Stres kardiomiopatija u bolesnice u uznapredovaloj fazi amiotrofične lateralne skleroze

Stress Cardiomyopathy in a Patient with Advanced Stage Amyotrophic Lateral Sclerosis

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SAŽETAK: Stres kardiomiopatija entitet je nepoznate etiologije karakteriziran prolaznom sistoličkom disfunkcijom lijeve klijetke i regionalnim poremećajima kontraktilnosti, koji upućuju na infarkt miokarda, ali bez angiografski značajne opstruktivne koronarne bolesti srca. Klinički, u bolesnika se očituje boli u prsima i/ili dispnejom, a promjene u EKG-u upućuju na akutni infarkt miokarda s elevacijom ST-segmenta. Bitan čimbenik razvoja stres kardiomiopatije povišene su razine katekolamina u plazmi kao rezultat hiperaktivnosti simpatikusa izazvane stresnim događajem. Amiotrofična lateralna skleroza (ALS) progresivna je neurodegenerativna bolest koja zahvaća gornji i donji motoneuron, a najčešće završava smrću zbog paralize mišića za disanje i respiratornog zatajenja. U bolesnika s ALS-om opisane su povišene razine katekolamina i aktivnosti simpatikusa, što čini rizik za razvoj stres kardiomiopatije. U radu je prikazana bolesnica u uznapredovaloj fazi ALS-a s razvojem stres kardiomiopatije.

SUMMARY: Stress cardiomyopathy is an entity of unknown etiology characterized by transient systolic dysfunction of the left ventricle and regional wall motion abnormality which suggest myocardial infarction, but with an absence of angiographic evidence of obstructive coronary artery disease. Patients present with chest pain or/and dyspnea, while ECG changes are similar to acute myocardial infarction with ST-elevation. An important factor in the development of stress cardiomyopathy are high catecholamine levels in the blood as a result of the hyperactivity of the sympathetic nervous system caused by a stressful event. Amyotrophic lateral sclerosis (ALS) is an incurable progressive neurodegenerative disease that causes muscle weakness and ultimately ends in death due to respiratory muscle paralysis and respiratory failure. High catecholamine levels and increased sympathetic activity have been described in patients with ALS, which suggests that ALS is a risk factor for developing stress cardiomyopathy. In this article, we present a patient at an advanced stage of ALS who developed stress cardiomyopathy.

KLJUČNE RIJEČI: stres kardiomiopatija, amiotrofična lateralna skleroza, akutni infarkt miokarda s elevacijom ST-segmenta.

KEYWORDS: stress cardiomyopathy, amyotrophic lateral sclerosis, acute ST-segment elevation myocardial infarction.

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Stres kardiomiopatija (Takotsubo kardiomiopatija) karakterizirana je prolaznom sistoličkom disfunkcijom lijeve klijetke i regionalnim poremećajima kontraktilnosti koji upućuju na infarkt miokarda (MI), ali bez angiografski značajne opstruktivne koronarne bolesti srca (CAD)[1]. Dijagnosticira se u otprilike 1 – 2 % svih slučajeva u kojih se sumnja na IM[1]. Kliničke su tegobe najčešće u obliku bola u prsima i/ili dispneje, elektrokardiografske promjene oponašaju akutni infarkt miokarda s elevacijom ST-segmenta (STEMI), a laboratorijski biljezi lezije

Stress cardiomyopathy (Takotsubo cardiomyopathy) is characterized by transient systolic dysfunction of the left ventricle and regional wall motion abnormality which suggest myocardial infarction (MI), but with an absence of angiographic evidence of obstructive coronary artery disease (CAD)[1]. It is diagnosed in approximately 1-2% of all cases in which MI is suspected[1]. Patients present with chest pain or/and dyspnea, while ECG changes are similar to acute myocardial infarction with ST-elevation (STEMI) and laboratory markers in the myocardial lesion are

