Porast *D dimera* u infekciji *COVID 19* kod ambulantnih pacijenata sa komorbiditetom

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D-dimer rise in outpatients with *COVID 19* and comorbidities

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Sažetak

Uvod. Koronavirusna bolest (*COVID-19*) je zarazna bolest koju izaziva novootkriveni koronavirus. Većina ljudi zaraženih virusom *COVID-19* doživjeće blagu do umerenu respiratornu bolest i oporaviće se bez potrebe za posebnim lečenjem. Stariji ljudi i lica s osnovnim medicinskim problemima, poput kardiovaskularnih bolesti, dijabetesa, hroničnih bolesti respiratornog sistema i karcinoma, imaju veći rizik za razvoj teške bolesti.

Prikaz slučaja. Pacijentkinja, 57 godina, lekar, javlja se na pregled zbog pojave infekcije *Sars Cov2*. U ličnoj anamnezi od preležanih bolesti navodi tromboemboliju pluća, na koju se, s obzirom na komplikacije koje mogu nastati, mora obratiti posebna pažnja u dijagnostici i lečenju.

Zaključak. Epidemija novim koronavirusom, koji je pre nešto više od godinu dana zadesio svet, stavljaju kako izabranog lekara opšte medicine, tako i ceo zdravstveni sistem na veliko iskušenje. Zbog toga naučna i medicinska zajednica, ali i šira javnost, u borbi sa *COVID-19* pandemijom moraju da se oslone na dosadašnje proverene činjenice, spremni da u budućnosti prihvate promenu aktuelne prakse kako budu pristizala nova saznanja iz pravilno dizajniranih, sprovedenih i prikazanih bazičnih istraživanja i kliničkih studija. Sa činjenicama i dosadašnjim dokazima iz kliničke prakse, potrebno je pristupiti svakom pacijentu posebno, rukovodeći se najnovijim smernicama iz kliničke prakse i time sprečiti komplikacije kod pacijenata sa pratećim komorbiditetima obolelih od virusa *COVID 19*.

Ključne reči: *D-dimer*, *COVID 19*, komorbiditet, plućna embolija, opšta medicina.

Abstract

Introduction: *COVID-19* is an infectious disease caused by a newly discovered Coronavirus. Most of the infected people will go through it with mild to moderate respiratory symptoms and recover without any specific treatment. Older people and people with medical issues, such as cardiovascular diseases, diabetes, chronic pulmonary diseases, malignant diseases are at higher risk for the severe form of the disease.

Case report: Female patient, 57, physician, presents with symptoms of *Sars-Cov-2* virus infection. Her personal history is significant for pulmonary thromboembolism (PTE). This is a disease which should be paid special attention to.

Conclusion: A new Coronavirus infection, which struck the world a year ago, presents a great challenge for general physicians (GPs) and the health system as a whole. The scientific and medical community and the general public must lean on verified facts in this fight against the *COVID-19* pandemic. They should be ready to change their treatment protocols, as new information appears from properly designed, implemented, and presented basic and clinical studies. Each patient should be approached with special care, using up-to-date facts and proofs from clinical practice, and guided by the newest treatment protocols thus reducing complications in *COVID-19* patients with comorbidities.

Keywords: *D-dimer*, *COVID-19*, comorbidity, pulmonary thromboembolism, general practice.

Uvod

Koronavirusna bolest (*COVID-19*) je zarazna bolest koju izaziva novootkriveni koronavirus. Većina ljudi zaraženih virusom *COVID-19* doživjeće blagu do umerenu respiratornu bolest i oporaviti se bez potrebe za posebnim lečenjem. Stariji ljudi i oni sa osnovnim medicinskim problemima, poput kardiovaskularnih bolesti, dijabetesa, hroničnih bolesti respiratornog sistema i karcinoma, imaju veći rizik za razvoj teške bolesti¹.

