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Case report

ARTERIAL THROMBOSIS IN A COVID-19 PATIENT

АРТЕРИСКА ТРОМБОЗА КАЈ ПАЦИЕНТ СО КОВИД 19

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Abstract

Arterial thrombosis is one of the complications descrybed in severe COVID-19. Our presented case had thrombosis of abdominal aorta and left renal artery despite prophylactic treatment with low molecular heparin - enoxaparine. Thrombotic lesions were defined with CT angiography. Treatment consisted of therapeutic doses of low molecular heparin and Bergman solution. After 42 day of hospital treatment, the patient was discharged and vascular surgeon consultations were performed. By presenting this case, we want to draw attention to the need for early diagnosis of this complication and to highlight the need for treatment with therapeutic doses of low molecular heparin in patients with severe Covid pneumonia or oxygen dependent patients and in risk for thrombosis.

Keywords: COVID-19, arterial thrombosis, heparin

Апстракт

Артериската тромбоза претставува една од компликациите опишувана при тешка форма на Ковид 19. Нашиот случај е презентиран со тромбоза на абдоминална аорта и тромбоза на лева бубрежна артерија. Дијагноза на тромботичните промени се потврди со КТ ангиографија. Третманот беше спроведен со тераписки дози на хепарин со ниска молекуларност-еноксапарин и раствор на Бергман. Пациентката се испишува по 42 дена на болничко лекување со препорака за понатамошно проследување од страна на васкуларен хирург. Со приказ на овој случај сакаме да осврнеме внимание на потребата за рана дијагноза на оваа компликација и да ставиме на виделина потребата за лекување со тераписки дози на нискомолекуларен хепарин кај пациенти со тешка Ковид пневмонија или кислородно зависни со ризик за развој на тромбоза.

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Клучни зборови: КОВИД 19, артериска тромбоза, хепарин

Introduction

Two years of clinical experience in a Covid-19 department showed us the importance of fast and timely diagnosis and treatment of different life-threatening complications in Covid-19 severe/critical illness. Thromboembolism as the most common urgent complication with the highest probability of evolving in the phase of the so known cytokine storm, taught us to be predicttive in taking proper steps in diagnosis and treatment. Successful treatment of the severe and critical COVID-19 disease requires a multidisciplinary approach.

The scientific data suggest that severe COVID-19 illness is associated with endothelial injury that leads to dysregulation of homeostasis and coagulopathy with the final result of immunothrombosis [1]. SARS-CoV 2 is a viral infectious disease that causes various manifestations and dysfunctions, including coagulopathy. Even though pulmonary thromboembolism is so far very often encountered in these patients, thrombosis in arterial blood vessels is also described, but rarely. In the everyday medical publications, we see information about thrombosis in different locations such as *truncus celiacus*, *arteria mesenterica superior*, *arteria renalis*, aorta etc. [3].

Case presentation

A 70-year-old woman with hypertension was admitted to our COVID department with a history of fever, malaise and cough during the past 7 days. Clinical examination on admission showed fever and rhonchi on pulmonary auscultation and O2 saturation of 88-89% on room air. PCR Covid swap resulted positive. Before admission, she had been treated during two days with antimicrobial therapy (Cefixime 400 mg once daily) and oral antiplatelet (Aspirin 100 mg once daily). Laboratory tests on admission showed mild lymphopenia, increased C-reactive protein levels, increased LDH and D-Dimer levels (Table 1). Chest x-ray (CXR) on

admission showed multilobar interstitial opacities (Figure 1A). The patient had a history of smoking and arterial hypertension treated with Enap 5 mg once daily. During the hospital stay, the patient was treated first with a combined parenteral antimicrobial therapy (third generation Cephalosporin (Ceftriaxone) - 2 g/daily, Quinolone (Ciprofloxacin) - 400 mg/twice daily), convalescent plasma substitution on the second day of treatment, anticoagulant therapy with low molecular heparin at a dose of 40 mg twice daily, oxygen supplementation with nasal cannula 3l/min. During the next five days of hospitalization, the patient continued to have persistent fever and an increase in oxygen requierements with non-rebreather mask (16l/min). CXR (Figure 1B) and CT thorax (Figure 1C, 1D) on day 5 of hospital treatment presented a rapid progression of opacities, and laboratory examinations showed an increase in acute inflammatory markers. Rales were noted on pulmonary auscultation on both sides.

