conservative treatment included Prostavasini - 2 amp. x 20 mg infusion. Anticoagulation resulted in salvaged limb. Antithrombotic prophylaxis was prescribed with Aspirin x100mg od and Cilostazol x100 mg bid.

Figures 10 and 11. Limb ischemia and thrombosis

Case 5

A 43-year-old male after treatment for a SARS-CoV-2 infection, also noticed coldness, numbness, and pain in his upper limb after discharge. On physical examination, he had limb ischemia. Ultrasound examination was consistent with lack of blood flow in a. brachialis. Thrombectomy was performed. The limb was salvaged due to the treatment. Patient underwent thromboprophylaxis.

Case 6

A 37-year-old male was diagnosed with COVID-19 in Belgium. After treatment and two negative PCR tests at a Belgian Hospital, he returned to Bulgaria. He reported no underlying medical condition. There is no other diseases. One week later, he presented with malaise and shortness of breath, fever and sweating. CT-PE was performed and pulmonary embolism was diagnosed (PTE). (Figure 12) After aggressive intensive and antithrombin therapy for 2 weeks the patient was discharged on thrombo-prophylactic therapy.

Figura 12. CT angiography of PTE

Discussion

The acute phase of Covid-19 infection is associated with a cytokine storm and resulting coagulopathy. About a week after the Covid-19 infection, antibody mediated response by the B-cells and sustained activation of T-cells by viral antigens may exacerbate tissue damage.[1]

The pathophysiology of thromboembolism in COVID-19 compared to that in non-COVID-19 conditions, seems more platelet-dependent and related to the viral-mediated endothelial inflammation, in addition to hypercoagulability associated with increased concentrations of coagulation factors, acquired antiphospholipid antibodies, and decreased concentrations of endogenous anticoagulant proteins. [2]

Fox *et al.* [3] performed autopsies on patients with lethal COVID - 19 infections. Apart from the diffuse interstitial fibrosis and alveolar damage, which is typical for pneumonias, they described hemorrhagic lung infarction with hyperplasia and micro thrombi in the small vessels. It seems likely that micro-angiopathy is an additional factor, contributing to the higher mortality rate in COVID - 19.

Micro- thromboses have been documented in other organs as well. According to Zhang [3] micro- vascular clots are typical for COVID-19 infections unlike infections with SARS1. Our observations and experience also record an increased rate of thrombotic complications in patients after infections with COVID -19.

In McGonagle's opinion [4], diffuse bilateral pulmonary inflammation, observed in infections with COVID- 19 is attributable to specific pulmonary vasculopathy, termed as pulmonary intravascular coagulopathy (PIC), that differs from DIC.

In view of this, coagulation studies are mandatory in patients with COVID- 19. In most of them a significant elevation of di- dimers levels are observed. In Lippi's opinion, [5] the elevated d- dimers level is an unfavorable prognostic indicator in COVID- 19 infections and is related with latent coagulopathy. This author provides evidence that in patients with initial milder infections the increasing d- dimer levels are associated with deterioration of their clinical condition. Most authors report elongated prothrombin time up to 13 seconds in patients with COVID-19 [6]. Some even report elongation up to 16 seconds in patients with a lethal outcome. [7]

It is a known fact that platelet count in severe COVID-19 infections is mildly to moderately decreased. [8] On the contrary, we report increased platelet count in patients post infection with covid-19, who are admitted with suspected acute thrombotic events.

Thomas et al. [9] considers that the risk for pulmonary embolism in patients with ARDS, related with COVID-19 infection compared to ARDS due to other causes. It seems likely that different clot formation mechanism is responsible for these events. Regardless of the standard anti-coagulation therapy, higher rates of deep venous thrombosis have been noted in COVID-19 patients. [10]

However, there is a consensus opinion, that low molecular weight heparins reduce the lethality from COVID-19 infection. [11]

There is lack of consensus as to when patients with COVID -19 are at higher risk of thrombotic events. Some authors consider that clot formation is more common during the initial infection, others note higher percentage of thrombotic events over the months following recovery from the initial infection. [12, 13]

Our experience shows a significant increase in thrombotic events after recovery from infection and discharge from hospital. This finding seems related with the adequate anticoagulation provided during the hospital stay. In our opinion, prophylactic anti-coagulation, should be continued for a couple of months after hospital discharge.