Cilj rada

Cilj rada je bio da ukažemo na značaj ranog otkrivanja komplikacija i pravovremene prevencije kod pacijenata koji su oboleli od *COVID 19* a imaju pridružene bolesti.

Prikaz slučaja

Pacijentkinja, 57 godina, lekar, od preležanih bolesti navodi plućnu emboliju nastalu postoperativno, nakon operacije kuka (artroplastika desnog kuka) pre 10 godina. Astmatičar je, na terapiji, te je astma dobro kontrolisana poslednjih 15 godina, pušač 20 godina (koristi do 20 cigareta dnevno), ostale bolesti negira, nema alergiju na lekove.

Prvi pregled

Pacijentkinja se dana 08.12.2020. javlja u Respiratorni centar Doma zdravlja Novi Sad. Centar je formiran radi zbrinjavanja pacijenata kod kojih se sumnja da imaju infekciju *COVID 19* ili je *COVID 19* infekcija već potvrđena. Sa simptomima bola u grlu, osećaja slabosti u mišićima i zglobovima, osećaja izmenjenog ukusa, afebrilna, pacijentkinja navodi da su tegobe počele pre dva dana. Epidemiološkom anketom otkriveno da je bila u kontaktu sa *COVID 19* pozitivnom osobom. Tokom pregleda, ždrela je hiperemično, zadnji zid i nepčani lukovi, nad plućima se auskultatorno čuje normalan disajni šum. Rađena je SaO_2 99 (saturacija kiseonika), puls 80/min, broj respiracija 20/min. Pri pregledu pacijentkinje korišćen je *MEWS score* (*Modified Early Warning Score*) test radi određivanja težine kliničke slike i procene potrebe za hospitalnim lečenjem. Laboratorijske analize krvi: brzi *SARS-CoV-2* test je bio pozitivan, leukociti 4,6 10⁹/L, eritrociti 4,04 12 E/L, hemoglobin 132 g/L, hematokrit 0,39 L/L, trombociti 155, neutrofilni granulociti 61,8%. Zbog lakše kliničke slike i odsustva febrilnosti, pacijentkinja je posavetovana o upotrebi simptomatske terapije i preporučeno je mirovanje i izolacija od 14 dana. U slučaju pogoršanja stanja ili razvoja febrilnosti, preporuka je da se odmah javi lekaru.

Introduction

COVID-19 is an infectious disease caused by a newly discovered Coronavirus. Most of the infected people will go through it with mild to moderate respiratory symptoms and recover without any specific treatment. Older people and people with medical issues, such as cardiovascular diseases, diabetes, chronic pulmonary diseases, malignant diseases are at higher risk for the severe form of the disease¹.

Objective

We aimed at stressing the importance of the early discovery of the complications and timely prevention in *COVID-19* patients with comorbidities.

Case report

Female patient, 57, physician, with a personal history of pulmonary thromboembolism (PTE) which appeared after a hip operation 10 years ago (right hip arthroplasty). She suffers from asthma for 15 years now, but uses therapy and is therefore well regulated, she's been smoking for 20 years (20 cigarettes a day). She denies having any allergies or other diseases.

First medical check-up

The patient presented at the Respiratory center of PHC Novi Sad on December 8th, 2020. The Center was established for the treatment of patients with confirmed or suspected *COVID-19* infection. The patient complains of sore throat, general malaise, change of the sense of taste. She is afebrile and states her symptoms appeared two days ago. Epidemiology contact investigation discovered she had contact with *COVID-19* infected person. The physical examination revealed hyperemia of the back pharyngeal wall and palatal arches. The lung examination reveals clear breath sounds in all fields. Pulse oxymetry was 99% on room air, puls 80 beats/min, respiratory rate 20/min. We used the *MEWS score test* (*Modified Early Warning Score*) to evaluate her clinical presentation and the necessity to be hospitalized. Lab works: *SARS-CoV-2* rapid antigen test was positive, WBC 4,6 10⁹/L, RBC 4.04 12 E/L, Hgb 132 g/L, Htc 0,39 L/L, PLT 155, neutrophil granulocytes 61,8%. Due to mild clinical presentation and lack of febrility, she was sent away with symptomatic treatment and advice for bed rest and isolation for 14 days. She was advised to return immediately should there be any deterioration or high febrility.

