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PLUĆNA TROMBOEMBOLIJA I PERIKARDNI IZLIV KAO KARDIOVASKULARNE KOMPLIKACIJE COVID-19 INFEKCIJE

Sažetak: Sistemska aktivacija koagulacije i pulmonalna trombo-inflamacija sa lokalnim vaskularnim oštećenjem uzrokovanim SARS-CoV-2 infekcijom povećava rizik za razvoj tromboembolijskih komplikacija: insulta, plućne arterijske tromboze (plućna tromboembolija) i duboke venske tromboze (venski tromboembolizam). Mioperikarditis se kod COVID-19 pacijenata može javiti u sklopu ili posle pojave respiratornih simptoma. Česte su manje perikardne efuzije do 1cm koje prate zahvaćenost perikarda. Kod naše pacijentkinje tokom hospitalizacije zbog obostrane upale pluća izazvane SARS-Cov-2 virusom tokom rutinske kontrole D-dimera uočene su povišene vrednosti 2.3 puta veće od referentnog opsega, uz povišene biomarkere inflamacije. Imala je simptome respiratorne infekcije, a bez izražene kliničke simptomatologije koja bi ukazivala na plućnu tromboemboliju. Urađena je MSCT pulmoangiografija i potvrđena je tromboembolija niskog stepena rizika. Započeta je antikoagulantna terapija– terapijske doze niskomolekularnog heparina (enoxaparin), koja je produžena nakon otpusta iz bolnice sa DOAC (Rivaroxaban) prema protokolu za lečenje plućne tromboembolije. Na kontrolnom pregledu nakon 3 nedelje utvrđen je perikarditis sa perikardnom efuzijom umerenog stepena. Produžena je antikoagulantna terapija (DOAC) uz uključanje colchicin-a u terapiju prema protokolu za lečenje perikarditisa sa efuzijom. Nakon 3 meseca od hospitalizacije kod naše pacijentkinje uz blažu respiratornu simptomatologiju došlo je do razvoja bronhopneumonije desnog plućnog krila uz lako povišene biomarkere zapaljenja i uredne vrednosti D- dimera. Uz ordiniranu antibiotsku terapiju i tekuću terapiju (DOAC i colchicine) došlo je do povlačenja simptoma i regresije perikardne efuzije i smanjenja opterećenja desne komore. Na kontrolnom pregledu nakon 5 meseci od hospitalizacije potvrđena je kompletna regresija perikardne efuzije uz uredne biomarkere zapaljenja i vrednosti D-dimera. Savetovano je isključenje antikoagulantne terapije (DOAC) uz nastavak terapije malim dozama aspirina.

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Uvod

COVID-19 oboljenje izazvano SARS-CoV-2 virusom predstavlja oboljenje koje se manifestuje širokim spektrom tegoba kojim je primarno zahvaćen respiratorni sistem sa različitom simptomatologijom i težinom kliničke slike: od asimptomatskih slučajeva, preko groznice i blažih respiratornih tegoba do razvoja akutnog respiratornog distres sindroma, šoka i multiorganske insuficijencije koji dovode do povećanog rizika od smrtnog ishoda. Pored respiratornih komplikacija pacijenti sa COVID-19 infekcijom mogu imati brojne simptome koje uključuju kardiološke i neurološke komplikacije i stanja kao posledica hiperkoagulabilnosti. Postoji širok spektar kardiovaskularnih i tromboembolijskih komplikacija u okviru akutnog COVID-19 kardiovaskularnog sindroma. Kardijalne komplikacije uključuju: akutni koronarni sindrom sa obstrukcijom koronarnih arterija, akutno oštećenje miokarda u sklopu neobstruktivne koronarne arterijske bolesti, srčana insuficijencija, kardiogeni šok, neishemijska kardiomiopatija, stres kardiomiopatija, miokarditis, aritmije, perikarditis, perikardna efuzija i tamponada miokarda (1).

Sistemska aktivacija koagulacije i pulmonalna trombo-inflamacija sa lokalnim vaskularnim oštećenjem uzrokovanim SARS-CoV-2 infekcijom povećava rizik za razvoj tromboembolijskih komplikacija: insulta, plućne arterijske tromboze (plućna tromboembolija) i duboke venske tromboze (venski tromboembolizam) (2).

Observacione studije su pokazale da je incidenca venskog tromboembolizma (VTE) od 15 do 25 %, sa porastom incidence sa težinom kliničke slike: 58-69% u jedinicama intenzivne nege i pored primene farmakološke tromboprofilakse (3).

SARS-CoV-2 virus ulazi u alveolarni epitel preko angiotenzin konvertirajućeg enzima 2 (ACE2) receptora dovodeći do ekstenzivnog oslobađanja proinflamatornih citokina (IL-1, IL-6, IL-8, TNF-alfa i dr.) koji dalje dovode do aktivacije epitelnih ćelija, monocita i neutrofila, koji dovode do vazokonstrikcije i započinju sistemski inflamacioni odgovor- „citokinska oluja” (4). Endotelne ćelije mogu biti direktno inficirane preko ACE2 receptora dovodeći do endotelne aktivacije i disfunkcije koja aktivira koagulacionu kaskadu stvarajući trombinske i fibrinske ugruške. To stanje dovodi do signifikantnog porasta fibrinogena, C-reaktivnog proteina (CRP), sedimentacije eritrocita (SE), interleukina-6 (IL-6) i nivoa feritina. COVID-19 infekcija dovodi i do sveobuhvatnog hiperkoagulabilnog stanja organizma koji dovodi do makrovaskularne i mikrovaskularne tromboze (5). Studije su pokazale da abnormalni koagulacioni parametri kod COVID-19 pacijenata su često udruženi sa lošijom prognozom i povećanim mortalitetom. Signifikatni porast D-dimera, kao znak aktivacije koagulacije i fibrinolize, je dobar indikator za identifikaciju visoko-rizične populacije

za razvoj venskog tromboembolizma (VTE) u okviru COVID-19 infekcije. D-dimer je test visoke senzitivnosti, ali niske specifičnosti za detekciju aktivnog trombotičkog procesa. Porast neutrofilno-limfocitnog odnosa (NLR) i smanjen broj limfocita povećavaju rizik za trombozu i razvoj VTE. Prolongirano protrombinsko vreme (PT) i povišen fibrinogen su udruženo sa težom kliničkom slikom i većim mortalitetom (6,7). U težim COVID-19 infekcijama su pronađena i antifosfolipidna antitela (lupus antikoagulans-LA, antikardiolipin i anti-beta-2 glikoproteinska antitela) što dalje povećava rizik za razvoj tromboze (8).

Faktori rizika za razvoj venskog tromboembolizma (VTE) kod COVID-19 pacijenata uključuju starije životno doba, muški pol, gojaznost, imobilizacija, pušenje i komorbiditeti kao što su šećerna bolest, prethodna istorija VTE, hronično oboljenje bubrega, maligniteti, srčana i respiratorna insuficijencija, sepsa, hipoksija, infekcija (9).

Kao i drugi virusi i SARS-Cov-2 virus može uzrokovati miokarditis izolovano ili u sklopu mioperikarditisa. Tamponada miokarda je retka kao komplikacija COVID-19 infekcije. Mioperikarditis se kod COVID-19 pacijenata može javiti u sklopu ili posle pojave respiratornih simptoma. Česte su manje perikardne efuzije do 1cm koje prate zahvaćenost perikarda. Prethodni kardiovaskularni komorbiditeti mogu povećati rizik COVID-19 mioperikarditisa. Troponin kao senzitivni marker miokardnog oštećenja je povišen kod gotovo svih slučajeva mioperikarditisa. Mioperikardno oštećenje se može diferencirati transtorakalnom ehokardiografijom (TTE) ili kardijalnom magnetnom rezonancom (MRI) (10). Na EKG-u se može uočiti ST elevacija u više odvoda ili nespecifične ST promene. Terapija mioperikarditisa uključuje: nesteroidne anti-inflamatorne lekove (NSAIL), acetil-salicilnu kiselinu, glukokortikoide i colchicin (11,12).

