CASE REPORT

WUNDERLICH'S SYNDROME IN COVID-19 PATIENT

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ABSTRACT

Up to this date, more than 180 million people worldwide have been affected with COVID-19 and more than 3.9 million people have died. The effect of COVID-19 on thrombosis is well known, and due to this, anticoagulant agents are prescribed. However, the use of anticoagulants is associated with the bleeding trend and occasionally major complications and death outcomes.
In this paper, we present the case of a COVID-19 patient treated with anticoagulant therapy who developed Wunderlich's syndrome. Up to our knowledge, this is the first case of this syndrome in a patient with COVID-19.

Keywords: *COVID-19, Wunderlich syndrome, iliopsoas hematoma, retroperitoneal haemorrhage, anticoagulants.*

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INTRODUCTION

Up to this date, more than 180 million people worldwide have been affected with COVID-19 and more than 3.9 million people have died (1). The effect of COVID-19 on thrombosis is well known, with the incidence of 33% of thrombotic events in these patients (2). Due to this, anticoagulant agents are prescribed and administered to a great number of COVID-19 patients (3). However, the use of heparin and other anticoagulant drugs is associated with the bleeding trend and occasionally major complications and death outcomes (4). The proportion of bleeding complications varies from 4.8% to 8% (5) and one of the rarest conditions from this spectrum is Wunderlich's syndrome (WS) which is defined as spontaneous, nontraumatic hemorrhage into the perirenal and retroperitoneal spaces (6). The etiology of this syndrome includes neoplastic and non-neoplastic causes such as vasculopathy, kidney diseases, and anticoagulant drugs (6-8). The golden standard for diagnosis of Wunderlich's syndrome is MDCT of abdomen and pelvis, together with the correlating clinical picture which includes Lenk's triade: an acute flank pain, flank mass, and hypovolemic shock (6, 9, 10). The syndrome is rare, with only 102 cases described since 2000 (6, 11, 12).

In this paper, we present the case of a COVID-19 patient treated with anticoagulant therapy who developed Wunderlich's syndrome. After thorough literature research using PubMed, Ebsco and Google Scholar databases, we discovered, that up to this day, there were no similar cases described.

CASE REPORT

A 79-year-old woman developed headache and fatigue and was tested positive ona a PCR test for COVID-19 on March 23rd, 2021. On the same day, she was admitted to the Clinic for Infectious diseases at the University Clinical Center Kragujevac, with blood oxygen saturation (SPO2) 90%, partial pressure of oxygen (pO2) 7.5 kPa and partial pressure of carbon-dioxide (pCO2) 6.1 kPa. She was afebrile but had a low gas exchange. Her medical history and heteroanamnestic data gave us information about her chronic illnesses: angina pectoris, cerebrovascular insult fifteen years ago and hypothireosis.

She was treated for 20 days in different COVID units at our hospital. During the hospitalization, the patient was treated with the following therapy: antiviral drug (Favipiravir), antibiotics (azithromycin, ceftriaxone, piperacillin/tazobactam), corticosteroids (methylprednisolone), anticoagulants (enoxaparine), antipyretic (paracetamol), vitamins C and D, gastroprotective (pantoprazole), diuretic (furosemide), potassium-chloride (due to the hypokalemia). Enoxaparine was applied subcutaneously in a dosage 0.6ml/12h, when D-dimer was higher than 1.0 and 0.6ml/24h if D-dimer was lower than 1.0. She also continued to take treatment for her chronic diseases: clopidogrel 75mg (1+0+0), lercanidipine 10mg (0+0+1), bisoprolol 5mg (1+0+0) and levothyroxine 75mg (1+0+0). During the hospitalization, she was also on oxygen therapy. Blood oxygen saturation and oxygen flow are shown in Table 1. The initial chest radiography was done on admission and showed small consolidation of lung parenchyma in the right basolateral part of the lung. Follow-up radiographies were done on the 7th day, 12th, 13th, 15th, and 20th day of the hospitalization. The worsening of lung condition was noticeable on the 12th day of hospitalization (Figure 1) and the following day the patient went into clinical worsening (gas exchange analyses on 15 l/min: SPO2 88%, pO2 6.7 kPa, pCO2 6.1 kPa, pH 7.48, potassium 4.0, HCO3 32.0 mmol/l) and there was a need to put her on High Flow Ventilator (fiO2 90%). On April 6th chest radiography showed regression (Figure 2) and the patient was switched into an oxygen mask with the flow 8 l/min. The laboratory results with the main findings are shown in Table 2. On April 11th patient was discharged home in improved condition with hemodynamically stable vital parameters and advice for oxygen concentrator use with oxygen flow 2 l/min at home.