Prva kontrola

Pacijentkinja se javlja na telefonsku kontrolu radi konsultacije i navodi da joj se dana 09. i 10.12.20. pojavilo pogoršanje stanja u vidu febrilnosti $38,2^{\circ}\text{C}$ i da dobija prolivaste stolice na 4 sata. Pacijentkinja navodi da nije primetila primese sluzi i krvi u stolici, zatim da ima bolove u stomaku tipa grčeva, bolove u mišićima, grudima, leđnoj kičmi, kukovima, karlici. Ponovo se, zbog navedenih simptoma, daje preporuka da se javi u Respiratorni centar usled pogoršanja zdravstvenog stanja. U Respiratornom centru urađena kontrolna laboratorija: kompletna krvna slika sa diferencijalnom formulom, *D*-dimer zbog pojave bolova u grudima i podatka iz anamneze o preležanim bolestima i da je imala plućnu emboliju. Laboratorijski nalazi pokazuju porast broja limfocita $34,9 \times 10^9/\text{L}$; neutrofilni granulociti $56,6 \times 10^9/\text{L}$; *D*-dimer 700 ng/L . Rendgenski snimak (RTG) pluća opisuje plućna polja koja su očuvane transparentije, bez znakova infiltracije plućnog parenhima, kostofrenični sinusi su slobodni, srčano-sudovna senka odgovara životnom dobu, nema pleuralnog izliva. Na osnovu kliničkog stanja pacijentkinje i na osnovu komorbiditeta, propisuje se terapija niskomolekularnim heparinom u dozi od $0,6 \text{ ml/24h}$ uz terapiju preparata acetylsalicilne kiseline od $100 \text{ mg } 1 \times 1 \text{ per os}$, uvodi se antibiotik iz grupe makrolidnih antibiotika (*azitromicin*) u dozi od $500 \text{ mg } 1 \times 1 \text{ per os}$, preporučuje se vitamiska terapija (preparati cinka, *D* vitamina i alfalipoijske kiseline). Imajući u vidu zdravstveno stanje pacijentkinje i na osnovu protokola lečenja infekcije COVID-19, upućuje se na ambulatno lečenje i na kontrolu za 7 dana².

Druga kontrola

Pacijentkinja se javlja na kontrolu nakon 7 dana. Na pregledu navodi da se brzo zamara i da ima osećaj lupanja srca, te kratak dah. Pregledana je od strane interniste i pulmologa i urađena je kontrolna laboratorijska analiza krvi, ponavlja se analiza *D*-dimera. Laboratorijske analize su uređene, vrednost *D*-dimera ($515,92 \text{ ng/ml}$) je u padu. Pregledom pulmologa uočava se blaga hiperemija sluzokože ždrela, retronazalno slivanje seroznog sekreta, nad plućima se auskultatorno čuje hipersonoran auskultatoni zvuk i normalno disanje. Rendgenski snimak pluća pokazuje znake lake hiperinflacije pluća, spirometrija: FVC (funkcionalni vitalni kapacitet) 131%; FEV (forsirani ekspirijumski volumen) 114%; FEV₁ (forsirani ekspiratorni volumen u prvoj sekundi) / FVC (funkcionalni vitalni kapacitet) = *Tiffeneau indeks* 0,94; PEF (maksimalna brzina izduvavanja vazduha) 97%. U terapiju se uvodi i inhalatorni dugodelujući kortikosteroid *ciklesonid* od 160 mcg/doza . Pregled interniste: TA (arterijska tenzija) $130/80 \text{ mmHg}$, auskultacija srca: bez patoloških šumova, ehokardiografija srca: EF (ejekciona frakcija) 62%, aortno i mitralno ušće b.o., šupljina desnog srca je u granicama normale, pulmonalna arterija i valvula b.o., perikard bez izliva. Savetovano da se terapija niskomolekularnim heparinom nastavi još 7 dana u istoj dozi od $0,6 \text{ ml/24h}$.

