Kapecitabinom inducirana kardiotoksičnost komplicirana razvojem akutnoga koronarnog sindroma i akutnim zatajivanjem srca: prikaz bolesnika i pregled znanstvenih podataka

Capecitabine-induced Cardiotoxicity Complicated with Acute Coronary Syndrome and Acute Heart Failure: A Case Report and Review of Scientific Data

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SAŽETAK: Kardiotoksičnost uzrokovana kapecitabinom razmjerno je česta te može uzrokovati ozbiljne kardiovaskularne komplikacije. Svrha je ovoga prikaza naglasiti važnost uzimanja u obzir potencijalnih toksičnih učinaka kapecitabina te brzog obustavljanja terapije i pravodobnog liječenja svih komplikacija. Predstavit ćemo slučaj 46-godišnjeg muškarca koji je na liječenje primljen s bolima u prsima i elevacijom ST-segmenta u prednjim i lateralnim odvodima, što je upućivalo na akutni infarkt miokarda s elevacijom ST-segmenta. Hitnom je koronarografijom otkrivena prisutnost tromba u prednjoj silaznoj grani lijeve koronarne arterije, nakon čega je provedena perkutana koronarna intervencija. Dva mjeseca prije prijma, bolesnik je bio podvrgnut kirurškom zahvatu zbog karcinoma rektuma. Navedeni simptomi pojavili su se tri dana nakon uvođenja terapije kapecitabinom, koja je odmah nakon prijma prekinuta. Tijekom zahvata nastupilo je kliničko pogoršanje s razvojem kardiogenog šoka. Ehokardiografski pregled proveden nakon zahvata pokazao je ozbiljno smanjenje funkcije lijeve klijetke (ejekcijska frakcija – EF 21 %). Zbog daljnjeg pogoršanja i kardiogenog šoka refraktornog na optimalnu inotropnu i vazopresorsku terapiju, primijenjena je veno-arterijska ekstrakorporalna membranska oksigenacija, a bolesnik je bio priključen na mehaničku ventilaciju. Nakon svih primijenjenih terapijskih mjera bolesnik je klinički stabiliziran. Ekstubiran je nakon dva dana te hemodinamski stabiliziran uz postupno poboljšanje funkcije lijeve klijetke. Kontrolna ehokardiografija devet dana nakon prijma pokazala je EF od 58 %. Ovaj je slučaj primjer uspješnog liječenja potencijalno ozbiljnih kardiotoksičnih komplikacija terapije kapecitabinom u mlađeg bolesnika te ističe nužnost multidisciplinarne suradnje u sličnim kliničkim situacijama.

SUMMARY: Capecitabine cardiotoxicity is relatively common and may lead to serios cardiovascular complications. The aim of this case report is to emphasize the importance of considering potential toxic effects, rapid therapy discontinuation, and prompt treatment of all complications. We present a case of a 46-year-old male patient who was admitted to our clinic with chest pain and ST segment elevation in the anterior and lateral leads as a sign of acute ST-segment elevation myocardial infarction. Urgent coronary angiography was performed with the finding of a thrombus in the left anterior descendent coronary artery, and percutaneous coronary intervention was subsequently performed. Two months before admission, the patient had undergone surgery for rectal cancer. The above symptoms started three days after the introduction of treatment with capecitabine, which was discontinued on admission. The patient clinically deteriorated during the procedure, with development of cardiogenic shock. An echocardiography exam performed after the procedure showed severe reduction of left ventricular (LV) function (ejection fraction (EF) 21%). Due to further deterioration and cardiogenic shock refractory to optimal inotropic and vasopressor support, veno-arterial extracorporeal membrane oxygenation support was applied and the patient was placed on mechanical ventilation. After all these treatment measures, the patient clinically stabilized. He was extubated after 2 days and hemodynamically stabilized with gradually improvement of LV function. Control echocardiography after 9 days from admission showed an EF of 58%. Our case is an example of successful treatment of the potential serious cardiotoxic complications of capecitabine therapy in a young patient. The case also emphasizes the necessity of multidisciplinary collaboration in similar clinical scenarios.