The precise underlying pathophysiological mechanism of severe infection with SARS-CoV-2 remains unclear, it is considered that pulmonary vasculopathy plays an important role in its development.

Klok et al. studies of complications after infection with SARS-CoV-2 document higher number of patients with arterial and venous thrombosis. [10, 14]

With the novel coronavirus, patients could suffer from thrombosis in the absence of traditional risk factors for acute thromboembolism. ¹ We consider that the presence of preceding coagulopathy or other vascular pathology place patients at a higher risk in cases of infection with COVID-19.

Thachil et al. [15] considers that patients could be subdivided in three groups: patients treated at home or in non- intensive units. It is considered that these patients have micro-clot formation. Group 2 includes patients under intensive care with proven thrombotic complications. Group 3 patients are the most severe cases with COVID-19 and evidence of DIC syndrome. Disseminated intravascular coagulation (DIC) is observed in lethal infections with COVID- 19 compared survivors.

Tang et al. [16] reports evidence of DIC in over 71% of patients with lethal COVID-19 infections compared to 0,6 % in survivors.

It has been proven that the coagulation state of patients is associated with disease progression, as the infection progresses, the levels of fibrinogen rise and the levels of antithrombin drop.

Deng et al. [17] have been reported differences in the coagulation parameters in DIC associated with COVID-19 compared to DIC in septic conditions.

Severe inflammatory response is typical for severe infections and increases the risk for thrombotic complications. However, Helms et al. [18] considers that patients with severe COVID-19 have higher risk of clot formation compared to patients under intensive care for other reasons. In patients with SARS-CoV-2 infections, the macro and micro- thrombotic events are attributable to the acute inflammatory response and subsequent endothelial dysfunction.

Our observations are consistent with those of other authors and show higher thrombotic risk in patients under intensive care as well as increased risk in severe infections – up to 35,5% of the cases, compared to mild infections – 2,6%. [3, 13]

Thrombotic complications are more common in elderly patients, more often in those requiring assisted ventilation and intensive care. In these patients, the levels of the d-dimers, C reactive protein and fibrinogen are elevated. [16]

High-risk factors in COVID-19 include age more than 65 years, serious underlying medical conditions, cancer, prior VTE, thrombophilia, severe immobility, and elevated D-dimer (>2 times the upper limit of the normal). [9]

A few patients with thromboses after COVID-19 infections have been under follow- up.

Vlachou et al. [19] report only 4 cases with thromboses after discharge, out of 370 patients with COVID -19 infections. Our opinion is consistent with that of other authors who consider that acute thrombotic events are usually not associated with the preceding infection and are not recorded as complications. However, similarly to other large hospitals, we observe increased rates of acute thrombotic events after the onset of the pandemic. In

most cases they present complications after infection with COVID-19.

Patients with advanced age and other comorbidities may be at a greater risk of post - discharge thrombosis.

The risk of venous thromboembolism (VTE) extends beyond the duration of the hospitalization, with up to 80% of the events occurring in the post-hospital discharge period (30-45 days) [20]

Our observations record occurrence of clot formation 45- to 55 days after the initial infection with COVID-19.

Post COVID-19 thrombotic complications are usually venous or arterial thromboembolism of the extremities and in the brain, coronary and other visceral vessels. The early diagnosis is this patient reduces the risk for amputations.

Comorbidities as arterial hypertension, high BMI and age over 60 years are at a higher risk for complications. We agree with other authors opinion that patients with peripheral vascular diseases and Diabetes mellitus present more than 30% of all patients requiring amputation. [21, 22]

We disagree with *Bastopcu's opinion* [23], that most events of thromboembolism are venous. In most patients we observed acute arterial thrombosis followed in some of them by venous.

All the patients reported of pain and numbness on the leg that started one day prior the thrombosis. [20]

McKeown et al. reported that coldness, pain, or discoloration sometimes could be the only symptoms. [24] In our opinion, these patients should be tested and monitored in order to prevent thrombotic complications.