First follow-up visit

The patient had a phone consultation and she said her symptoms got worse on December 9th and 10th in the form of high fever (up to 38.2°C) and diarrhea every 4 hours. She didn't notice any signs of mucus or blood in her stools and she had stomach cramps, as well as muscle pain, chest pain, back pain, pain in her hips and pelvis. Due to the deterioration of her symptoms, she was advised to check in again with the Respiratory center. Upon her arrival, complete lab work was performed: CBC with Le formula, *D*-dimer (due to chest pain and her earlier history of PTE). Lab results showed an increase in lymphocyte count $34,9 \times 10^9/\text{L}$; neutrophil granulocytes were $56.6 \times 10^9/\text{L}$; *D*-dimer 700 ng/L . Chest X-ray showed clear lungs, with no signs of pulmonary infiltration, free costo-phrenic sinuses, and heart shape was normal for the patient's age, with no signs of pleural effusion. Based on her clinical presentation and earlier comorbidities she was prescribed *low molecular weight heparin* (LMWH) $0,6 \text{ ml/24h}$, acetylsalicylic acid $100 \text{ mg/day, per os}$, azithromycin $500 \text{ mg/day, per os}$, and vitamins (D, Zn, Alpha-lipoic acid). Based on her current state and according to protocols for COVID-19 treatment guidelines, she was treated as an outpatient and her next follow-up was scheduled for 7 days².

Second follow-up visit

On her second follow-up, after 7 days, she complains of fatigue, heart palpitations, shortness of breath. She was examined by an internal medicine specialist and pulmonologist and control lab work was performed, with *D*-dimer. Lab results were normal and *D*-dimer was decreasing (515.92 ng/ml). A pulmonologist found mild hyperemia of the pharyngeal mucosa, retronasal mucosal secret discharge, vesicular breathing was heard in all lung fields. Chest X-ray showed signs of slight hyperinflation of the lungs. Spirometry findings: FVC (forced vital capacity) 131%; FEV (forced expiratory volume) 114%; FEV₁ (forced expiratory volume in one second) / FVC (forced vital capacity) = *Tiffeneau index* 0.94; PEF (peak expiratory flow) 97%. A long-lasting inhaled corticosteroid *ciclesonide* 160 mcg/dose was added to her therapy regime. Physical findings by an internal medicine specialist: BP $130/80 \text{ mmHg}$, heart auscultation showed no heart murmurs or thrills. Cardiac ultrasound findings: EF (*ejection fraction*) 62%, mitral and aortic orifices normal, as well as the right heart, pulmonary arteries, and their valves, no pericardial effusion. She was advised to continue with LMWH therapy, at the same dose (0.6 ml/24h) for 7 more days.

Treća kontrola

Pacijetkinja se javlja na kontrolu nakon 14 dana, prekinuta je obavezna izolacija po epidemiološkim preporukama. Na pregledu, nema temperaturu ali navodi da se i dalje oseća slabo i malaksalo i da se brzo zamara. Ponavlja se laboratorijska analiza krvi i *D*-dimera. Laboratorijski nalaz je uredan, *D*-dimer je u preporučenom opsegu. Auskultatorni nalaz pluća i srca su uredni, TA (arterijska tenzija) 120/80 mmHg, EKG (elektrokardiografija srca) beleži sinusni ritam, srčana frekvencija 90/min, *rS* u *D*₃ i *aVF* bez poremećaja ritma i bez sigurnih znakova ishemije i lezije miokarda. Preporučuje se nastavak simptomatske terapije, ukida se primena niskomolekularnog heparina i savetuje nastavak *per os* terapije samo sa preparatima acetilsalicilne kiseline u dozi od 100 mg 1x1. Takođe je savetovana kontrola pulmologa i interniste, kao i kontrola laboratorijskih analiza za mesec dana.