KLJUČNE RIJEČI: kapecitabin, kardiotoksičnost, zatajivanje srca, akutni infarkt miokarda s elevacijom ST-segmenta

KEYWORDS: capecitabine, cardiotoxicity, heart failure, ST-segment elevation myocardial infarction.

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Uvod

Kapecitabin je oralni prolijek 5-fluorouracila (5-FU) na bazi fluoropirimidina koji se uporabljuje kao antineoplastični lijek. Trenutačno je odobren za liječenje metastatskog raka dojke, a, prema smjernicama koje je propisao *National Comprehensive Cancer Network*, preporučuje se za adjuvantno liječenje kao monoterapija ili u kombinaciji u liječenju uznapredovaloga kolorektalnog karcinoma[1].

Profil nuspojava kapecitabina razlikuje se od nuspojava 5-FU-a. Kapecitabinom inducirana miokardna toksičnost rijetka je, no uključuje ozbiljne nuspojave. Nekolicina retrospektivnih analiza dosad objavljenih u literaturi opisuje širok raspon manifestacija, od aritmija i akutnih ishemijskih događaja do zatajivanja srca (ZS) i kardiogenog šoka[2].

U ovom prikazu predstavljamo klinički slučaj bolesnika u kojeg se, zbog liječenja kapecitabinom, razvio akutni infarkt miokarda s elevacijom ST-segmenta (STEMI) uz akutno ZS s posljedičnim stanjem šoka, a potpun oporavak funkcije miokarda nastupio je unutar devet dana nakon primjene odgovarajuće terapije. Taj je slučaj primjer potencijalne kardiotoksičnosti kapecitabina uz ozbiljne kardiovaskularne komplikacije. Iako kemoterapija kapecitabinom malokad uzrokuje kardiotoksičnost, kardiolozi moraju biti svjesni potencijalnih komplikacija zbog mogućeg nastupa za život opasnih srčanih događaja. Onkolozi i kardiolozi trebaju postaviti visok stupanj sumnje na manje uobičajene manifestacije i održavati blisku suradnju, jer neki od ovakvih događaja mogu imati smrtonosan ishod.

Prikaz bolesnika

Bolesnik dobi od 46 godina primljen je u kliniku s jakom boli u prsima i elevacijom ST-segmenta u prednjim odvodima. Dva mjeseca prije prijma bio mu je dijagnosticiran zloćudni tumor rektuma te je podvrgnut laparoskopskoj resekciji prednjeg dijela rektuma s kolorektalnom anastomozom. Nakon kirurškog zahvata bolesnik je usmjeren na onkološki odjel radi daljnjih pretraga i kemoterapije. Liječenje kapecitabinom započeto je prema specifičnom režimu: 1500 mg ujutro i 2000 mg navečer *per os*. Tri dana nakon uvođenja takve terapije u bolesnika su se razvili simptomi zbog kojih je upućen na kliniku. Vitalni znakovi pri prijmu bili su sljedeći: arterijski tlak (AT) 150/85 mmHg, frekvencija srca 100/min, sPO_2 96 %, respiratorna frekvencija 22/min, tjelesna temperatura 36,3 °C. Dvanaestokanalni EKG pri prijmu pokazao je blok desne grane (RBBB; prema engl. *right bundle branch block*) s elevacijom ST-segmenta u prednjim odvodima (**slika 1**). Laboratorijski su nalazi pokazali povišene vrijednosti hs-troponina (3990 ng/L; normalne vrijednosti 15,6 ng/L) i NT-proBNP-a (5251 pg/mL), zbog čega je indicirana hitna koronarografija.