miokarda obično su blago do umjereno povišeni[2-5]. Ehokardiografski se tipično nalazi akinezija i baloniranje apeksa lijeve klijetke (LV) uz reduciranu sistoličku funkciju[6]. Postoje i atipične varijante, od kojih su najčešće hipokinezija srednjeg dijela LV-a, dok je apeks pošteđen te varijanta pri kojoj se nalazi akinezija bazalnih segmenata LV-a i hiperkinezija apeksa, a naziva se »obrnutom« Takotsubo kardiomiopatijom[6]. Sindrom se mnogo češće pojavljuje u žena u menopauzi, a obično mu prethodi epizoda emocionalnog, psihičkog ili fizičkog stresa[7]. Među bolesnicima sa stres kardiomiopatijom veća je prevalencija neuroloških i psihijatrijskih poremećaja[7]. Jasni uzroci i patofiziologija stres kardiomiopatije nisu dovoljno razjašnjeni (vazospazam, mikrovaskularna bolest itd.)[8], a opisana je i uloga povišene razine katekolamina u plazmi kao rezultat hiperaktivnosti simpatikusa izazvane stresnim događajem[9]. Dokazana je aktivacija određenih područja mozga (hipokampus, moždano deblo i bazalni gangliji) mjerenjem povećanoga moždanog protoka jednofotonskom emisijskom kompjutoriziranom tomografijom te smanjenoga protoka u prefrontalnom korteksu u bolesnika s Takotsubo kardiomiopatijom[10].

Amiotrofična lateralna skleroza (ALS) neizlječiva je neurodegenerativna bolest koja se očituje progresivnom slabošću mišića, a završava smrću zbog paralize mišića za disanje i respiratornog zatajenja[11]. Zahvaća gornje i donje motoneurone i klinička je slika najčešće kombinacija disfunkcije gornjeg i donjeg motoneurona[12]. Može se prezentirati asimetričnom slabošću i atrofijom mišića udova koji su voljno inervirani (slabost najčešće počinje u mišićima šaka) ili pojavom bulbarnih simptoma, a poslije razvojem mišićne slabosti ili isključivo simptomima koji uključuju donji motoneuron (slabost mišića, mišićna atrofija, fascikulacije). Oko 50 % bolesnika ima simptome frontotemporalne demencije[11]. ALS se u 90 % oboljelih pojavljuje sporadično, dok je u 10 % slučajeva porodična bolest[11]. Porodični se oblik najčešće nasljeđuje autosomno dominantno, no postoje autosomno recesivni i X-vezani oblici bolesti[12]. Utvrđena je mutacija gena na 21. kromosomu koji kodira enzim Cu/Zn superoksid dizmutazu (SOD1)[13]. Patogenetski čimbenici ALS-a nisu razjašnjeni, a, osim mutacije gena, dokazi podupiru autoimunosne mehanizme i okolišne čimbenike (teški metali, trauma, zračenje, virusne infekcije, pušenje itd.) kao moguće čimbenike koji pridonose patogenezi ALS-a[12]. Muškarci obolijevaju češće nego žene, iako se u kasnijoj dobi prevalencija obolijevanja prema spolu sve više izjednačuje. Najčešće se očituje u dobi između 58. i 63. godine u sporadičnom obliku te između 47. i 52. godine u porodičnom obliku[11].

U radu je prikazana 63-godišnja bolesnica u uznapredovaloj fazi ALS-a s razvojem stres kardiomiopatije.

Prikaz bolesnika

Bolesnica u dobi od 63 godine s anamnestičkim podatkom o ALS-u unatrag petnaestak godina i razvijenom kroničnom globalnom respiratornom insuficijencijom, uz primjenu trajne oksigenoterapije u kućnim uvjetima, s posljedičnom paraplegijom, multiplim diskus hernijama vratne kralježnice te dislipidemijom, javila se u hitnu službu u kliničkoj slici akutnoga koronarnog sindroma (ACS) s pojavom bolova u prsnom košu otprilike sat vremena prije dolaska i elevacijom ST-spojnice u odvodima V2 – V5 do 0,2 mV (**slika 1**). S obzirom na opisanu kliničku sliku i EKG promjene, bolesnica je s radnom dijagnozom STEMI-ja anterolateralne lokalizacije upućena na žurnu