Table 1. Laboratory test results

Variable	Reference	On admission	12th day of illness	16th day illness	19th day of illness	28th day of illness	30th day of illness	31st day of illness	43th day illness	50th day illness
Hb(g/l)	(115-180)	137	123	128	132	107	89	92	95	93
RBC (x10-3)	(4000-5500)	5160	4640	4940	4990	4020	3330	3430	3480	3460
WBC (x10-3)	(4.0-11)	5.2	5.4	18	15.5	14.2	14.2	9.1	7.5	6,1
Plat.(x10-3)	(150-400)	232	321	465	349	399	312	306	308	304
Hct	(41-50)	0.41	0.38	0.4	0.4	0.33	0.28	0.29	0.3	0,29
Ne	(0.25-0.70)	0.78	0.85	0.89	0.93	0.84	0.91	0.86	0.61	0,64
Ly	(0.21-0.25)	0.16	0.11	0.07	0.03	0.1	0.04	0.07	0.2	0,21
NLR		4.8	7.7	12.7	31	8.4	22.7	12.2	3	3
CRP(mg)	(0-10)	24	254	71	395	12		12	15	23
LDH(UI)	(120-246)	285	533	895	3578	1081	826		319	271
CK(UI/)	(30-170)	55	623	205	125	22	24	20	20	20
ALT(UI/)	(10-52)	42	46	59	312	147			49	34
AST (UI/ml)	(10-47)	49	72	55	312	49			19	15
Troponin (pg/ml)	(<34.2)				5,2	3.3	28.1	6,2		
ser.Fe ++(mmol/l	(12.5-26)			8.2		12.3			8.6	5.4
Glob. (g/l	(20-35)					26			23	
Glob. (g/l	(20-35)					26			23	
Alb (g/l	(34-54)					27			28	
tot.prot.(g/l)	(60-83)					53			51	

Hb-hemoglobine; RBc-red blood cells; WBC- white blood cells; Plat.-platelet count; Hct-hematocrit; Ne-neutrophiles; Ly-lymphocites; NLR-neutrophil/lymphocyte ratio; CRP- reactive protein C; LDH-lactat dehydrogenase; CK-creatin kinase; ALT-alanin aminotransferase; AST-aspartat aminotransferase; glob.-globulines; alb-albumines; tot.prot-total proteins