U međuvremenu se pogoršalo kliničko stanje, uz padom AT-a i porast razine laktata (3,8 mmol/L). Obavljena je hitna koronarografija, pri čemu je pronađen tromb u prednjoj silaznoj grani lijeve koronarne arterije (LAD; prema engl. *left anterior descendent coronary artery*). Provedena je perkutana koronarna intervencija LAD-a s implantacijom stenta, pri čemu je u konačnici postignut TIMI 3 protok. Tijekom zahvata bolesnik je bio u kliničkoj slici kardiogenog šoka te je premješten u jedinicu intenzivne koronarne skrbi radi daljnjeg liječenja. Liječen je inotropnom i vazopresorskom terapijom (dobutamin i noradrenalin), antikoagulantnom i antitrombo-

Introduction

Capecitabine is a fluoropyrimidine-based oral prodrug of 5-fluorouracil (5-FU) used as an anti-neoplastic agent. It is currently approved for treatment of metastatic breast cancer and, according to the National Comprehensive Cancer Network guidelines, it is recommended for adjuvant treatment as monotherapy or in combination with other agents in advanced colorectal cancer[1].

The side effect profile of capecitabine varies from that of 5-FU. Capecitabine-induced myocardial toxicity is rare but includes serious adverse events. The few retrospective analyses published in the literature so far describe a wide range of cardiac manifestation, ranging from arrhythmias and acute ischemic events to heart failure (HF) and cardiogenic shock[2].

In this report, we present the clinical case of a patient developing ST-segment elevation myocardial infarction (STEMI) and acute HF resulting in shock as a consequence of capecitabine treatment, with a complete recovery of the myocardial function within 9 days after appropriate treatment. Our case is an example of potential capecitabine therapy cardiotoxicity followed by serious cardiovascular complications. Although capecitabine chemotherapy rarely causes cardiotoxic events, cardiologists must be aware of the potential complications due to the possible life-threatening cardiac events. Oncologists and cardiologists must maintain a high index of suspicion for less common presentations and collaborate closely, because some of these events may lead to a fatal outcome.

Case report

A 46-year-old patient was admitted to our clinic with severe chest pain and ST-segment elevation in the anterior leads. Two months before admission, he was diagnosed with malignant neoplasm of the rectum and underwent laparoscopic resection treatment of the anterior rectum cum colo-rectal anastomosis. After the surgical treatment, the patient was referred to the oncology department for further tests and chemotherapy. Treatment with capecitabine was initiated in a specific regimen: 1500 mg in the morning and 2000 mg at night *per os*. 3 days after the introduction this regimen, he presented with the current symptoms. The patient's vital signs on admission were as follows: blood pressure (BP) 150/85 mmHg; heart rate 100/min; sPO_2 96%; respiratory rate 22/min; body temperature 36.3 C. The admission ECG showed right bundle branch block (RBBB) with ST-segment elevation in the anterior leads (**Figure 1**). Laboratory findings showed hs-Troponin 3990 ng/L (normal values 15.6ng/l) and NT-proBNP 5251 pg/mL, and emergency coronary angiography was thus indicated.

In the meantime, the patient's status deteriorated, with a drop in BP and elevation in the lactate (3.8 mmol/L). Emergency coronary angiography was performed, with finding of a thrombus in the left anterior descendent coronary artery (LAD). Subsequent percutaneous coronary intervention of the LAD was performed with endovascular prothesis implantation, and the final TIMI 3 flow result was obtained. The patient was in cardiogenic shock during the procedure, and transferred to the Intensive Coronary Unit (ICU) for further treatment. He was treated with inotropic and vasopressor support (dobutamine with noradrenalin) anticoagulant, antithrombotic therapy and statins. The next day, the patient's arterial