Figure 1. Chest radiography on 12th hospitalization day

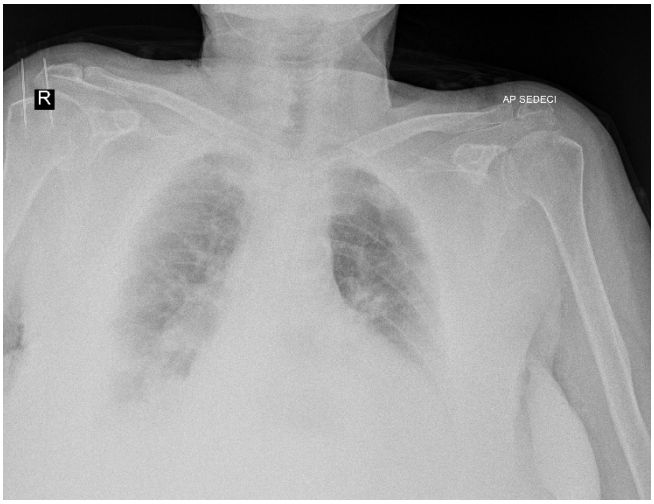


Figure 2. Chest radiography on 15th hospitalization day

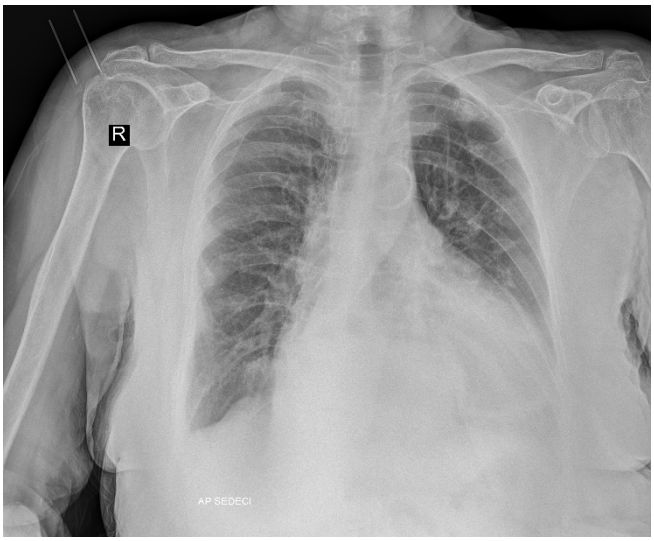


Table 1. Blood oxygen saturation and oxygen flow during each day of hospitalization