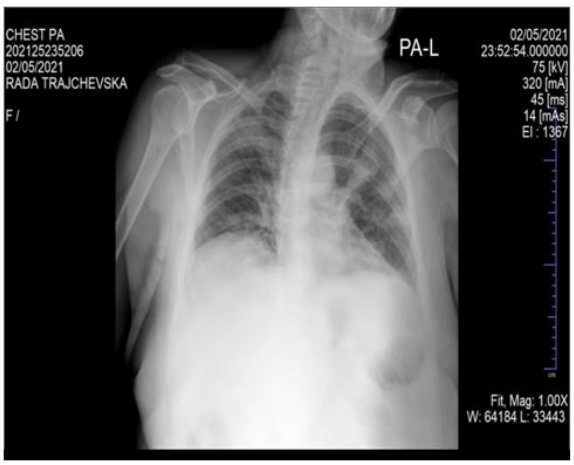

Fig. 1(A). CXR on admission

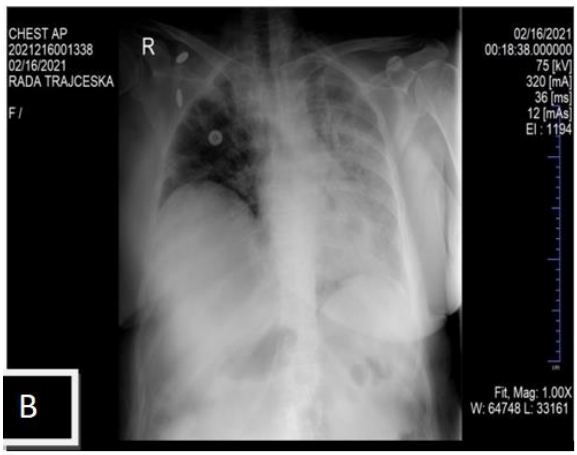

Fig. 1(B). CXR on 12th day of illness

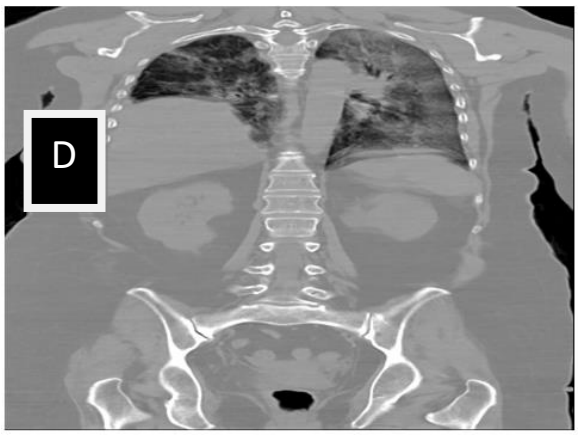

Fig. 1(C). Computed thomography of thorax billateral opacities

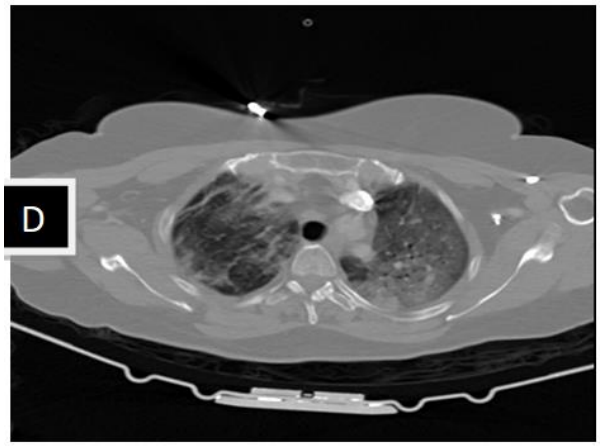

Fig. 1 (D). Ground glass images on CT

On day 12 of illness, treatment was complemented with Remdesivir parenterally (200 mg/24h the first day, continued with 100 mg/24h the next 4 days). In absence of other immunomodulators like tocilizumab or baricitinib, and taking into account high levels of inflammatory markers and increase on oxygen supplementation we started treatment with corticosteroids parenterally [8]. On day 10 of hospitalization (17^{th} day of illness) hemorrhagic diarrhea, abdominal pain and livid cold right foot were noticed. Microbiological testing-coproculture and C. difficille toxin resulted negative, in adverse stool blood test was positive. CT angiography of abdomen and thorax (Figure 2A, 2B, 2C) was obtained to define lesions and their etiology. The imaging showed thrombosis of abdominal aorta and left renal artery with consecutive infarction of the left kidney. Vascular surgeon preferred conservative treatment with therapeutic doses of low molecular heparin (Enoxaparine 80 mg/twice daily administered subcutaneously) and parenteral Bergman solution. We performed continuous examination of blood hemostasis and anti-Xa with proper corrections on dosage according to the results (Table 2). Following the treatment, two days later, symptoms had fast clinical resolution with regression of diarrhea and normal coloring of the right foot. On day 15 of treatment, the patient complained of severe chest pain.