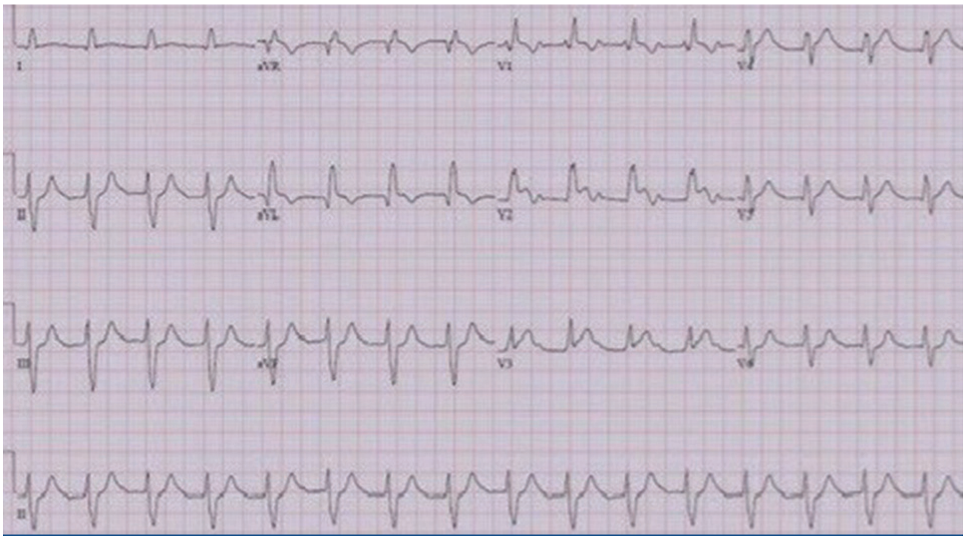

FIGURE 1. Admission electrocardiography showing right bundle branch block with wide QRS and ST-segment elevation in the anterior leads.

tičkom terapijom te statinima. Sljedećeg je dana nastupilo daljnje pogoršanja u vrijednostima arterijskih plinova u krvi (ABG) uz porastom razine laktata na 8,3 mmol/L. Ehokardiografski je pregled pokazao ozbiljno smanjenje ejekcijske frakcije (EF) lijeve klijetke na 21 % (**slika 2**), uz umjerenu mitralnu i trikuspidalnu regurgitaciju. Globalni longitudinalni *strain* lijeve klijetke bio je znatno smanjen, s vrijednošću od –5 % (**slika 3**). Na dan prijma, na temelju konzultacije s onkologom, prekinuta je terapija kapecitabinom zbog sumnje na kardiotoksičnost. Zbog stalne hemodinamske nestabilnosti nije bilo moguće obaviti dijagnostički pregled magnetnom rezonancijom srca.

Drugog dana boravka u bolnici zabilježena je nova pojava fibrilacije atrija, nakon čega je uslijedilo kliničko pogoršanje uz razvoj fibrilacije ventrikula, a potom asistolije nakon primjene elektrošoka, što je zahtijevalo kardiopulmonalnu reanimaciju. Bolesnik je tijekom reanimacije više puta defibriliran te intubiran i priključen na mehaničku ventilaciju, uz primjenu norepinefrina i dobutamina zbog kardiogenog šoka. Budući da je imao hemodinamsku nestabilnost, premješten je na

blood gasses (ABG) showed worsening, with further elevation in lactate values (8.3 mmol/L). Echocardiography examination showed a severe reduction in the left ventricular ejection fraction (EF) of 21% (**Figure 2**), with moderate mitral and tricuspid regurgitation. LV global longitudinal strain was severely reduced with a value of -5% (**Figure 3**). On the day of admission, the treatment with capecitabine was discontinued in consultation with an oncologist due to the suspected cardiotoxicity. Because of the constant hemodynamic instability, cardiac magnetic resonance was not feasible as diagnostic option.