Prikaz slučaja

Pacijentkinja životne dobi 68 godina javlja se na prvi ambulantni pregled kardiologa, nakon preležane COVID-19 infekcije. Tri nedelje pre ambulantnog pregleda pacijentkinja je 8 dana bila hospitalizovana na infektivnom odeljenju zbog obostrane pneumonije. Tri dana pre hospitalizacije imala zamaranje, suv kašalj, bolove u mišićima, febrilnost tokom 2 dana- najviše izmerene vrednosti telesne temperature do 37,6 C, zbog čega se i javila na ambulantni pregled u COVID ambulantu. U urađenim laboratorijskim analizama bila povišena sedimentacija: SE: 28 mm/h i CRP: 36 mg/L (normalno manje od 5 mg/L) uz leukopeniju ($Le-2.7 \times 10^9$), limfopeniju ($Ly-0.9 \times 10^9$), blagu trombocitopeniju ($Tr-131 \times 10^9$) i povišene vrednosti LDH: 405 U/l (normalno manje od 241 U/L) i feritina: 560 ng/mL (normalni opseg 15-160 ng/mL). Na urađenom rentgenskom snimku pluća viđene obostrano bazalno nehomogene trakaste senke koje su ukazivale na obostranu bronhopneumoniju uz auskultatorno oslabljen disajni šum pri bazama pluća. Upućena je na hospitalno lečenje na infektivno odeljenje. Testirana na SARS-CoV-2 (urađen nazofaringealni bris) koji je bio pozitivan.

Lečena je terapijom po protokolu za COVID-19 infekciju. Primala i profilaktičke doze LMWH (enoxaparin). Tokom hospitalizacije je imala blagu dispneju uz suv kašalj i sve vreme je bila afebrilna. Nije imala bolove u grudima, niti ubrzan rad srca. Bila je bez kiseonične potpore, a saturacija kiseonika je bila u normalnom opsegu (SpO_2 : 94-96%). Pacijentkinja negira ranija hronična oboljenja i bez faktora rizika za kardiovaskularna oboljenja. Drugog dana hospitalizacije testiran je D dimer koji je bio povišen: 2320 ng/mL (normalno manje od 500 ng/mL) uz uredne vrednosti troponina TnI-0.1 ng/mL (normalno manje od 0,3 ng/mL). Pacijentkinja je bila hemodinamski stabilna –vrednosti krvnog pritiska bile u opsegu 110-120/70-80 mm Hg uz vrednosti pulsa (70-85/min). Zbog sumnje na tromboemboliju pluća urađena je MSCT pulmoangiografija na kojoj su viđeni defekti u punjenju grane plućne arterije za lateralni i prednji segment gornjeg reznja desno. Urađena je procena težine plućne tromboembolije, a anamnestički je bila bez značajnijih faktora rizika za razvoj venskog tromboembolizma. Ordinirana je terapijska doza LMWH (enoxaparin) po protokolu za lečenje tromboembolije niskog rizika (13). Vrednosti azotnih materija u krvi su bile u normalnom opsegu (urea-6.7 mmol/L, kreatinin-85 umol/L). Nakon 2 dana od uvođenja terapijskih doza LMWH, pacijentkinja je bila bez tegoba i sedmog.dana od započete terapije LMWH prevedena je na DOAC (Rivaroksaban 2x15 mg naredne 3 nedelje, a potom 20 mg jedanput dnevno) uz predlog za dalje kontrole kardiologa –prva predviđena kontrola kardiologa nakon 3 nedelje od otpusta.

Na kontrolnom pregledu nakon 3 nedelje od hospitalizacije pacijentkinja je bila bez tegoba - bez zamaranja, uz dobru toleranciju napora i bez aritmija. Auskultatorno nad plućima čujan normalan disajni šum, a na srcu duž donje leve ivice sternuma sistolni šum bez propagacije. Vrednosti krvnog pritiska u normalnom opsegu (TA: 110/70 mm Hg). EKG nalaz: sinusni ritam, fr: 65/min, niža voltaža, inkompletan RBBB, redukovani R od V1-4 uz ST depresiju do 0.5 mm u inferiornim odvodima. Na urađenom transtorakalnom ehokardiografskom pregledu uočava se aorta uredne širine u celom torakalnom delu: koren-29 mm, bulbus-32 mm, ascendens-29 mm, luk-26 mm, descendenta aorta-19 mm. Aortna valvula je trolisna, urednog protoka preko valvule-1.0 m/s sa malom aortnom regurgitacijom (AR:1+). Uočavaju se voluminozniji mitralni zalisci, bez kriterijuma za prolaps, uz mitralnu regurgitaciju (MR:1-2+) u normalnu levu pretkomoru (LP:35 mm). Leva komora je urednih dimenzija zidova: septum-9 mm, zadnji zid-9 mm i urednih endokavitarnih dimenzija (EDDLK/ESDLK:45/24 mm), usporene relaksacije-dijastolna disfunkcija prvog stepena, bez ispada segmentne kinetike, dobre kontraktilnosti i dobre EF: 65%. Desna komora (DK) je granične veličine: 28mm, dobre kontraktilnosti, bez prisustva trombnih masa. Uočava se trikuspidalna regurgitacija (TR:2-3+) uz SPDK:40-45 mmHg. Perikard je hiperehogeniji i zadebljao iza zadnjeg i donjeg zida, a iza zadnjeg zida leve komore izliv (efuzija perikarda) do 8 mm, a ispred desne komore izliv do 10 mm bez znakova kolapsa desne komore. Na color-duplex scan-u arterija i vena donjih ekstremiteta uočava

vaju se duboke i površinske vene donjih ekstremiteta urednog protoka, bez staze i bez znakova tromboze. Uočavaju se diskretni varikoziteti venskih grana sliva v.saphene magne i parvae u distalnom delu obe potkolenice, izraženije na levoj nozi. Arterije donjih ekstremiteta bez značajnih stenozantnih lezija, bez patoloških dilatacija, uz fiziološke talase protoka nad njima. Vrednosti D- dimera u referentnom opsegu: 84.28 ng/mL (normalno manje od 500 ng/mL), kao i vrednosti troponina TnI-0.02 ng/mL (normalno manje od 0,3 ng/mL) uz lako povišene vrednosti CRP: 9 mg/L i sedimentacije: 18 mm/h. Predložen je nastavak terapije sa DOAC (Rivaroxaban 20 mg dnevno) uz inhibitor protonske pumpe (Omeprazol 40 mg jedanput ujutro) i u terapiju uveden Colchicine 2 x 0.5 mg. Savetovano je izbegavanje težeg fizičkog napora.

Na kontrolnom pregledu nakon 6 nedelja od hospitalizacije je bila bez tegoba, bez zamaranja uz dobru toleranciju umerenog fizičkog napora. Na kontrolnom transtorakalnom ehokardiografskom pregledu uočava se perikardna efuzija u regresiji: iza zadnjeg zida leve komore izliv do 6 mm, a ispred desne komore izliv do 8 mm, bez znakova kolapsa desne komore, koja je manjih dimenzija u odnosu na prethodni pregled-27 mm, uz SPDK: 35-40 mm Hg. U laboratorijskim analizama vrednosti D dimera u referentnom opsegu: 87.6 ng/mL (normalno manje od 500 ng/mL), uz lako povišene vrednosti CRP: 6 mg/L, sedimentacije: 25 mm/h i feritina: 221 ng/mL (normalni opseg 15-160 ng/mL). Ostali biohemijski parametri krvi u referentnom opsegu. Uz tekuću terapiju savetovano da uzima malu dozu beta blokatora (Bisoprolol 1.25 mg ujutro).