Diskusija

Od prvih izveštaja iz Kine na početku pandemije *COVID-19*, kod ovih pacijenata je opisana velika učestalost trombotičnih pojava na različitim vaskularnim sistemima, posebno na plućnom, mada i u dubokom venskom sistemu donjih udova (DVT-duboka venska tromboza), mozga i srca, dostižući u nekim slučajevima ispunjavanje kriterijuma diseminovane intravaskularne koagulacije³. *D*-dimer je jedan od fragmenata proteina i glavni proizvod razgradnje fibrina plazminom. Nastaje u završnoj fazi stvaranja ugruška, poznat je i kao fragment *D*-dimera i fragment razgradnje fibrina. Obično nije moguće da se otkrije, ili se otkriva na vrlo niskom nivou, osim ako telo stvara i razgrađuje krvne ugruške. Tada se njegov nivo u krvi može znatno povećati⁴. Nivoi *D*-dimera su povišeni u plazmi u prisustvu akutne tromboze, zbog istovremene aktivacije koagulacije i fibrinolize. Negativna prediktivna vrednost ispitivanja *D*-dimera je visoka, a normalan nivo *D*-dimera čini akutnu plućnu emboliju ili duboku vensku trombozu malo verovatnim⁵. Kliničko ispoljavanje *COVID-19* infekcije može varirati od asimptomatskih oblika sve do razvoja teških formi pneumonija koje mogu dovesti i do smrtnog ishoda. Najčešći simptomi i znaci kod obolelih su povišena telesna temperatura, kašalj, osećaj nedostatka vazduha i kratkog daha, mialgije, artralgijske, glavobolje. Kod nekih bolesnika se mogu javiti i bol u stomaku, gubitak apetita, mučnina i povraćanje, dijareja⁶, vrtoglavica i dugotrajna gubitak osećaja za miris i ukus. Najčešći laboratorijski nalazi podrazumevaju leukopeniju i limfopeniju u krvnoj slici, kao i povišene vrednosti sedimentacije eritrocita, CRP-a (C reaktivni protein), *D*-dimera, feritina⁷, LDH (laktat dehidrogenaza)⁸.

Detaljni opisi prevencije i kontrole infekcije *COVID-19* (*SARS-CoV-2*) virusom nalaze se u odgovarajućim nacionalnim

Third follow-up visit

This follow-up was 14 days after the onset of her symptoms and her isolation was discontinued following epidemiological recommendations. She was afebrile, but she said she still felt weak, fatigued, and breathless. Lab work and *D*-dimer were repeated and they were all in the normal range. Physical findings of the lungs and heart were normal, BP 120/80 mmHg, ECG – sinus rhythm, HR 90 beats/min, *rS* in *D*₃ and *aVF*, with no rhythm disorders and signs of ischemia and lesions of the myocardium. She was advised to continue with symptomatic treatment and acetylsalicylic acid 100 mg/day but LWMH was discontinued. She was advised to make another appointment with a pulmonologist and internal medicine specialist and repeat her lab work in a month.