On the second day spent in the hospital, a new onset of atrial fibrillation was noted; shortly after, a clinical worsening presenting with ventricular fibrillation followed by asystole after the electrical shock progressed to a complete reanimation. The patient was defibrillated several times within the cardiopulmonary resuscitation protocol, and he was intubated and placed on mechanical ventilation as well as norepinephrine and dobutamine due to the cardiogenic shock. Because of the hemodynamic instability, the patient was transferred to Cardiac Surgery Department for further treatment with veno-arterial

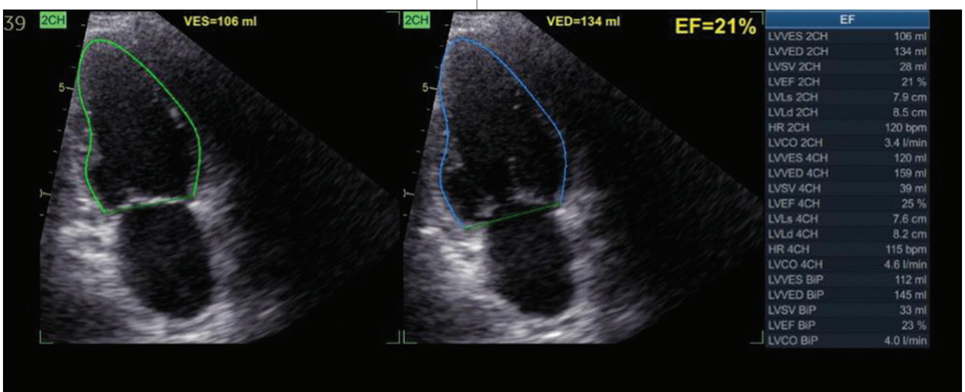

FIGURE 2. Echocardiography after coronary revascularization showing a severely reduced ejection fraction of 21%; cardiac index 2.1 L/min/m².

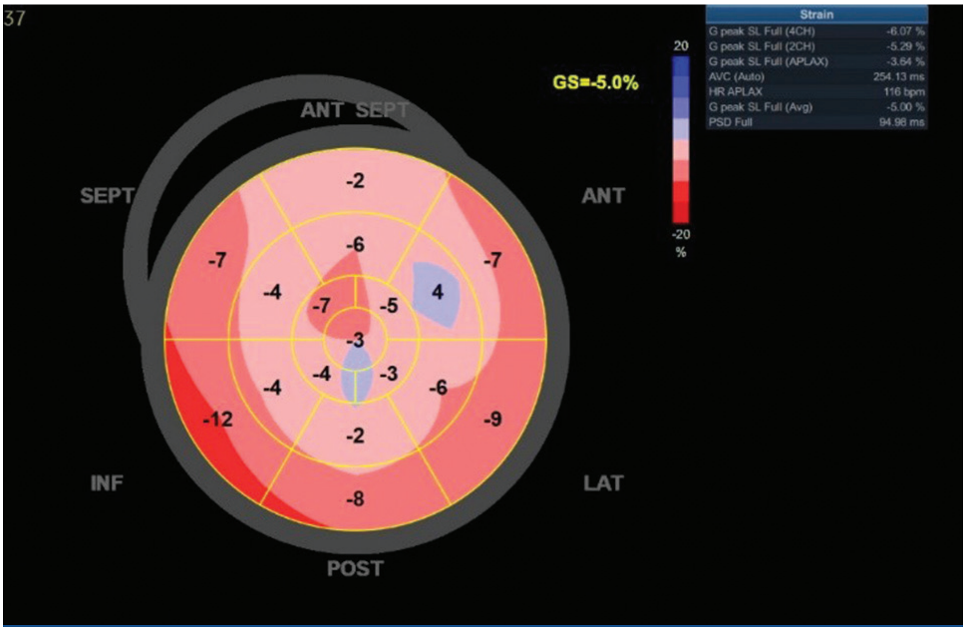

FIGURE 3. Left ventricular global longitudinal strain after coronary revascularization showing severely impaired systolic function (-5.0%).