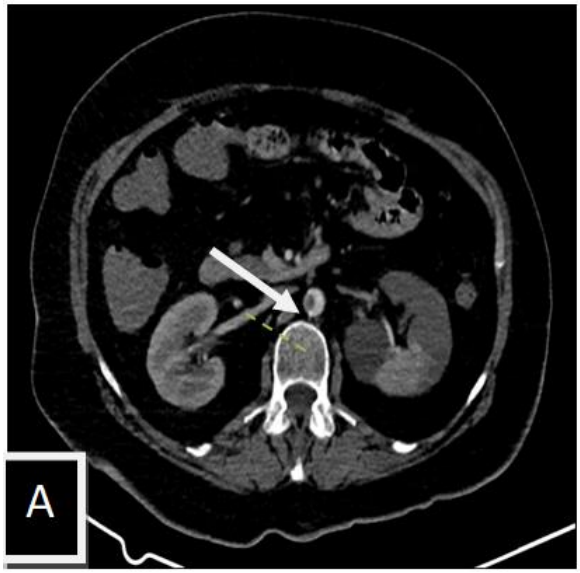

Fig. 2 (A). Thrombosis in abdominal aorta

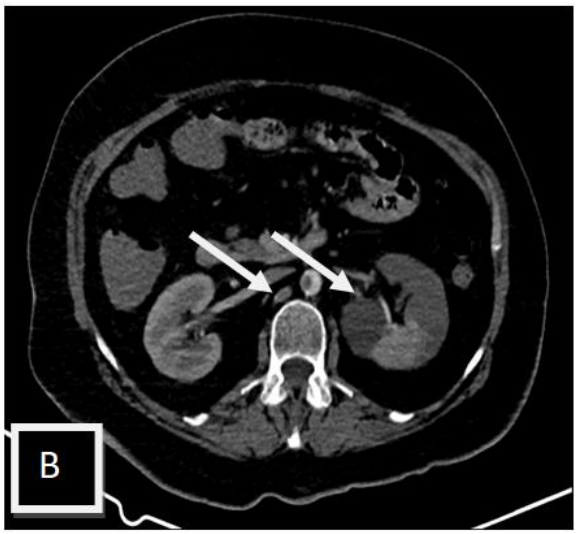

Fig. 2 (B). Thrombosis of left kidney artery

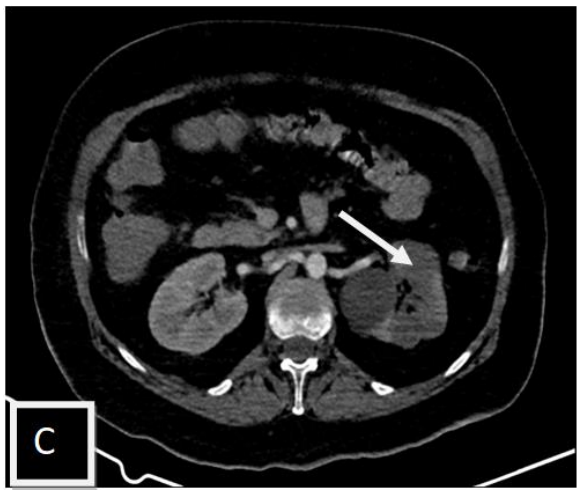

Fig. 2 (C). Consecutive infarction of left kidney

Cardiologic examination was performed including electrocardiogram (ST elevations, troponin levels 28.1 pg/ml..6.2 pg/ml). Conservative treatment with antiplatelet drugs (clopidogrel and aspirin) suggested by a cardiologist led to fast resolution of symptoms. During hospital stay, continuous clinical progression was observed and oxygen therapy was weaned off (oxygen saturation (SpO2) 92% on room air measured by pulse oxymeter) three days before release. The patient was successfully discharged on day 42, and vascular evaluation was continued. After 6 months, the patient was diagnosed with adenocarcinoma colon transversum, so surgical and oncological treatment is continued.