usually mildly to moderately elevated[2-5]. ECG typically shows akinesis and apical ballooning of the left ventricle (LV) with reduced systolic function[6]. There are also atypical variants, of which the most common are hypokinesis of the middle part of the LV with apical sparing and the variant with akinesis of the basal LV segments and apical hyperkinesis, which is called "reverse" Takotsubo cardiomyopathy[6]. The syndrome is significantly more common in menopausal women, and is usually preceded by an episode of emotional, mental, or physical stress[7]. There is a higher prevalence of neurological and psychiatric disorders among patients with cardiomyopathy[7]. The etiology and pathophysiology of stress cardiomyopathy have not yet been sufficiently elucidated (vasospasm, microvascular disease, etc.)[8], but elevated levels of catecholamines as a result of the hyperactivity of the sympathetic nervous system caused by a stressful event have been described as a cause[9]. The activation of specific parts of the brain (hippocampus, brain stem, and basal ganglia) has been demonstrated by measuring increased blood flow in the brain as well as reduced flow to the prefrontal cortex using single photon emission computed tomography (SPECT) in patients with Takosubo cardiomyopathy[10].

Amyotrophic lateral sclerosis (ALS) is an incurable progressive neurodegenerative disease that causes muscle weakness and ultimately ends in death due to respiratory muscle paralysis and respiratory failure[11]. It affects the upper and lower motoneurons, and the clinical picture is usually a combination of upper and lower motoneuron dysfunction[12]. It can manifest as asymmetric weakness and muscle atrophy in the exterminates that are volitionally innervated (the weakness usually starts in the muscles of the hands) or with manifestation of bulbar symptoms, and later with the development of muscle weakness or exclusively symptoms that include the lower motoneuron (muscle weakness, muscle atrophy, fasciculations). Approximately 50% of patients have symptoms of frontotemporal dementia11. ALS manifests sporadically in 90% of cases and is a familial disease in 10%[11]. The familial form of the disease is usually autosomal dominant, but there are also autosomal recessive and X-associated disease types[12]. A gene mutation has been found on chromosome 21 that codes the Cu/Zn superoxide dismutase 1 enzyme (SOD1)[13]. The pathogenic factors of ALS have not been fully elucidated, and in addition to gene mutation the evidence also indicates autoimmune mechanisms and environmental factors (heavy metals, trauma, radiation, viral infections, smoking, etc.) as possible factors that contribute to the pathogenesis of ALS[12]. The disease is more prevalent in men than in women, although at older ages the disease prevalence starts becoming increasingly similar between the sexes. The disease usually manifests between 58 and 63 years of age in the sporadic form and between 47 and 52 years of age in the familial form[11].

Herein we report the case of a 63-year-old patient with ALS at an advanced phase who developed stress cardiomyopathy.

Case report

A 63-year-old female patient with a medical history of ALS that was diagnosed fifteen years ago and with chronic global respiratory insufficiency with the application of continuous home oxygen therapy and consequent paraplegia, multiple spinal discus hernias in the neck area and dyslipidemia, was admitted to the emergency room with a clinical picture of acute coronary syndrome with chest pain starting approximately an hour before arrival and ST-elevation in the V2-V5 to