Odjel za kardijalnu kirurgiju radi daljnjeg liječenja veno-arterijskom ekstrakorporalnom membranskom oksigenacijom (ECMO) zbog kardiogenog šoka refraktornog na optimalnu inotropnu i vazopresorsku terapiju. Nakon tih su intervencija bolesnikovi parametri bili stabilni i zadovoljavajući, pa je nastavljeno pomno praćenje, bez potrebe za dodatnom mehaničkom cirkulatornom potporom. Dva dana poslije bolesnik je ekstubiran uz poboljšanje vrijednosti ABG-a i općega kliničkog stanja. Kontrolna transtorakalna ehokardiografija u bolničkom krevetu pokazala je blag oporavak funkcije lijeve klijetke. Liječenje ZS-a započeto je perindoprilom 2 mg jednom na dan, spironolaktonom 25 mg jednom dnevno te furosemidom 40 mg intravenski, uz nastavak antitrombotske i antikoagulantne terapije – acetilsalicilatna kiselina 100 mg jednom na dan, klopidogrel 75 mg jednom dnevno i enoksaparin 6000 i. j. dvaput na dan, uz postupno ukidanje inotropa i vazopresora. EKG je pokazao povlačenje ST-elevacije, a uz

extracorporeal membrane oxygenation (ECMO) due to cardiogenic shock refractory to optimal inotropic and vasopressor support as the next step in the treatment. The patient's parameters were stable and satisfactory in this setting, and we continued the close follow-up and proceeded without the need of mechanical circulatory support. Two days later, the patient was extubated with improvement in the ABG and general clinical status. Control bedside transthoracic echocardiography showed slight recovery of LV function. The treatment for HF started with perindopril 2 mg once a day (OAD), spironolactone 25 mg OAD, and furosemide 40 mg intravenous infusion, with continued antithrombotic and anticoagulant therapy with aspirin 100 mg OAD, clopidogrel 75 OAD, and enoxaparin 6000IE BID, with weaning off inotropes/vasopressors. ECG showed resolution of ST-segment elevation, RBBB with ST-segment descendent depression and a negative T wave in V1-V3 (**Figure 4**). On the 8th day, the echocardiography findings

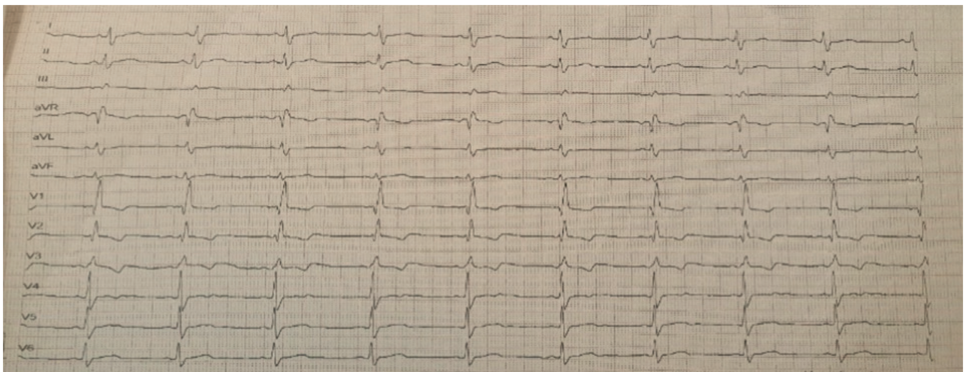

FIGURE 4. Electrocardiography showing resolution of the ST-segment elevation, right bundle branch block with ST-segment depression and negative T wave in V1-V3 on the eight day after admission.