Na kontrolnom pregledu nakon 10 nedelja od hospitalizacije i dalje je bila bez tegoba. Na kontrolnom transtorakalnom ehokardiografskom pregledu perikardna efuzija u regresiji: iza zadnjeg zida perikardna efuzija do 4 mm, a ispred desne komore efuzija do 6 mm bez znakova kolapsa desne komore, koja je dimenzija 27mm uz SPDK: 35 mmHg. U laboratorijskim analizama vrednosti D dimera u referentnom opsegu: 190 ng/mL (normalno manje od 500 ng/mL), uz lako povišene vrednosti CRP: 10 mg/L i sedimentacije: 15 mm/h. Ostali biohemijski parametri krvi u referentnom opsegu. Savetovano je da uradi kontrolnu MSCT pulmoangiografiju. Predloženo je da nastavi sa tekućom terapijom.

Na kontrolnom pregledu nakon 3 meseca od hospitalizacije, osećala se dobro do pre 10 dana kada se ispoljila povišena temperatura do 37,4 C uz malaksalost tokom jednog dana, blagu dispneju i povraćanje. Uradila je laboratorijske analize u kojima su bili povišeni parametri zapaljenja: vrednosti CRP: 33.7 mg/L i sedimentacije: 23mm/h. Vrednosti D dimera su bile u referentnom opsegu: 224 ng/mL (normalno manje od 500 ng/mL). Na urađenom MSCT grudnog koša: desno postero-bazalno u plućnom parenhimu se vidi šira zona nehomogene, slabo intenzivne konsolidacije izgleda mlečnog stakla. Levo bazalno u plućnom parenhimu se uočavaju trakaste fibrozne promene. Oba pleuralna prostora bez tečnog sadržaja. Torakalna aorta i plućne arterije urednih dimenzija. Bez perikardnog izliva. Nalaz MSCT toraksa odgovara

bronhopneumoniji desnog plućnog krila. Testirana na SARS-CoV-2-urađen nazofaringealni bris koji je bio negativan. Lečena je ambulantno antibiotskom terapijom. Od tada nije imala febrilnosti i malaksalosti. Prisutan je suv kašalj, povremeno glavobolja i zamaranje koje je izraženije pri hodu uz stepenice. U urađenim kontrolnim laboratorijskim analizama parametri zapaljenja bili su lako povišeni: CRP: 6 mg/L, sedimentacija: 17 mm/h, kao i vrednosti LDH: 395 U/l (normalno manje od 241 U/L). Nalaz krvne slike u referentnom opsegu: leukociti: 5.2×10^9 , hemoglobin-144 g/L, trombociti- 187×10^9 . Vrednosti kreatinin kinaze i kardiospecifične kreatinin-kinaze su u normalnom opsegu (CK: 56 u/L, CK-MB: 14 u/L), kao i vrednosti D dimera: 74 ng/mL (normalno manje od 500 ng/mL). Na kontrolnom transtorakalnom ehokardiografskom pregledu perikardna efuzija u regresiji u odnosu na pretodni pregled: iza zadnjeg zida leve komore perikardna efuzija do 2mm, a ispred desne komore efuzija do 3 mm, bez znakova kolapsa desne komore, koja je urednih dimenzija: DK- 26mm, uz SPDK: 30-35 mmHg. Preporučeno je da nastavi da uzima ordiniranu antibiotsku terapiju još 3 dana. Savetovano je da nastavi terapiju Colchicine 2 x 0.5 mg još mesec dana, a potom da isključi iz terapije, a do naredne kontrole da nastavi sa DOAC (Rivaroxaban), inhibitor protonske pumpe (Omeprazol) i malu dozu beta blokatora (Bisoprolol).

Na kontrolnom pregledu nakon 5 meseci od hospitalizacije pacijentkinja navodi da je još 3 nedelje od prošle kontrole imala povremeno suv kašalj i zamaranje pri hodu uz stepenice, a unazad mesec dana je bez tegoba. Colchicine je prestala da uzima pre mesec dana kako je i savetovano. U urađenim kontrolnim laboratorijskim analizama parametri zapaljenja bili su u referentnom opsegu: CRP: 4.3 mg/L, sedimentacija: 10 mm/h, kao i vrednosti D dimera: 300 ng/mL (normalno manje od 500 ng/mL). Na kontrolnom transtorakalnom ehokardiografskom pregledu bez znakova perikardne efuzije. Perikard je zadebljao i hiperehogeniji iza zadnjeg i donjeg zida leve komore, desna komora je urednih dimenzija-26 mm, uočava se trikuspidalna regurgitacija (TR2+) uz SPDK:32 mmHg. Ostali ehokardiografski parametri srca su kao pri prvom pregledu. Preporučeno je da nastavi terapiju DOAC (Rivaroxaban 20 mg dnevno) još mesec dana, a potom da nastavi sa terapijom: acetil-salicilna kiselina (Aspirin 75 mg dnevno), mala doza beta blokatora (Bisoprolol 1.25 mg ujutro) i inhibitor protonske pumpe (Omeprazol 40 mg ujutro). Savetovan je kontrolni pregled za 2 meseca.

Diskusija

Venski tromboembolizam (VTE) je veoma česta komplikacija u kliničkom toku kod pacijenata sa COVID-19 infekcijom, bez obzira što primaju tromboprofilaksu (14). Metaanalize 11 kohortnih studija ukazuju da je među hospitalizovanim COVID-19 pacijentima 23,9% razvilo venski tromboembolizam (VTE), bez obzira što su primali antikoagulantnu terapiju tokom hospitalizacije. Plućna embolija (PE) je detektovana

kod 11,6%, a duboka venska tromboza (DVT) kod 11,9 %. Pacijenti u jedinicama intenzivne nege su imali viši rizik za VTE (30,4%) u odnosu na pacijente van intenzivne nege (13%). Plućna embolija (PE) tokom kliničke prezentacije često se preklapa sa pneumonijom kod COVID-19 infekcije, što otežava prepoznavanje simptoma PE kod pacijenata koji najčešće imaju i dispnoične tegobe (15).

Venski tromboembolizam (VTE) se javlja i kod hospitalizovanih pacijenata sa blažom formom COVID-19 infekcije, koji su hospitalizovani van jedinica intenzivne nege. U jednoj retrospektivnoj kohortnoj studiji od 289 pacijenata sa blažom kliničkom slikom, VTE je detektovana kod 17% pacijenata. PE je detektovana kod 14,5% pacijenata, cerebralna venska tromboza kod 1% i DVT kod 4,2% pacijenata (16).

Plućni embolizam (PE) u okviru COVID-19 infekcije se može razviti u odsustvu prepoznatljivih rizika za razvoj duboke venske tromboze i najčešće se razvija primarna in-situ tromboza (pulmonalna arterijska tromboza) pre nego embolizam, rezultujući u trombotičnoj okluziji malih i srednjih plućnih arterija i subsekventnim infarktima plućnog parenhima. COVID-19 pacijenti imaju široko rasprostranjenu trombozu sa mikroangiopatijom. Alveolarna kapilarna mikrotromboza ima 9 puta veću prevalencu kod COVID-19 pacijenata u odnosu na pacijente sa influencom. Ovaj vid tromboembolizma karakteriše hiperkoagulabilnost, udružena sa intenzivnom imuno-inflamatornom reakcijom, što rezultira u difuznoj okluzivnoj trombotičnoj mikroangiopatiji sa alveolarnim oštećenjem i vaskularnom angiogenezom. Oštećena fibrinoliza koja koegzistira sa egzacerbacijom trombotičnih procesa dovodi do perzistencije mikrotromboze (17).