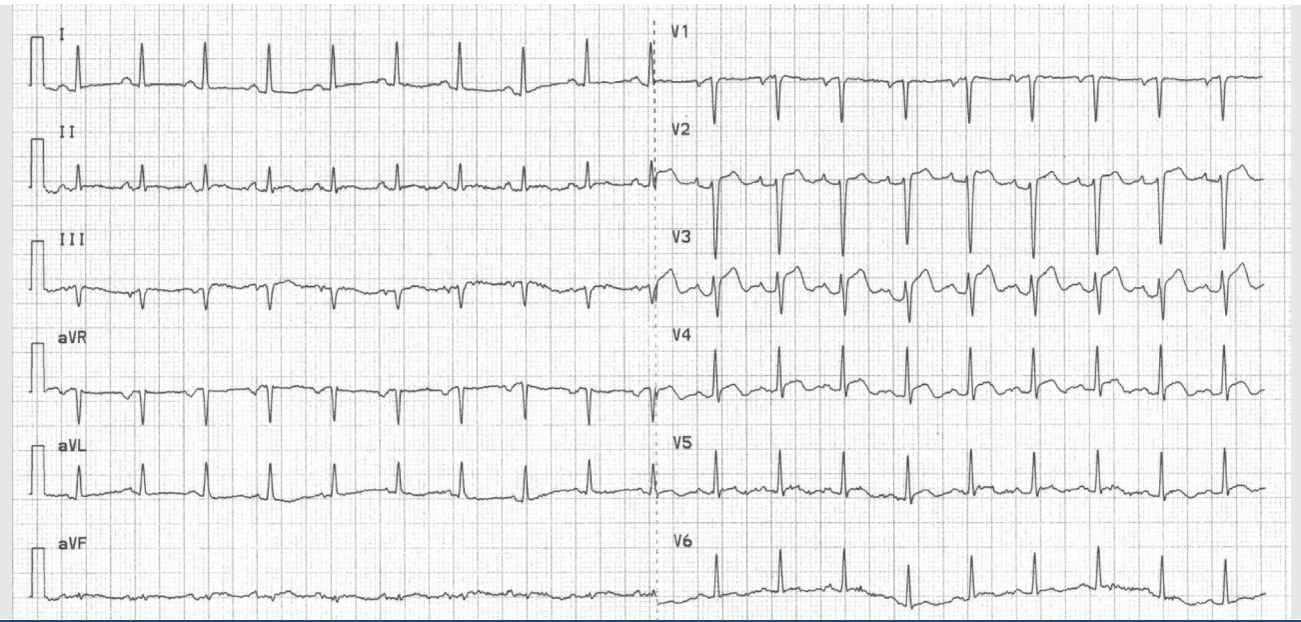

FIGURE 1. ECG in emergency room (elevation of ST-segment up to 0.2 mV which suggests acute ST-segment elevation myocardial infarction of the anterior wall).

koronarografiju. Koronarografijom je isključena značajna opstruktivna CAD (**slika 2**) te je liječenje nastavljeno u jedinici intenzivnog liječenja. Ehokardiografski su utvrđeni hipokinezija i diskretno baloniranje septoapikalnog segmenta LV-a uz graničnu globalnu sistoličku funkciju od 50 %. Serijskim praćenjem biljega nekroze miokarda nije bilo dinamike tipične za ACS (vršna koncentracija visokosenzitivnog troponina bila je tek 53,3 ng/L). Nakon otprilike 3 sata od početka prvih tegoba bolesnica više nije imala bolove u prsima. Drugog dana liječenja u bolesnice se razvija klinička slika refraktorne globalne respiratorne insuficijencije (saturacija O_2 76 %; pH 7,09) s

0.2 mV leads (**Figure 1**). Based on the clinical picture and ECG, a tentative diagnosis of STEMI with anterolateral localization was established and the patient was referred to urgent coronarography. Coronarography excluded significant obstructive CAD (**Figure 2**) and treatment was continued at the Intensive Care Unit. Echocardiography showed hypokinesis and discreet ballooning of the septoapical segment of the LV with a borderline global systolic function of 50%. Serial monitoring of myocardial necrosis markers did not find dynamics typical of ACS (peak high-sensitivity troponin concentrations were only 53.3 ng/L). After approximately 3 hours since the onset of