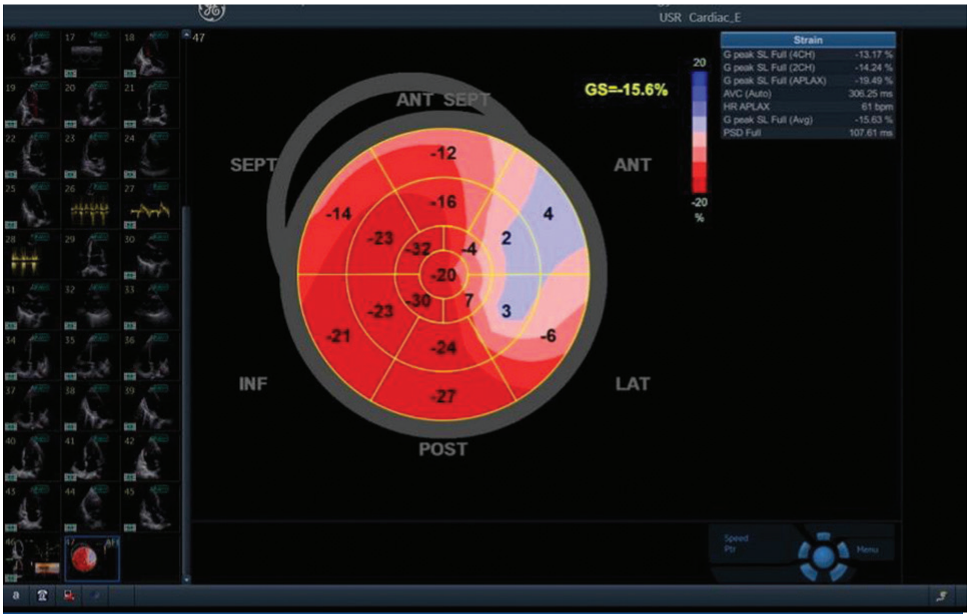

FIGURE 5. Left ventricular global longitudinal strain showing significant improvement in the global and regional longitudinal strain compared with the admission findings: slight reduction of global and regional strain in the lateral and basal anterior and anteroseptal wall segments.

RBBB vide se silazna depresija ST-segmenta i negativan T-val u odvodima V1 – V3 (**slika 4**). Osmog je dana ehokardiografski nalaz pokazao potpun oporavak funkcije lijeve klijetke, uz hipokineziju prednje stijenke i EF-a od 58 %, uz blagu mitralnu i trikuspidalnu regurgitaciju te znatno poboljšanje globalnoga longitudinalnog *straina* (**slika 5**).

Nakon devet dana te mnogobrojnih izazovnih odluka o kliničkom i terapijskom pristupu, bolesnik je otpušten u klinički stabilnom stanju, uz nastavak liječenja ZS-a (ACE inhibitor, antagonist mineralokortikoidni receptori, beta-blokator, dvojna antitrombotska terapija i statin u visokoj dozi) te uz preporuku daljnje onkološke konzultacije i pomno kardiološko praćenje.

Rasprava

Kapecitabin je pirimidinski antimetabolit koji inhibira timidilat sintazu[1-3]. Primjenjuje se kao oralni prolijek koji se enzimatski pretvara u aktivni 5-FU u tkivima i klinički nalikuje na intravensku primjenu 5-FU[4]. Incidencija od 5-FU-om inducirane kardiotoksičnošću, prema literaturnim navodima, iznosi od 2,8 do 3,5%, iako se vjeruje da je stvarni broj veći s obzirom na poznate asimptomatske promjene ST-segmenta na elektrokardiografiji[5-8]. Ostale manifestacije 5-FU-inducirane kardiotoksičnosti uključuju ZS, hipertenziju ili hipotenziju, kardiomiopatiju, akutni koronarni sindrom (AKS), aritmije, smetnje provođenja te, rjeđe, kardiogeni šok i srčani zastoj[8]. Iako je kardiotoksičnost često reverzibilna nakon prekida primjene lijeka, smrtonosne komplikacije mogu nastupiti u manjega broja bolesnika, neovisno o kumulativnoj dozi lijeka. Stope ukupne smrtnosti u literaturi kreću se od 2,2 % do čak 13,3 %[9]. Većina je neželjenih događaja povezana s vazospazmom arterija i stvaranjem tromba u koronarnim arterijama, a bolesnici obično imaju znakove i simptome AKS-a[4,6]. Među-

showed complete resolution of the LV dysfunction with hypokinesia on the anterior LV wall and an EF of 58%, along with mild mitral and tricuspid regurgitation and significant improvement of the global longitudinal strain (**Figure 5**).