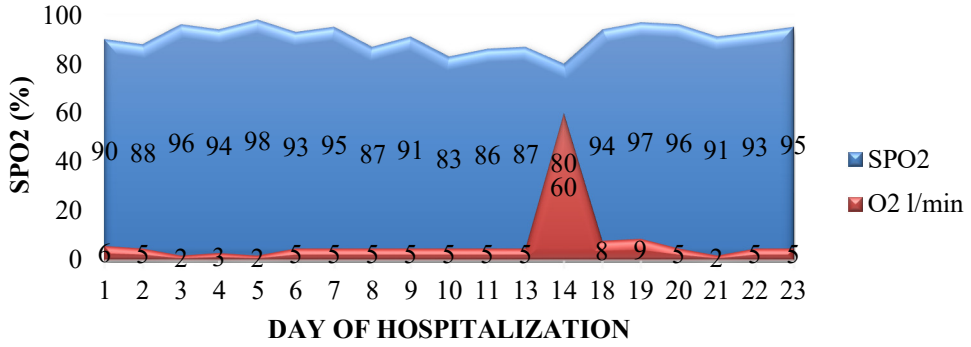


Table 2. Main laboratory findings

	Reference range	Day 1	Day 7	Day 12	Day 20	Day 21	Day 22
WBC	3.7-10.0 (10^9/L)	4.10	3.71	6.92	7.48	38.03	47.74
LYM	1.2-3.4 (10^9/L)	1.10	0.82	1.05	1.17	1.17	1.74
RBC	3.86-5.08 (10^{12}/L)	4.52	4.65	4.69	4.89	3.47	3.86
HGB	110-157 (g/L)	132	140	137	145	107	116
PLT	135-450 (10^9/L)	133	109	162	233	196	96
PT	9.1-12.1 (s)	11.5	10.1	10.5		14.6	23.6
INR	0.9-1.1	1.010	0.890	0.920		1.280	2.060
PT%	70-120	111	146	135		76	39
D-DIMER	<0.50 (ug/ml FEU)	0.62	1.17	0.45	0.47	0.61	1.20
AST	0-40 (IU/L)		26	16		5296	
ALT	0-40 (IU/L)	18	22	12		3843	
GLUC	3.8-6.1 (mmol/L)	5.5	4.5	7.6	8.1	12.8	9.5
UREA	3.0-8.0 (mmol/L)	9.8	7.5	9.3	12.3	24.2	28.1
CREA	49-106 (mmol/L)	107	78	81	91	332	420
CK	0-171 (U/L)	88	27	54		1801	3861
CK-MB	<25.0 (U/L)		14	19		192	
CRP	0.0-5.0 (mg/L)	1.1	10.9	28.7	1.5	21.5	85
TROPONIN	<0.0156 (ng/mL)	<0.01	<0.01	<0.01		0.0913	0.3255
Procalcitonin	0.5-2.0 >2.0 risk for sepsis(ng/mL)	0.068	0.02	0.02	0.046	0.456	1.510
proBNP	negative <125, grey area 125-450, insufficiency >450 (pg/mL)	500	1611	986		4028	
LDH	220-450 (U/L)		446	503		17157	
GGT	7-50 (IU/L)	11	21			23	
Potassium	3.5-5.3 (mmol/L)		4	4.6	4.8	5.6	
Sodium	137-147 (mmol/L)		140	140	140	138	
Albumin	35-52 (g/L)	38	35			32	30

* WBC-white blood cells, LYM-lymphocytes, RBC-red blood cells, HGB-hemoglobin, PLT- platelets, PT-prothrombin time, INR-international normalized ration, AST- aspartate aminotransferase, ALT- alanine transaminase, GLUC-glucose, CREA-creatinine, CK-creatin kinase, CRP-C reactive protein, proBNP-brain natriuretic peptide, LDH- lactate dehydrogenase, GGT- gamma-glutamyl transferase