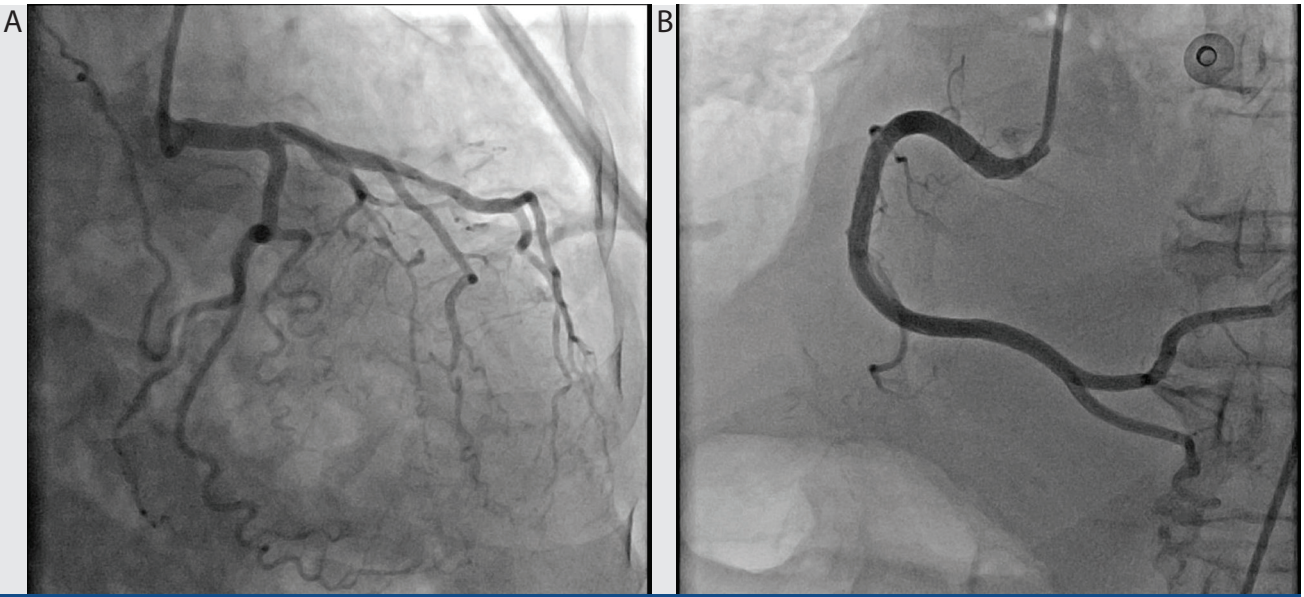

FIGURE 2. (A) Coronary angiogram of the patient – left main coronary artery / left anterior descending artery / circumflex artery. (B) Coronary angiogram of the patient – right coronary artery.

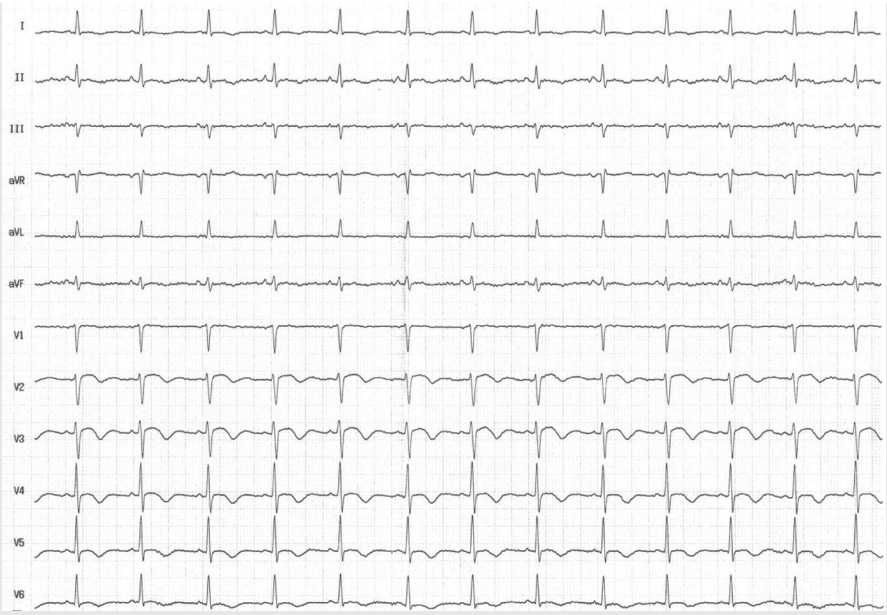

FIGURE 3. **Patient ECG on day 3 of medical treatment (incomplete resolution of ST elevation with biphasic T waves).**

posljedičnom karbonarkozom (pCO_2 15,3 kPa), zbog čega je intubirana i strojno ventilirana. U daljnjem tijeku liječenja bila je potpuno ovisna o strojnoj ventilaciji, bez mogućnosti odvajanja od respiratora. U EKG-u se prati nepotpuna rezolucija prethodno opisane elevacije ST-segmenta na prednjoj stijenci uz pojavu bifazičnih T-valova u odvodima V2 – V5 (**slika 3**). Kontrolni ehokardiografski pregledi pokazali su potpun oporavak kinetike uz oporavak LVEF-a na 60 %. U daljnjem tijeku nije bilo znakova srčanog zatajivanja ni značajnih poremećaja srčanog ritma, a liječena je simptomatski. Tijek liječenja bio je prolongiran i kompliciran razvojem respiratorne (*Pseudomonas aeruginosa*) i urinarnih infekcija (*E. coli, K. pneumoniae* ESBL), zbog čega je liječena rezervnim antibioticima. S obzirom na respiratorni status i stajalište da će strojna ventilacija biti destinacijska terapija, u bolesnice je obavljena traheotomija te je opskrbljena vlastitim kućnim respiratorom. Radi bolesničina daljnjega kroničnog zbrinjavanja i kondicioniranja te edukacije obitelji, bolesnica je 46. dana liječenja premještena u specijalizirani pulmološki centar.