Table 2. Homeostasis and d-dimers

Variables	Reference	7th day of illnes	12th day of illness	16th day of illness	20th day of illness	25th day of illness	28th day of illness	31st day of illness	40th day of illness	before discharge
Plat.	**150-450**	**202**	**252**	**411**	**238**	**309**	**338**	**291**	**259**	**324**
Hct	**35-50**	**39.1**	**36.2**	**37.6**	**35.2**	**29.4**	**29.7**	**29.5**	**28.4**	**29.1**
PT	**9.8-14.2**	**12.8**	**11**	**11.8**	**11.5**	**11.56**	**12**	**11.2**	**10.83**	**10.5**
aPTT	**27.9-37.7**	**34.3**	**31.1**	**30.7**	**25.8**	**28.2**	**26.9**	**25.8**	**27.21**	**25**
TT	**16.1-22.2**	**17.9**	**17.3**	**20.9**	**18.9**	**25**	**22.2**	**22.5**	**24.59**	**18**
DD	**0-500**	**995.4**	**1626**	**2857**	**8867**	**1973**	**1392**	**1101**	**963**	**674**
anti Xa	**0.5-1.2**				**0.4**	**0.87**	**1.3**	**1.3**	**1.24**	
CLt	**0-106**				**57**	**76**				

Plat.-platelet count; Hct-hematocryt; PT- prothrombine time; aPTT- activated prothrombine time; TT- thrombin time; DD- d-dimers; CLt- clopidogrel test

Discussion

Nowadays, accumulated scientific data about the pathophysiology of SARS - CoV-2 as a viral infectious disease complicated with vascular disease injury suggest the hypercoagulability and immunothrombosis in the genesis of severe clinical features of COVID-19 [2]. Vascular thrombosis, much more venous than arterial, as a complication of the severe clinical form is often described in medical publications [3]. The cytokine storm as an exaggerated immune response to the virus leads to a hyperinflammatory process, hypoxia, diffuse intravascular coagulation and consecutive immobilization of patients [4]. In our case, thrombosis occurred in blood vessels with high flow. Some studies suggest that this is related with changes in platelet function found in COVID-19 patients [5]. It is suggested that this phenomenon occurs *in situ* rather than due to embolism. Prophylaxis with low molecular heparin in some cases does not stop the evolving immunothrombosis in patients with severe disease [6]. Some studies suggest that antiplatelet drugs may have benefit especially in long-term use before infection with SARS-CoV-2 [7]. Meizlish *et al*. suggest that retrospective data from patients who received Aspirin as an antiplatelet drug had lower mortality rate. Different approaches in various studies are evolved in the spectrum of dosage of low molecular heparin, but diagnosing thrombosis leads to the need of therapeutic antithrombotic dosage of low molecular heparin. In our everyday practice, patients with severe hypoxemia and a high risk of thrombosis are treated with therapeutic doses of low molecular heparin with final aim to reach therapeutic doses in blood and this is regularly controlled by checking anti-Xa levels. In patients with severe COVID-19 disease and high risk of thrombosis, we support usage of therapeutic doses of anticoagulant drugs with high precautions on possible complications [8,9].

Restrictions and limitations

In this case presentation, the limitations were no opportunity to examine interleukin 6, ferritin and fibrinogen levels. We also did not perform a control CT angiography to define the resolution of thrombosis and lesions, so the evaluation is based on clinical features. Antiviral treatment with Remdesivir was started on day 12th of illness due to technical problems even though it is recommended as soon as possible.

Conclusion

Patients with severe COVID-19 despite treatment with low molecular heparin are at high risk of thrombosis. Our patient was diagnosed early regarding onset of symptoms, and treatment with therapeutic doses of low molecular heparin- enoxaparine gave improving clinical results. So, this raises questions regarding treatment with therapeutic doses of low molecular heparin in patients who are treated in hospital conditions and who require oxygen supplemental therapy with high risk of trombosis, in adverse of prophylactic dosage.

Conflict of interest statement. None declared.

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