The following day, in the late evening of April 12th, the patient was brought by ambulance to the Clinic for infectious diseases due to disorientation and collapse. The patient was admitted and physical examination showed pale skin, multiple hematomas on the arms, and tenderness and mass in the right lower abdominal quadrant. Two hours after the hospitalization, the patient went into clinical worsening: hypotension 90/45 mmHg, SPO2 91%, pO2 9.1 kPa, pCO2 4.2 kPa, and developed haematuria and rectal bleeding. Laboratory analyses are presented in Table 2. Lung X-ray showed an interstitial pattern with no consolidations. Due to the bleeding and progressive anaemia, the general surgeon was consulted, who indicated MDCT of abdomen and pelvis and transfusion of deplasmated erythrocytes. Also, troponin, creatine kinase, and myocardial creatine kinase were significantly elevated and due to that cardiologist was consulted, who stopped anticoagulant drugs and included diuretic treatment due to the higher values of proBNP. The MDCT of the abdomen and pelvis showed a large hematoma located perirenal, posterior, within the right muscles' ileus and psoas and lowering down into the right inguinal region (Figure 3), with a small amount of blood located subhepatic and perihepatic. The dimensions of the hematoma were 87x74x168mm. The Wunderlich's syndrome diagnosis was made based to MDCT findings, together with the Lenk's triade, which was presented during clinical examination.

After the imaging diagnosis, the patient was transferred to the Emergency Department at our hospital. The vascular surgeon didn't indicate surgical treatment but insisted on conservative therapy. The patient was treated with symptomatic treatment, gastro-protective drugs, deobstructive drugs, antibiotics, diuretics, infusions, transfusions, and vitamins, but she continued to be anaemic, hypotensive and hemodynamically unstable. Laboratory findings on April 13th (22nd day of hospitalization) presented in Table 2 showed signs of blood loss, renal failure, and heart damage. The patient developed cardiac asystole with no reaction to cardiopulmonary resuscitation and applied treatment, which led to death in the early morning of April 14th, 2021. Clinical autopsy was not performed due to the patient's COVID-19 infection and the World Health Organization guidelines for this condition.

DISCUSSION

Wunderlich's syndrome is a rare condition and it could be missed due to the ambiguous signs and symptoms and various comorbidities which may camouflage it (6, 12). In addition to this, the more infrequent causes are non-neoplastic conditions (6), which was the case with our patient. Since our patient didn't have neoplasms such as angiolipoma or renal cell carcinoma which are the most frequent etiological factors that lead to the WS and had no trauma, non-neoplastic conditions are considered during the diagnostic process. However, our patient was treated with anticoagulant therapy (enoxaparin) for 21 days during hospitalization due to the COVID-19, which is the described cause for the development of WS. Up to our knowledge, this is the first case of WS in a patient with a COVID-19 diagnosis.

Figure 3. MDCT of abdomen and pelvis showing large hematoma in transversal, sagittal and coronal planes



Nevertheless, there are similar published case reports and case series which describe other bleeding complications due to the anticoagulation treatment in COVID-19 patients, such as retroperitoneal haemorrhage, rectus sheath hematoma, and

iliopsoas hematoma (13). It is known that rectus sheath and retroperitoneal hematomas, which develop as a result of therapeutic anticoagulants, have mortality up to 20% (2). The incidence of iliopsoas hematomas in the general population is between 0.3% to 0.4%, while the incidence of considerable bleeding during anticoagulant treatment is between 0.9% and 16.5% in the same population (13, 14). Spontaneous iliopsoas hematomas have high mortality rates which fluctuate between 30% and 50% during hospitalization, and only one-third of these patients present with Lenk's triad which was seen in our patient (13, 15). Published literature suggests various predisposing components for this condition, such as anticoagulant treatment, advancement in age, and haemodialysis (13). Our patient had two out of three predisposing factors, together with COVID-19 as an underlying condition. It is known that COVID-19 patients have a modified coagulation profile due to the increase of pro-inflammatory cytokines, such as IL-6 which cause a hypercoagulable state and require anticoagulant therapy such as heparin (16). Due to the COVID-19 infection and the increased values of D-dimer, the patient needed to be on the anticoagulant treatment, which was the only known predisposing factor for the development of the spontaneous, nontraumatic hemorrhage into the perirenal and retroperitoneal spaces that was later on diagnosed as WS. Patient's age and other comorbidities only added to the progression of the clinical picture and fatal outcome.