Diskusija

U prikazane bolesnice s uznapredovalom fazom ALS-a razvila se stres kardiomiopatija, nakon čega je vrlo brzo postala respiratorno insuficijentna s potrebom za trajnom strojnom ventilacijom. Uzimajući u obzir klinički tijek i dostupne rezultate pretraga i prethodno kliničko iskustvo[14], riječ je bila upravo o stres kardiomiopatiji, premda je u prvim satima liječenja, diferencijalnodijagnostički razmatrana mogućnost prolongiranoga spazma koronarne arterije ili spontana rezolucija intrakoronarnog ugruška.

Kao jedan od bitnijih patogenetskih mehanizama razvoja Takotsubo kardiomiopatije ističe se katekolaminska kardiotoksičnost povezana s hiperaktivnošću simpatikusa[15]. U bolesnika s ALS-om dokazane su povišene razine katekolamina[16].

the first symptoms, the patient no longer had any chest pain. On the second day of hospitalization the patient developed a clinical picture of refractory global respiratory insufficiency (O_2 saturation at 76%; pH 7.09) with consequent hypercapnia (pCO_2 15.3 kPa), due to which the patient was intubated and placed on mechanical ventilation. In further course of treatment, the patient was completely dependent on assisted ventilation and could not be removed from the respirator. ECG showed incomplete resolution of the ST-segment elevation on the front wall with the appearance of biphasic T waves in the V2-V5 leads (**Figure 3**). Echocardiographic control examinations showed complete recovery of kinetics with LVEF recovery to 60%. There were no subsequent signs of heart failure or significant heart rhythm disorders, and the patient was treated symptomatically. The treatment course was prolonged and complicated by the development of respiratory (Pseudomonas aeruginosa) and urinary infections (*E. coli, K. pneumoniae* ESBL), for which reserve group antibiotics were administered. Given the respiratory status of the patient and since mechanical ventilation would be the destination therapy, the patient received a tracheotomy and was equipped with a home respirator. Due to further chronic care and conditioning requirements of the patient and education of the family, the patient was transferred to a specialized pulmonary center.

Discussion

The patient with advanced ALS we have described developed stress cardiomyopathy followed by rapid development of respiratory insufficiency requiring permanent mechanical ventilation. Considering the clinical course and the available test results as well as our previous clinical experience[14], we established the diagnosis of stress cardiomyopathy despite considering the differential diagnosis of prolonged coronary artery spasm or spontaneous resolution of an intracoronary clot during the first hours of the treatment.