Visoki nivoi D-dimera u inicijalnoj prezentaciji oboljenja su prediktivni za komplikacije povezane sa koagulacijom tokom hospitalizacije, razvoju kritičnog oboljenja i mortaliteta. D- dimer veći od 2500 ng/mL povećava rizik za trombozu za 6.79 puta, a za pojavu krvarenja 3,56 puta. Drugi biomarkeri tokom inicijalne prezentacije prediktivni za intrahospitalne tromboze uključuju trombocitozu (broj trombocita veći od 450×10^9), C-reaktivni protein (CRP) veći od 100 mg/L i sedimentacija eritrocita (SE) veća od 40 mm/h. Fibrinogen, feritin i prokalcitonin su povećani kod pacijenata sa trombotičkim komplikacijama u odnosu na one bez tromboze (18).

Strategija tromboprofilakse predstavlja ključni faktor za izbegavanje potencijalnih letalnih komplikacija. Potencijalne terapijske mogućnosti za prevenciju tromboze kod COVID-19 infekcije uključuju: niskomolekularni heparin (LMWH), nefrakcionisani heparin (UFH), direktne oralne antikoagulanse (DOAC), antitrombocitne lekove, inhibitore FXII i trombolitičke lekove. Većina ovih lekova poseduje pleomorfne efekte, pored antitrombotičkih i antiinflamatorne ili antivirusne efekte (19).

Kod dokumentovanog ili visokosuspektnog venskog tromboembolizma (VTE) antikoagulantna terapija predstavlja osnov terapije. Niskomolekularni heparin (LMWH) predstavlja najčešće korišćen i najsigurniji terapijski protokol. LMWH ima prednost u odnosu na nefrakcionisani heparin (UFH) zbog jednostavnije primene (jed-

nom ili dva puta tokom dana), manje mogućnosti kontaminacije osoblja, predvidljive farmakokinetike sa manje vezivanja za plazma proteine i ne zahteva praćenje aPTT koji je tokom COVID-19 infekcije nestabilan. Svi vodiči za terapiju COVID-19 infekcije se slažu da bi svi pacijenti hospitalizovani zbog COVID-19 infekcije trebalo da primaju tromboprofilaksu, najpogodnije niskomolekularni heparin (LMWH), bez obzira na nivo D- dimera u krvi. Direktni oralni antikoagulansi (DOAC), apixaban i rivaroxaban, imaju prednost zbog lakše primene i u kućnim uslovima i nije potrebno testiranje parametara iz krvi. U slučajevima submasivne plućne embolije (PE) trebalo bi razmotriti sistemsku fibrinolizu, sa primenom direktnim kateterom kroz plućnu arteriju kao alternativnom opcijom. Kod pacijenata sa PE koji su hemodinamski nestabilni sistemsku fibrinolizu ili direktna kateter terapija trebalo bi da budu terapije izbora. Interventne procedure, kao što je aspiraciona trombektomija, mogu redukovati trombnе mase i popraviti protok u plućnim arterijama, što može dovesti do kliničkog poboljšanja kod pacijenata sa masivnom ili submasivnom PE (20).

Opservaciona kohortna studija koja je obuhvatila 163 pacijenta sa COVID-19 infekcijom koji su otpušteni iz bolnice bez antikoagulantne terapije ukazuje da su imali kumulativnu incidencu tromboze (arterijske i venske trombotične događaje) od 2,5% tokom 30 dana nakon otpusta iz bolnice, od kojih je VTE bio kod 0,6%, a veliko krvarenje kod 0,7% (21).

Ne postoji jasan konsenzus o primeni profilaktičke antikoagulantne terapije nakon otpusta iz bolnice pacijenata sa COVID-19 infekcijom, a koji nisu imali tromboembolijski događaj. Pacijenti sa D-dimerom 6 puta većim od normalnih vrednosti pri otpustu iz bolnice, kao i pacijenti sa većim rizikom za tromboembolijske događaje (gojaznost, imobilizacija, postpartalni period) trebalo bi da primaju tromboprofilaksu nakon otpusta iz bolnice, uzimajući u obzir i procenu individualnog rizika od krvarenja (22, 23).

Ekstrapulmonalne manifestacije COVID-19 infekcije su u porastu i često su udružene sa promenama na plućima. Akutni efuzivni perikarditis je retka manifestacija COVID-19, posebno bez udruženog pulmonalnog oboljenja ili oštećenja miokarda (24).

Patofiziologija efuzivnog perikarditisa u COVID-19 je nepoznata, ali postoje hipoteze da se pojavljuje sekundarno tokom sistemskog inflamatornog odgovora kao posledica citotoksičnih i imuno-posredovanih efekata povezanih sa SARS-CoV2 infekcijom. Inflamatorni markeri i testovi autoantitela su često abnormalni tokom akutne infekcije i često zahtevaju kliničko ispitivanje za definisanje etiologije perikarditisa. Validni testovi za ispitivanje SARS-CoV-2 u perikardnoj tečnosti još su u procesu razvoja i preporučuje se kompletna biohemijska, bakteriološka i citološka analiza perikardne tečnosti u cilju isključenja drugih etiologija perikardne efuzije (25).

Trenutno nema ustanovljenih vodiča za terapiju perikarditisa tokom i nakon COVID-19 infekcije. U dosadašnjim objavljenim slučajevima pacijenti su tretirani sa colchicinom, hidrosihlorokinom, kortikosteroidima i antivirusnim lekovima.

Visoke doze aspirina i NSAIL predstavljaju osnovu, tj. prvu liniju terapije akutnog perikarditisa. Drugi terapijski protokol uključuje colchicin. Kortikosteroidi u manjim dozama su rezervisani za slučajeve sa kontraindikacijama ili neuspehom prve linije terapije. U nekim slučajevima kortikosteroidi i NSAIL su pogoršavali kliničko stanje pacijenata sa COVID-19 i njih treba izbegavati kod pacijenata sa pridruženim oštećenjem miokarda (STEMI i NSTEMI). NSAIL koji se koriste u hroničnim stanjima ne moraju se prekidati kod pacijenata sa COVID-19. Ne postoje jasni dokazi da primena NSAIL (ibuprofena) može izazvati neželjene kardiovaskularne ili respiratorne efekte kod COVID-19 pacijenata. Preporuka je da pacijenti sa infarktom miokarda i akutnim perikarditisom startuju sa visokim dozama aspirina. Upotrebu visokih doza aspirina u terapiji pacijenata sa akutnim perikarditisom tokom COVID-19 infekcije trebalo bi individualizovati. Colchicin se može dodati NSAIL ili Aspirinu za tretman akutnog virusnog perikarditisa, a može se koristiti kao monoterapija u dozi 2 x 0.5 mg dnevno do 3 meseca i dobro se toleriše. Nema kontraindikacija za primenu colchicina u terapiji perikarditisa kod COVID-19 pacijenata (26, 27).