CONCLUSION

Up to our knowledge, this is the first case of Wunderlich's syndrome in a patient with COVID-19. Nevertheless, it is important to point out the anticoagulant treatment of COVID-19 and spontaneous bleeding as its possible complication. Also, this type of bleeding located in the psoas muscle might have a fatal outcome because signs and symptoms might present after the large hematoma formation. Because of that, instantaneous radiological diagnosis and appropriate treatment of bleeding are required.

REFERENCES

1. Worldometer. Coronavirus. Retrieved June 24, 2021 from https://www.worldometers.info/coronavirus/
2. Ottewill C, Mulpeter R, Lee J, Shrestha G, O'Sullivan D, Subramaniam A, et al. Therapeutic Anti-coagulation in COVID-19 and the Potential Enhanced Risk of Retroperitoneal Haematoma. QJM 2021:hcab059. doi: 10.1093/qjmed/hcab059.
3. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol 2020; 189(5): 846-847.
4. Javid A, Kazemi R, Dehghani M, Bahrami Samani H. Catastrophic retroperitoneal hemorrhage in COVID-19 patients under anticoagulant prophylaxis. Urol Case Rep 2021; 36: 101568.
5. Shah A, Donovan K, McHugh A, Pandey M, Aaron L, Bradbury CA, et al. Thrombotic and haemorrhagic complications in critically ill patients with COVID-19: a multicentre observational study. Crit Care 2020; 24(1): 561.
6. Pytlewski A, Siwek M, Leszek D, Delikat M, Smietana D,Sobieraj E, et al. Wunderlich's syndrome associated with anticoagulant treatment, heart failure, and post-radiation vasculopathy (RCD code: I-O). Journal of Rare Cardiovascular Diseases 2019; 4 (2): 51–55.
7. Yamamato K, Yasunaga Y. Antiplatelet therapy and spontaneous perirenal hematoma. Int J Urol 2005; 12: 398–400.
8. Akuzawa N, Kurabayashi M. Multiple spontaneous hemorrhages after commencing warfarin therapy. SAGE open Med case reports 2018; 6: 2050313X18 778 380.
9. Wunderlich C. Handbuch der Pathologie und Therapie. 2nd ed. St. 1856.
10. Daliakopoulos SI. Spontaneous retroperitoneal hematoma: a rare devastating clinical entity of a pleiada of less common origins. J Surg Tech Case Rep 2011; 3:8–9.
11. Sierra-Díaz E, Belmonte-Hernández MV, Villanueva-Pérez MA, et al. Non-traumatic spontaneous retroperitoneal bleeding: the effect of an early and accurate diagnosis. Cir Cir 2015; 83: 206–10.
12. González-Castro A, Ortiz-Lasa M, García-Reyero J, et al. Wünderlich syndrome due to a ruptured iliac vein secondary to deep venous thrombosis. Rev Española Patol 2018; 51: 197–202.
13. Nakamura H, Ouchi G, Miyagi K, Higure Y, Otsuki M, Nishiyama N, et al. Case Report: Iliopsoas Hematoma during the Clinical Course of Severe COVID-19 in Two Male Patients. Am J Trop Med Hyg 2021; 104(3): 1018–21.
14. Teta M, Drabkin MJ. Fatal retroperitoneal hematoma associated with Covid-19 prophylactic anticoagulation protocol. Radiol Case Rep. 2021; 16(7): 1618-1621.
15. Artzner T, Clere-Jehl R, Schenck M, Greget M, Merdji H, De Marini P, et al. Spontaneous ilio-psoas hematomas complicating intensive care unit hospitalizations. PLoS One 2019; 14: e0211680.
16. Patel I, Akoluk A, Douedi S, Upadhyaya V, Mazahir U, Costanzo E, et al. Life-Threatening Psoas Hematoma due to Retroperitoneal Hemorrhage in a COVID-19 Patient on Enoxaparin Treated With Arterial Embolization: A Case Report. J Clin Med Res 2020; 12(7): 458-461.