Autonomna disfunkcija u ALS-u još nije dovoljno razjašnjena, međutim, postoje dokazi o smanjenoj parasimpatičkoj i povećanoj simpatičkoj aktivnosti[17,18]. Hiperaktivnost simpatikusa i povećane koncentracije plazmatskog noradrenalina pokazane su već u ranoj fazi ALS-a[19], iako se hiperaktivnost simpatikusa u ALS-u ne smatra nužno primarnom, nego sekundarnom u skladu s progresijom bolesti[20]. Takotsubo kardiomiopatija pojavljuje se u raznim neurološkim bolestima[21,22]. Literatura opisuje 20 slučajeva Takotsubo kardiomiopatije u bolesnika s ALS-om, a njezina klinička važnost, patofiziologija i ishodi nisu dovoljno istraženi[23-31]. Zbog prije navedenih promjena autonomnoga živčanog sustava, pri čemu lokalno otpuštanje noradrenalina u pojačanoj simpatičkoj aktivnosti ima ključnu ulogu, ALS je rizični čimbenik za razvoj Takotsubo kardiomiopatije, koja se može očitovati kada se pojavi stresan čimbenik (npr. infekcija, respiratorna insuficijencija, kirurški zahvat itd.)[31,32]. Ova pretpostavka upućuje na etiološke razlike između Takotsubo kardiomiopatije u ALS-u prema onoj u akutno nastalome neurološkom poremećaju, kada bolest „per se" uzrokuje kardiomiopatiju[31]. Veća je incidencija Takotsubo kardiomiopatije u ALS-u u usporedbi s ostalim formama heterogene grupe bolesti motornog neurona[32] te s obzirom na sinukleopatije (Parkinsonova bolest, demencija Lewyjevih tjelešaca, multipla sistemska atrofija), što se također može pripisati povećanoj aktivnosti simpatikusa[31]. Ishod je takvih bolesnika obično lošiji u usporedbi s onima koji nemaju bolest motornog neurona, a vjerojatno zbog slabosti respiratorne muskulature u primarnoj bolesti[32]. Posljednja istraživanja sugeriraju da bi se u bolesnika s poznatim ALS-om, pogotovo u uznapredovaloj fazi bolesti, koji se prezentiraju bolovima u prsnom košu i dispnejom, trebalo posumnjati na Takotsubo kardiomiopatiju[30].

Zaključak

U bolesnice s uznapredovalom fazom ALS-a na temelju kliničke slike i provedene obrade postavljena je dijagnoza Takotsubo kardiomiopatije. Time je izbjegnuta obilna medikacija koja bi se, prema smjernicama, trebala primijeniti u akutnom MI-ju. Poželjno je u bolesnika s bolestima motornog neurona i kliničkom slikom akutnog MI-ja posumnjati na Takotsubo kardiomiopatiju i na taj način izbjeći primjenu nepotrebne i dugoročne medikamentne terapije nepostojeće CAD.

Catecholamine cardiotoxicity associated with sympathetic nervous system hyperactivity has been emphasized as one of the more important pathogenic mechanisms for the development of Takotsubo cardiomyopathy[15]. Increased levels of catecholamines have been demonstrated in patients with ALS[16]. Autonomic dysfunction in ALS is still not sufficiently elucidated, but there is evidence of reduced activity of the parasympathetic and increased activity of the sympathetic nervous system[17,18]. Sympathetic hyperactivity and elevated concentrations of plasma noradrenaline have been found already in the early stage of ALS[19], although sympathetic hyperactivity is not considered to necessarily be primary in ALS but rather secondary and dependent on the disease progression[20]. Takotsubo cardiomyopathy manifests in different neurological diseases[21,22]. The literature describes 20 cases of Takotsubo cardiomyopathy in patients with ALS, and its clinical significance, pathophysiology, and outcomes have not been sufficiently investigated[23-31]. Due to the previously described changes in the autonomic nervous system in which the local release of noradrenaline as a consequence of increased sympathetic activity plays a crucial role, ALS represents a risk for the development of Takotsubo cardiomyopathy, which can manifest in the presence of a stress-inducing factor (e.g. infection, respiratory insufficiency, surgical procedure, etc.)[31,32]. This implies the existence of etiological differences between Takotsubo cardiomyopathy in ALS and those in acute neurological disorders where the disease itself causes cardiomyopathy[31]. The incidence of Takotsubo cardiomyopathy is higher in ALS in comparison with other forms in the heterogenous group of motor neuron diseases[32] and in comparison with synucleinopathies (Parkinson's disease, Lewy body dementia, multiple system atrophy), which can also be ascribed to increased sympathetic activity[31]. Outcomes in such patients are generally poorer in comparison with those who do not have motor neuron disease, most likely due to weakness of primary musculature as a consequence of the primary illness[32]. Latest studies suggested that Takotsubo cardiomyopathy should be suspected in patients with diagnosed ALS who present with chest pain and dyspnea, especially in the advanced phase of the disease[30].

Conclusion

Our patient with advanced ALS was diagnosed with Takotsubo cardiomyopathy on the basis of the clinical picture and patient processing. This avoided prescription of the copious amounts of medication that guidelines recommend for acute MI. Takotsubo cardiomyopathy should be suspected in patients with motor neuron disease and the clinical picture of acute MI, thus avoiding the application of long-lasting and unnecessary medication treatment for non-existent CAD.

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