Kod naše pacijentkinje tokom hospitalizacije zbog obostrane upale pluća izazvane SARS-CoV-2 virusom tokom rutinske kontrole D-dimera uočene su povišene vrednosti 2,3 puta veće od referentnog opsega, uz povišene biomarkere inflamacije. Imala je simptome respiratorne infekcije, a bez izražene kliničke simptomatologije koja bi ukazivala na plućnu tromboemboliju. Zbog povećane prevalencije tromboembolijskih komplikacija tokom COVID-19 infekcije i povećane vrednosti D-dimera u daljem dijagnostičkom postupku urađena je MSCT pulmoangiografija i potvrđena je tromboembolija niskog stepena rizika. Nije imala povišene biomarkere miokardnog oštećenja. Prema protokolu za lečenje plućne tromboembolije započeta je antikoagulantna terapija – terapijske doze niskomolekularnog heparina (enoxaparin), koja je produžena nakon otpusta iz bolnice sa DOAC (Rivaroxaban) prema protokolu za lečenje plućne tromboembolije (13). Na kontrolnom pregledu nakon 3 nedelje rutinskim transtorakalnim ehokardiografskim pregledom utvrđen je perikarditis sa perikardnom efuzijom umerenog stepena koja nije dovela do kolapsa srčanih šupljina, sa blažim opterećenjem desne komore nakon plućne tromboembolije – blago povećanje sistolnog pritiska desne komore (SPDK) i umerena trikuspidalna regurgitacija (TR). Nije imala povišene biomarkere miokardnog oštećenja, što je ukazivalo na izolovani perikarditis sa efuzijom bez miokardne lezije, kao komplikacija COVID-19 infekcije pluća i plućne tromboembolije. Dopunskom dijagnostikom color-duplex scan krvnih sudova donjih ekstremiteta nisu uočeni znaci duboke i površinske venske tromboze, što bi moglo ukazivati da se plućni tromboembolizam razvio in-situ u sklopu COVID-19 infekcije. Produžena je antikoagulantna terapija (DOAC), uz uključanje colchicina u terapiju prema protokolu za lečenje perikarditisa sa efuzijom. Zbog primene antikoagulantne terapije nije savetovano da pacijentkinja uzima aspirin ili NSAIL (kao terapija prve linije idiopatskog perikarditisa), zbog povećanog rizika od krvarenja (12).

Na kontrolnom pregledu nakon 6 nedelja od hospitalizacije ehokardiografskim pregledom utvrđena je regresija perikardne efuzije, uz smanjenje opterećenja desne komore i uredne biomarkere zapaljenja i vrednosti D-dimera.

Nakon 3 meseca od hospitalizacije kod naše pacijentkinje uz blažu respiratornu simptomatologiju došlo je do razvoja bronhopneumonije desnog plućnog krila, uz lako povišene biomarkere zapaljenja i uredne vrednosti D dimera. Nalaz nazofaringalnog brisa na SARS-CoV-2 je bio negativan. Uz ordiniranu antibiotsku terapiju i tekuću terapiju (DOAC i colchicine) došlo je do povlačenja simptoma i regresije perikardne efuzije i smanjenja opterećenja desne komore. Predloženo je da nastavi terapiju colchicinom do 3 meseca od početka primene leka prema preporukama, a produžena je antikoagulantna terapija (DOAC) i nakon 3 meseca od tromboembolije pluća, s obzirom na novonastalu infekciju i mogući povećan rizik od tromboembolijskih komplikacija, uz nizak individualni rizik od krvarenja.

Na kontrolnom pregledu nakon 5 meseci od hospitalizacije naša pacijentkinja je bila bez simptoma. Ehokardiografskim pregledom potvrđena je kompletna regresija perikardne efuzije uz uredne biomarkere zapaljenja i vrednosti D-dimera. S obzirom na to da nije bilo povećanog rizika za tromboembolijske događaje savetovano je isključenje antikoagulantne terapije (DOAC) uz nastavak terapije malim dozama aspirina.

Zaključak

Tokom SARS-CoV-2 infekcije sa dominantnom respiratornom simptomatologijom moguće je ispoljavanje kardijalnih komplikacija, od kojih je najčešća plućna tromboembolija kao posledica tromboinflamatornog procesa u toku COVID-19 infekcije. Značajno povišene vrednosti D-dimera mogu imati prediktivnu vrednost za tromboembolijske komplikacije. Perikarditis sa perikardnom efuzijom kao kardijalna komplikacija može pratiti respiratornu simptomatologiju COVID-19 infekcije ili se javiti izolovano, o čemu bi kliničari trebalo da razmišljaju tokom dijagnostike i praćenja pacijenata sa COVID-19 infekcijom.

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PULMONARY THROMBOEMBOLISM AND PERICARDIAL EFFUSION AS CARDIOVASCULAR COMPLICATIONS OF COVID-19 INFECTION

Summary: Systemic activation of coagulation and pulmonary thrombo-inflammation with local vascular damage caused by SARS-CoV-2 infection increases the risk of developing thromboembolic complications: stroke, pulmonary arterial thrombosis (pulmonary thromboembolism) and deep vein thrombosis. Myopericarditis may occur in COVID-19 patients as part of or after the onset of respiratory symptoms. Minor pericardial effusions up to 1 cm that accompany pericardial involvement are common. In our patient during hospitalization due to bilateral pneumonia caused by SARS-Cov-2 virus during a routine control of D-dimer, elevated values 2.3 fold higher than the reference range were observed, with elevated biomarkers of inflammation. She had symptoms of a respiratory infection and no pronounced clinical symptoms that would indicate pulmonary thromboembolism. MSCT pulmonary angiography was performed and low-risk thromboembolism was confirmed. Anticoagulant therapy was started - therapeutic doses of low molecular weight heparin (enoxaparin), which was extended after discharge from the hospital with DOAC (Rivaroxaban) according to the protocol for the treatment of pulmonary thromboembolism. At the control examination after 3 weeks, pericarditis with moderate pericardial effusion was determined. Anticoagulant therapy (DOAC) was extended with the inclusion of colchicine in the therapy according to the protocol for the treatment of pericarditis with effusion. After 3 months of hospitalization in our patient with mild respiratory symptoms, bronchopneumonia of the right lung developed with slightly elevated biomarkers of inflammation and normal values of D-dimer. With prescribed antibiotic therapy and current therapy (DOAC and colchicine), there was a withdrawal of symptoms and regression of pericardial effusion and a reduction in right ventricular overload. At the follow-up examination 5 months after hospitalization, complete regression of pericardial effusion was confirmed with normal

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biomarkers of inflammation and D-dimer values. It is advisable to exclude anticoagulant therapy (DOAC) with continued low-dose aspirin therapy.

Keywords: COVID-19, SARS-CoV-2, pulmonary thromboembolism, pericarditis, pericardial effusion, D-dimer, anticoagulant therapy.

Introduction

COVID-19 disease caused by the SARS-CoV-2 virus is a disease that manifests itself in a wide range of disorders that primarily affect the respiratory system with different symptoms and severity of the clinical conditions: from asymptomatic cases, through fever and mild respiratory disorders to the development of acute respiratory distress syndrome, shock and multiorgan failure leading to an increased risk of death. In addition to respiratory complications, patients with COVID-19 infection may have several symptoms that include cardiac and neurological complications and conditions as a consequence of hypercoagulability. There is a wide range of cardiovascular and thromboembolic complications within acute COVID-19 cardiovascular syndrome. Cardiac complications include acute coronary syndrome with coronary artery obstruction, acute myocardial damage as part of non-obstructive coronary artery disease, heart failure, cardiogenic shock, nonischemic cardiomyopathy, stress cardiomyopathy, myocardial infarction, arrhythmia, pericarditis, pericardial effusion, and cardiac tamponade (1).

Systemic activation of coagulation and pulmonary thrombo-inflammation with local vascular damage caused by SARS-CoV-2 infection increases the risk of developing thromboembolic complications: stroke, pulmonary arterial thrombosis (pulmonary thromboembolism) and deep vein thrombosis (2).

Observational studies have shown that the incidence of venous thromboembolism (VTE) is 15 to 25%, with an increase in the incidence with the severity of the clinical conditions: 58-69% in intensive care units despite the use of pharmacological thromboprophylaxis (3).