Our patients report numbness and pain a few days before the actual ischemic events.

On examination the extremity was cold, the distal part appeared ischemic, and mottling of the skin was evident. We observed sensory loss and paralysis of the muscles. Also pulls distally was absent.

In our opinion continue anticoagulation after discharge is advisable.

Schunemann et al. shown in a retrospective cohort study, the rate of limb loss was 18% in patients hospitalized for COVID-19, complicated with arterial thromboembolism. [20]

Patients with chronic vascular disorders and symptoms consistent with ischemia are at a greater risk for complications resulting in limb amputations. We are in agreement with *McKeown et al.* [24] that COVID-19 infection causes deterioration of pre-existing vascular conditions, thus leading to higher lethality and amputation rate.

Based on Rutherford's classification, that determines the degree of tissue damage, stage II-a is characterized by minimal sensory impairment without muscle involvement and an acceptable venous filling, class II-b present with significant sensory deficit, muscle weakness, absent arterial pulse distally and significantly reduced venous filling. In class III we have complete ischemia which necessitates emergent amputation. [25]

Some authors report an amputation rate of up to 18% in patient with acute thromboembolism after infection with COVID-19. [26]

In most cases, high level amputations, at the knee or at the thigh are performed. The amputation rates for patients with COVID-19 infections, may reach as high as 35 % and in patients with severe pre-existing vascular disorders and thromboembolism- up to 23%. [27]

We consider that severe COVID-19 infection, the prolonged recovery period and rehabilitation prevent the adequate healing of the amputation stump and often result in complications. Presented patients are immune- compromised and with concomitant infectious complications. *Ramachandran et al.* [28] reports a number of cases in which after successful thrombectomy and thrombolysis, repeated arterial thrombosis occurs, which requires high amputation. In such cases, amputation is lifesaving procedure.

In our opinion, hypercoagulability after infection with SARS-CoV-2 could present with various symptoms and requires adequate prophylaxis, rapid diagnosis and adequate management.

Many authors note that mortality rates are higher in patients with acute arterial thrombosis after COVID-19 infection compared to other patients. [29]

The corona virus disease- 19 is associated with arterial thrombosis of lower extremities, characterized by larger clot accumulation and worse prognosis.

Similarly, to the American College of Chest Physicians (ACCP) and the American Society of Hematology (ASH) we recommend post discharge thrombo-prophylaxis with LMWH for all high-risk hospitalized patients with COVID-19 who have a low risk of bleeding. [20]

Conclusions

Regardless of the variable clinical presentation of COVID-19, coagulation changes are always present. Depending on the disease stage and severity, complications always worsen prognosis. This is especially true for thrombotic events, that often could result in fatalities. It is obvious that even after recovery from the infection, there is a risk of clot formation, that requires follow- up and continuous administration of anticoagulants. For this reason, the timely diagnosis and risk assessment requires routine testing of coagulation parameters. This approach facilitates the proper choice of treatment. Surgical interventions are aimed mainly an elimination of local infection and are life saving for the patients.

Author Contributions

VA. conceived and designed the analysis, collected the data, treatment of all the patients in the article, observed the patients, contributed the data and analyses tools, performed the analysis and Interpretations, literature search, wrote the paper, other contributions (take the pictures), supervisor of the project, critical reviewer. EZ comprehended and

designed the analysis, treatment of all the patients in the article, contributed the data and analyses tools, performed the analysis, wrote the paper, critical reviewer. EK conceived and designed the analysis, collected the data, treatment of all the patients in the article, wrote the paper, other contributions (take the pictures), critical reviewer, literature search. VB considered and designed the analysis, collected the data, treatment of all the patients in the article, wrote the paper, other contributions (take the pictures), critical reviewer, literature search

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval and consent to participate – all the patients/their parents have signed informed consent.

Consent for photography- all the patients/their parents have signed informed consent

Consent for publication - all the patients/their parents have signed informed consent

Clinical trial registration information provided – not applicable

We confirm that the manuscript, including related data, figures and tables has not been previously published and that the manuscript is not under consideration elsewhere.

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