Discussion

Since the first reports from China, at the beginning of the *COVID-19* pandemic, a high incidence of thrombotic events was found in these patients, in different vascular systems, especially pulmonary, as well as the deep vein thrombosis of the lower extremities, brain, and heart. In some cases, it met the criteria of disseminated intravascular coagulation.³ *D*-dimer is a protein fragment and the main product of fibrin degradation by plasmin. It appears in the final phase of clot-forming, and it's also known as *D*-fragment and fibrin disintegration fragment. It's usually untraceable or traced at very low levels. But if the body creates or disintegrates blood clots its levels can be very high⁴. Plasma levels of *D*-dimer are high in acute thrombotic events due to simultaneous coagulation activation and fibrinolysis. The negative predictive value of the *D*-dimer test is high and normal levels of *D*-dimer make the diagnosis of acute PTE or DVT less likely⁵. Clinical manifestations of *COVID-19* infection may vary broadly, from asymptomatic forms to severe forms of pneumonia, even with lethal outcome. The most common signs and symptoms of the diseased are high fever, cough, breathlessness, and shortness of breath, myalgias, arthralgias, headaches. Some patients experience stomachache, loss of appetite, feeling sick, vomiting, diarrhea⁶, dizziness, and long-term loss of the sense of smell and taste. CBC is usually remarkable for leucopenia and lymphocytopenia, as well as elevated ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), *D*-dimer, ferritin⁷, LDH (lactate dehydrogenase)⁸.

A detailed description of the prevention and treatment of the *COVID-19* infection (*SARS-CoV-2*) may be found in the national guidelines, recommendations, and instructions, documents of the WHO (World Health Organisation) and other significant institutions in this area of interest – CDCs (Centers for disease control of the European Union⁹, USA¹⁰, and China¹¹). Complications arising during the treatment of *COVID-19* patients should be treated following adequate

vodičima, preporukama i uputstvima² dokumentima Svetske zdravstvene organizacije i drugih renomiranih institucija u ovoj oblasti (Centri za prevenciju i kontrolu bolesti Evropske unije⁹, Sjedinjenih Američkih država¹⁰ i Kine¹¹) Komplikacije koje nastaju tokom lečenja bolesnika sa *COVID-19* treba da se leče u skladu sa odgovarajućim vodičima dobre kliničke prakse i drugim sličnim preporukama. Primera radi, niskomolekularni heparini i nefrakcionisani heparin se koriste prema indikacijama za profilaksu tromboembolizma uz praćenje vrednosti *D*-dimera.

Zaključak

Epidemija novim koronavirusom koji je pre nešto više od godinu dana zadesio svet i proširio se do sada neviđenom brzinom, stavlja kako izabranog lekara opšte medicine, tako i ceo zdravstveni sistem na veliko iskušenje. Novi soj korona virusa, do sada nepoznat ljudskom organizmu, dovodi do toga da su istraživanja intenzivna i kliničko iskustvo se postepeno obogaćuje. Zbog toga, naučna i medicinska zajednica, ali i šira javnost, u borbi sa *COVID-19* pandemijom moraju da se oslone na dosadašnje, proverene činjenice, spremni da u budućnosti prihvate promenu aktuelne prakse kako budu pristizala nova saznanja iz pravilno dizajniranih, sprovedenih i prikazanih bazičnih istraživanja i kliničkih studija^{12,13,14}.

Na osnovu činjenica i dosadašnjih dokaza iz kliničke prakse, potrebno je pristupiti svakom pacijentu posebno rukovodeći se najnovijim smernicama iz kliničke prakse i na taj način sprečiti komplikacije kod pacijenata sa pratećim bolestima obolelih od *COVID-19*.

guidelines and recommendations. For example, LWMH and unfractionated heparin should be used according to indications for thromboembolism prophylaxis, simultaneously following *D*-dimer values.

Conclusion

A new coronavirus epidemic that hit the world a year ago and spread with lightning speed challenged GPs and the health systems worldwide. This new coronavirus strain, unknown to mankind until now, led to the intensification of scientific research and the clinical experience grows every day. Therefore, the scientific and medical community and the general public must lean on verified facts in this fight against the *COVID-19* pandemic. They should be ready to change their treatment protocols in the future, as new information appears from properly designed, implemented, and presented basic and clinical studies^{12,13,14}.

Based on the scientific facts, each patient should be approached with special care, using up-to-date facts and proofs from clinical practice, and guided by the newest treatment protocols thus reducing complications in *COVID-19* patients with comorbidities.

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