The SARS-CoV-2 virus enters the alveolar epithelium via angiotensin-converting enzyme 2 (ACE2) receptors leading to the extensive release of proinflammatory cytokines (IL-1, IL-6, IL-8, TNF-alpha, etc.) which further leads to activation of epithelial cells, monocytes and neutrophils, which lead to vasoconstriction and initiate a systemic inflammatory response - "cytokine storm" (4). Endothelial cells can be directly infected via ACE2 receptors leading to endothelial activation and dysfunction that activates the coagulation cascade that generates thrombin and fibrin clots. This condition leads to a significant increase in fibrinogen, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6) and ferritin levels. COVID-19 infection also leads to a comprehensive hypercoagulable state of the organism that leads to macrovascular and microvascular thrombosis (5). Studies have shown that

abnormal coagulation parameters in COVID-19 patients are often associated with poorer prognosis and increased mortality. A significant increase of D-dimer, as a sign of coagulation activation and fibrinolysis, is a good indicator for the identification of a high-risk population for the development of venous thromboembolism (VTE) within COVID-19 infection. D-dimer is a test of high sensitivity, but low specificity for detection of an active thrombotic process. An increase in the neutrophil-lymphocyte ratio (NLR) and a decreased lymphocytes count increases the risk of thrombosis and the development of VTE. Prolonged prothrombin time (PT) and elevated fibrinogen are associated with a more severe clinical picture and higher mortality (6,7). Antiphospholipid antibodies (lupus anticoagulants-LA, anticardiolipin and anti-beta-2 glycoprotein antibodies) have also been found in severe COVID-19 infections, which further increases the risk of thrombosis (8).

Risk factors for the development of venous thromboembolism (VTE) in COVID-19 patients include older age, male gender, obesity, immobilization, smoking, and comorbidities such as diabetes, previous history of VTE, chronic kidney disease, malignant tumour, heart and respiratory failure, sepsis, hypoxia, infection (9).

Like other viruses, the SARS-Cov-2 virus can cause myocarditis by itself or as part of myopericarditis. Cardiac tamponade is rare as a complication of COVID-19 infection. Myopericarditis may occur in COVID-19 patients as part of or after the onset of respiratory symptoms. Minor pericardial effusions up to 1 cm that accompany pericardial involvement are common. Previous cardiovascular comorbidities may increase the risk of COVID-19 myopericarditis. Troponin as a sensitive marker of myocardial damage is elevated in almost all cases of myopericarditis. Myopericardial damage can be differentiated by transthoracic echocardiography (TTE) or cardiac magnetic resonance imaging (MRI) (10). On the ECG, ST elevation in multiple leads or nonspecific ST changes can be observed. Treatment of myopericarditis includes nonsteroidal anti-inflammatory drugs (NSAIDs), acetyl-salicylic acid, glucocorticoids and colchicine (11,12).

Case report:

A 68-year-old female patient appears at the first cardiologist examination, after COVID-19 infection. Three weeks before the examination, the patient was hospitalized for 8 days with an infectious disease ward due to bilateral pneumonia. Three days before hospitalization, she had fatigue, dry cough, muscle pain, fever for 2 days - the highest measured body temperature was up to 37.6 C, and that was caused her to go to the COVID ambulance. Laboratory analyzes showed increased erythrocyte sedimentation rate (ESR): 28 mm/h and CRP: 36 mg/L (normally less than 5 mg/L) with leukopenia ($Le-2.7 \times 10^9$), lymphopenia ($Ly-0.9 \times 10^9$), mild thrombocytopenia ($Plt- 131 \times 10^9$) and elevated LDH values: 405 U/l (normally less than 241U/L) and

ferritin: 560 ng/mL (normal range 15-160 ng/mL). Lungs X-ray showed bilateral basally inhomogeneous banded shadows that indicated bilateral bronchopneumonia with auscultatory attenuated respiratory sound at the lung bases. She was referred for hospital treatment in the infectious clinic. Tested for SARS-CoV-2 (nasopharyngeal swab) with a positive result. Treatment protocol therapy for COVID-19 infection was conducted along with prophylactic doses of LMWH (enoxaparin). During hospitalization, she was afebrile and had mild dyspnea with a dry cough without chest pain or a fast pulse. She didn't need oxygen support therapy; oxygen saturation was in the normal range (SpO₂: 94-96%). The patient denies previous chronic diseases and no indications of risk factors for cardiovascular diseases. On the second day of hospitalization, D- dimer was tested and it was high values: 2320 µg/L (normally less than 500 µg/L) with normal troponin values TnI-0.1 ng/mL (normally less than 0.3 ng/mL). The patient was hemodynamically stable - blood pressure values were from 110-120/70-80 mm Hg with pulse values (70-85/min). MSCT pulmonary angiography was performed showing pulmonary artery flow defects with occlusive thrombus for the lateral and anterior segment of the upper lobe of the right lung. An assessment of the severity of pulmonary thromboembolism was performed. Anamnestic data were without significant risk factors for the development of venous thromboembolism. A therapeutic dose of LMWH (enoxaparin) was prescribed according to the protocol for the treatment of low-risk thromboembolism (13). Blood urea nitrogen values were in the normal range (BUN-6.7mmol/L) and creatinine-85 µmol/L. Two days after starting with therapeutic doses of LMWH, our patient was without symptoms and on the seventh day of starting LMWH therapy, she was switched to DOAC (Rivaroxaban 2x15 mg for the next 3 weeks, and then 20 mg once a day) advising further cardiologist check-ups 3 weeks after discharge.

Three weeks after hospitalization on control check-up, the patient was without symptoms - no fatigue, with good effort tolerance and without arrhythmias. Auscultatory on the lungs audible normal respiratory sound, and the lower-left edge of the sternum systolic murmur without propagation. Blood pressure values were in the normal range (BP: 110/70mm Hg). ECG findings: sinus rhythm, HR: 65/min, lower voltage, incomplete RBBB, reduced R from V1-4 with ST depression to 0.5 mm in inferior leads. On the performed transthoracic echocardiographic (TTE) examination: the dimension of the thoracic aorta: root-29 mm, bulbous-32 mm, ascending aorta-29 mm, aortic arch-26 mm, descending aorta-19 mm. The aortic valve is three-leafleted, of normal flow over the valve-1.0 m/s with little aortic regurgitation (AR: 1+). More voluminous mitral valves are observed, without criteria for prolapse, with mitral regurgitation (MR: 1-2+) in the normal left atrium (LA: 35 mm). The left ventricle has normal wall dimensions: septum-9 mm, posterior wall-9 mm and regular endocavitary dimensions of the left ventricle (EDDLV/ESDLV: 45/24 mm), with first-degree diastolic dysfunction, and with good contractility and good ejection fraction (EF):

65%. The right ventricle has a discreet oversize: 28mm, good contractility, without the presence of thrombus masses and with tricuspid regurgitation (TR:2-3+) and right ventricle systolic pressure (RVSP): 40-45 mm Hg. The pericardium is hyperechogenic and thickened behind the posterior and inferior wall and behind the posterior wall is the pericardial effusion up to 8 mm and in front of the right ventricle the pericardial effusion up to 10 mm without signs of right ventricular collapse. On the colour-duplex scan of the arteries and veins of the lower extremities, deep and superficial veins of the lower extremities of normal flow are observed, without signs of thrombosis. Discrete varicose veins of the vessel branches in the distal part of both lower legs, more shown on the left leg; arteries of the lower extremities without significant stenotic lesions, without pathological dilatations, with physiological waves of flow over them. D-dimer values was in the reference range: 84.28 ng/mL (normally less than 500 ng/mL), as well as troponin values TnI-0.02 ng/mL (normally less than 0.3 ng/mL) with slightly elevated CRP values: 9 mg/L and erythrocyte sedimentation rate (ESR): 18 mm/h. It was suggested to continue therapy with DOAC (Rivaroxaban 20 mg daily) with proton pump inhibitors (PPIs) -Omeprazole 40 mg once daily and Colchicine 2 x 0.5 mg were included in therapy. Avoiding physical exertion is advised.

Six weeks after the hospitalization on control check-up, the patient was without symptoms, without fatigue and with good tolerance of moderate physical effort. On control transthoracic echocardiographic examination pericardial effusion was in regression: behind the posterior wall of left ventricle pericardial effusion up to 6 mm, and in front of the right ventricle effusion up to 8 mm, without signs of right ventricular collapse, which is smaller than the previous examination RV-27 mm, with RVSP: 35-40 mmHg. In laboratory tests D-dimer values in the reference range: 87.6 ng/mL (normally less than 500 ng/mL), with slightly elevated CRP values: 6 mg/L, ESR- 25 mm/h and ferritin: 221 ng/mL (normal range 15-160ng/mL). Other biochemical parameters of blood were in the reference range. With current therapy, she was advised to take a small dose of beta-blockers (Bisoprolol 1.25 mg in the morning).

At the control check-up after 10 weeks of hospitalization, the patient was without symptoms. On control transthoracic echocardiographic examination, pericardial effusion was in regression: pericardial effusion behind the posterior wall of left ventricle up to 4 mm, and in front of the right ventricle effusion up to 6 mm, without signs of right ventricular collapse, RV dimension-27 mm with RVSP: 35 mm Hg. In laboratory analyzes, D-dimer values was in the reference range: 190 ng/mL (normally less than 500 ng/mL), with slightly elevated CRP values: 10 mg/L, ESR: 15 mm/h. Other biochemical parameters of blood were in the reference range. She was advised to do a control MSCT pulmonary angiography. Continuation of current therapy was advised.

At the follow-up examination 3 months after hospitalization, she felt well until 10 days ago, when she developed a fever of up to 37.4 C with a weakness for one day, mild dyspnea and vomiting. She performed laboratory analyzes in which the ignition

parameters were elevated: CRP values: 33.7 mg/L and ESR values: 23 mm/h. D-dimer values were in the reference range: 224 ng/mL (normally less than 500 ng/mL). On the performed MSCT of the chest: a wider zone of inhomogeneous, weakly intensive consolidation of the appearance of the "ground glass" on the right posterior-basal in the lung parenchyma and fibrous changes was observed in the left basal lung parenchyma. Both pleural spaces without fluid content; thoracic aorta and pulmonary arteries of regular dimensions. No pericardial effusion. The finding of MSCT thorax corresponds to bronchopneumonia of the right lung. Tested for SARS-CoV-2 - nasopharyngeal swab was done with a negative result. She was treated with antibiotic therapy. She has not had a fever or weakness since then. There is a dry cough, occasional headache and fatigue, which is more pronounced when walking up the stairs. In the performed control laboratory analyzes, the inflammation parameters were slightly elevated: CRP: 6 mg/L, ESR: 17 mm / h, as well as LDH values: 395 U/l (normally less than 241 U/L). Blood count finding in the reference range: leukocytes: 5.2×10^9 , haemoglobin-144 g L, platelets count- 187×10^9 . Creatinine kinase and cardio specific creatinine kinase values were in the normal range (CK: 56 u/ L, CK-MB: 14 u/L), as well as D dimer values: 74 ng/mL (normally less than 500 ng/ mL). On control transthoracic echocardiographic examination pericardial effusion was in regression compared to the previous examination: behind the posterior wall of left ventricle pericardial effusion up to 2 mm and in front of the right ventricle effusion up to 3 mm without signs of the collapse of the right ventricle; RV dimension-26 mm with RVSP: 30-35 mm Hg. It was recommended that he continue to take the prescribed antibiotic therapy for another 3 days. It was advised to continue therapy with Colchicine 2 x 0.5 mg for another month and then to exclude from therapy, and to continue with DOAC (Rivaroxaban), a proton pump inhibitor (Omeprazole) and a low dose of beta-blocker (Bisoprolol) until the next control.

At the control check-up after 5 months from hospitalization, she states that for another 3 weeks from the last check-up, she occasionally had a dry cough and fatigue when walking up the stairs, and for the past month she has had no symptoms. She stopped taking Colchicine a month ago as advised. In the performed control laboratory analyzes, the inflammation parameters were in the reference range: CRP: 4.3 mg/L, ESR: 10 mm/h, as well as D- dimer values: 300 ng/mL (normally less than 500 ng/mL). On control transthoracic echocardiographic examination there was without signs of pericardial effusion. The pericardium is thickened and hyperechogenic behind the posterior and inferior wall of the left ventricle, the right ventricle is of normal dimensions-26 mm, tricuspid regurgitation (TR: 2+); RVSP: 32 mm Hg. Other echocardiographic parameters of the heart were as like on the first examination. It was recommended to continue DOAC (Rivaroxaban 20 mg daily) for another month, followed by acetylsalicylic acid (Aspirin 75 mg daily), a small dose of beta-blocker (Bisoprolol 1.25 mg in the morning) and Omeprazole 40 mg in the morning. A check-up in 2 months was advised.

Discussion

Venous thromboembolism (VTE) is a common complication in the clinical course in patients with COVID-19 infection, regardless of receiving thromboprophylaxis (14). The meta-analyses of 11 cohort studies indicated that among hospitalized COVID-19 patients, 23.9% developed venous thromboembolism (VTE), regardless of receiving anticoagulant therapy during hospitalization. Pulmonary embolism (PE) was detected in 11.6% and deep vein thrombosis (DVT) in 11.9%. Patients in intensive care units had a higher risk for VTE (30.4%) compared to patients outside intensive care units (13%). Pulmonary embolism (PE) during clinical presentation often overlaps with pneumonia in COVID-19 infection, which makes it difficult to recognize PE symptoms in patients who most often have dyspnoea (15).

Venous thromboembolism (VTE) also occurs in hospitalized patients with a milder form of COVID-19 infection in hospitalized patients. In a retrospective cohort study of 289 patients with a milder clinical condition, VTE was detected in 17% of patients. PE was detected in 14.5% of patients, cerebral venous thrombosis in 1% and DVT in 4.2% of patients (16).

Pulmonary embolism (PE) within COVID-19 infection can develop in the absence of recognisable risks for the development of deep vein thrombosis and most often develops primary in-situ thrombosis (pulmonary arterial thrombosis) rather than embolism, resulting in thrombotic occlusion of small and medium pulmonary arteries and successive pulmonary parenchymal infarcts. COVID-19 patients have widespread thrombosis with microangiopathy. Alveolar capillary micro thrombosis has a 9 fold higher prevalence in COVID-19 patients than in patients with influenza. This type of thromboembolism is characterized by hypercoagulability associated with an intense immuno-inflammatory response, resulting in diffuse occlusive thrombotic microangiopathy with alveolar damage and vascular angiogenesis. Impaired fibrinolysis that coexists with exacerbation of thrombotic processes leads to the persistence of micro thrombosis (17).

High levels of D-dimer in the initial presentation of the disease are predictive of complications associated with coagulation during hospitalization, critical illness development, and mortality. A D-dimer higher than 2500 ng/mL increases the risk for thrombosis by 6.79 fold and bleeding by 3.56 fold. Other biomarkers during initial presentation predictive of intrahospital thrombosis included platelet count greater than 450×10^9 , C-reactive protein (CRP) greater than 100 mg/L, and erythrocyte sedimentation rate (ESR) greater than 40 mm/h. Fibrinogen, ferritin and procalcitonin are increased in patients with thrombotic complications compared to those without thrombosis (18).

The thromboprophylaxis strategy is a key factor to prevent potentially lethal complications. Potential therapeutic options for the prevention of thrombosis in CO-

VID-19 infection include low molecular weight heparin (LMWH), unfractionated heparin (UFH), direct oral anticoagulants (DOAC), antiplatelet drugs, FXII inhibitors, and thrombolytic drugs. Most of these drugs have pleomorphic effects, in addition to antithrombotic and anti-inflammatory or antiviral effects (19).

In documented or highly suspected venous thromboembolism (VTE), anticoagulant therapy is the mainstay of therapy. Low molecular weight heparin (LMWH) is the most commonly used and safest therapeutic protocol. LMWH has an advantage over unfractionated heparin (UFH) due to easier administration (once or twice daily), less possibility of staff contamination, predictable pharmacokinetics with less plasma protein binding and does not require monitoring of aPTT which is unstable during COVID-19 infection. All guidelines for the treatment of COVID-19 infection agree that all patients hospitalized for COVID-19 infection should receive thromboprophylaxis most preferably low molecular weight heparin (LMWH), regardless of the level of D-dimer in the blood. Direct oral anticoagulants (DOAC): apixaban and rivaroxaban, have the advantage of being easier to use at home and do not require testing of blood parameters. In cases of submassive pulmonary embolism (PE), systemic fibrinolysis should be considered, with the use of a direct catheter through the pulmonary artery as an alternative. For patients with PE who are hemodynamically unstable, systemic fibrinolysis, or direct catheter therapy should be the therapy of choice. Interventional procedures such as aspiration thrombectomy can reduce thrombus masses and improve flow in the pulmonary arteries which may lead to clinical improvement in patients with massive or submassive PE (20).

An observational cohort study of 163 patients with COVID-19 infection discharged from the hospital without anticoagulant therapy had a cumulative incidence of thrombosis (arterial and venous thrombotic events) of 2.5% within 30 days of discharge, of which VTE was 0.6% and major bleeding in 0.7% (21).

There is no clear consensus of the use of prophylactic anticoagulant therapy after discharge from the hospital of patients with COVID-19 infection who did not have a thromboembolic event. Patients with D-dimer 6 fold higher than normal values on discharge from hospital, as well as patients at higher risk for thromboembolic events (obesity, immobilization, postpartum period) should receive thromboprophylaxis after discharge from hospital, taking into account individual risk assessment from bleeding (22,23).

Extrapulmonary manifestations of COVID-19 infection are on the rise and are often associated with changes in the lungs. Acute effusive pericarditis is a rare manifestation of COVID-19, especially without associated pulmonary disease or myocardial damage (24).

The pathophysiology of effusive pericarditis in COVID-19 is unknown, but there are hypotheses that it occurs secondarily during the systemic inflammatory response as a consequence of cytotoxic and immune-mediated effects associated with SARS-

CoV2 infection. Inflammatory markers and autoantibody tests are often abnormal during acute infection and often require a clinical examination to define the aetiology of pericarditis. Valid tests for testing SARS-CoV-2 in a pericardial fluid are still under development and a complete biochemical, bacteriological, and cytological analysis of pericardial fluid is recommended to rule out other etiologies of pericardial effusion (25).

There are currently no established guidelines for the treatment of pericarditis during and after COVID-19 infection. In the cases published so far, patients have been treated with colchicine, hydroxychloroquine, corticosteroids and antiviral drugs.

High doses of aspirin and NSAIDs are the basis, ie the first line of therapy for acute pericarditis. Another therapeutic protocol includes colchicine. Corticosteroids in smaller doses are reserved for cases with contraindications or failure of first-line therapy. In some cases, corticosteroids and NSAIDs have worsened the clinical condition of patients with COVID-19 and should be avoided in patients with associated myocardial damage (STEMI and NSTEMI). NSAIDs used in chronic conditions do not have to be discontinued in patients with COVID-19. There is no clear evidence that the use of NSAIDs (ibuprofen) can cause adverse cardiovascular or respiratory effects in COVID-19 patients. It is recommended that patients with myocardial infarction and acute pericarditis start with high doses of aspirin. The use of high doses of aspirin in the treatment of patients with acute pericarditis during COVID-19 infection should be individualized. Colchicine can be added to NSAIDs or Aspirin for the treatment of acute viral pericarditis, and can be used as monotherapy at a dose of 2 x 0.5 mg daily for up to 3 months and is well tolerated. There are no contraindications for the use of colchicine in the treatment of pericarditis in COVID-19 patients (26,27).

In our patient during hospitalization due to bilateral pneumonia caused by SARS-CoV-2 virus during a routine control of D-dimer, elevated values 2.3 fold higher than the reference range were observed, with elevated biomarkers of inflammation. She had symptoms of a respiratory infection and no pronounced clinical symptoms that would indicate pulmonary thromboembolism. Due to the increased prevalence of thromboembolic complications during COVID-19 infection and the increased value of D-dimer in the further diagnostic procedure, MSCT pulmonary angiography was performed and low-risk thromboembolism was confirmed. She had no elevated biomarkers of myocardial damage. According to the protocol for the treatment of pulmonary thromboembolism, anticoagulant therapy was introduced - therapeutic doses of low molecular weight heparin (enoxaparin), which was extended after discharge from the hospital with DOAC (Rivaroxaban) according to the protocol for the treatment of pulmonary thromboembolism (13). At the control examination after 3 weeks, routine transthoracic echocardiographic examination revealed pericarditis with moderate pericardial effusion that did not lead to the collapse of the heart cavities, with a mild overload on the right ventricle after pulmonary thromboembolism - a slight increase in right ventricular systolic pressure (RVSP) and mildly tricuspid regurgitation (TR).

It did not have elevated biomarkers of myocardial damage, which indicated isolated pericarditis with effusion without myocardial lesion, as a complication of COVID-19 lung infection and pulmonary thromboembolism. Additional diagnostics of the colour-duplex scan of blood vessels of the lower extremities did not show signs of deep and superficial venous thrombosis, which could indicate that pulmonary thromboembolism developed in-situ as part of COVID-19 infection. Anticoagulant therapy (DOAC) was continued with the inclusion of colchicine in the therapy according to the protocol for the treatment of pericarditis with effusion. Due to the use of anticoagulant therapy, the patient shouldn't take aspirin or NSAIDs (as first-line therapy for idiopathic pericarditis), due to increased risk of bleeding (12).

At the control examination after 6 weeks of hospitalization, echocardiographic examination revealed regression of pericardial effusion with a reduction in the overload on the right ventricle and regular biomarkers of inflammation and D-dimer values.

After 3 months of hospitalization our patient with mild respiratory symptoms, bronchopneumonia of the right lung developed with slightly elevated biomarkers of inflammation and normal values of D-dimer. The finding of the nasopharyngeal swab on SARS-CoV-2 was negative. With prescribed antibiotic therapy and current therapy (DOAC and colchicine), there was a withdrawal of symptoms and regression of pericardial effusion and a reduction in right ventricular overload. It is proposed to continue colchicine therapy for up to 3 months from the start of the drug according to the recommendations, and anticoagulant therapy (DOAC) was extended after 3 months of pulmonary thromboembolism, given the new infection and possible increased risk of thromboembolic complications, with the low individual risk of bleeding.

At the follow-up examination five months after hospitalization, our patient was asymptomatic. The echocardiographic examination confirmed the complete regression of pericardial effusion with normal biomarkers of inflammation and D-dimer values. Since there was no increased risk of thromboembolic events, it was advisable to exclude anticoagulant therapy (DOAC) with continued low-dose aspirin therapy.

Conclusion

During SARS-CoV-2 infection with dominant respiratory symptoms, cardiac complications may be manifested, the most common of which is pulmonary thromboembolism as a consequence of the thromboinflammatory process during COVID-19 infection.

Significantly elevated D-dimer values may have a predictive value for thromboembolic complications. Pericarditis with pericardial effusion as a cardiac complication may follow the respiratory symptoms of COVID-19 infection or occurs isolated, which clinicians should consider when diagnosing and monitoring patients with COVID-19 infection.

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