After nine days and many challenging decisions about the clinical and therapeutic approach, the patient was discharged in a clinically stable state, with continued heart failure therapy (ACE inhibitor, MRA antagonist, beta blocker, dual antithrombotic therapy, and high dose statin), and with a recommendation for further oncology consultations and close cardiology follow-up.

Discussion

Capecitabine is a pyrimidine antimetabolite that inhibits thymidylate synthase[1-3]. It is an oral prodrug which is enzymatically converted to active 5-FU in tissues, and it clinically resembles intravenous administration of 5-FU[4]. The incidence of 5FU-induced cardiotoxicity in the literature ranges from 2.8% to 3.5%, although it is believed that the true number may be higher, given the fact that silent ST-segment deviations on electrocardiography are known to occur[5-8]. Other manifestations of 5FU-induced cardiotoxicity include HF, hyper- or hypotension, cardiomyopathy, acute coronary syndrome (ACS), arrhythmias, conduction disturbances, and, less frequently, cardiogenic shock and cardiac arrest[8]. Although cardiotoxicity is often reversible with discontinuation of the drug, fatal complications can still occur in a minority of patients, irrespectively of cumulative doses. Reported overall mortality rates range from 2.2% to as high as 13.3%[9]. Most of the events are related to artery vasospasm and thrombus formation in the coronary arteries, and patients usually present with signs and symptoms of ACS[4,6]. However, HF and cardiogenic shock requiring inotropic and vasopressor therapy have been described in the literature, raising tim, u literaturi se opisuju slučajevi ZS-a i kardiogenog šoka koji zahtijevaju inotropnu i vazopresorsku terapiju, što je opasnost zbog mogućega smrtonosnog ishoda. McAndrew *i sur.* proveli su istraživanje na seriji bolesnika sa ZS-om koje je dovelo do kardiogenog šoka ubrzo nakon izloženosti kapecitabinu[9]. Objavljeni slučajevi pokazuju da se simptomi obično pojavljuju unutar dva do tri dana od početka terapije kapecitabinom[10]. Rizični markeri za potencijalne kardiotoksične učinke proučavani su u nizu istraživanja. Kwakmall *i sur.* proveli su retrospektivnu analizu i otkrili da je ishemijska bolest srca rizičan čimbenik za kardiotoksičnost u bolesnika liječenih kapecitabinom[11].

Ovaj prikaz bolesnika naglašava nekoliko ključnih točaka koje treba uzeti u obzir u bolesnika sa sumnjom na kardiotoksičnost uzrokovanu kapecitabinom. Kao prvo, početna klinička slika s bolima u prsima, promjenama na EKG-u i znatno povišenim srčanim biljezima snažno upućuje na AKS. Iako je vazospazam najčešći uzročni mehanizam koji dovodi do ovakve kliničke slike, nekoliko slučajeva u literaturi upućuje na to da se, osim vazospazma, nakon terapije kapecitabinom može pojaviti i koronarna tromboza kao moguć izravan učinak ovog lijeka[12,13]. S obzirom na činjenicu da koronarni vazospazam nije uvijek osnovni uzročnik, bolesnici na terapiji kapecitabinom u kojih se razvije AKS trebaju biti upućeni na primarnu perkutanu koronarnu intervenciju kako bi se spriječili potencijalno katastrofalni događaji.

U ovom je slučaju ehokardiografija pokazala smanjenu EF lijeve klijetke i globalnu hipokineziju, što nije odgovaralo segmentnoj distribuciji velikih koronarnih arterija. Ugradnja stenta u LAD nije dovela do poboljšanja kliničkog stanja, a nakon premještaja na Odjel intenzivne njege, u bolesnika se razvio refraktarni šok. To je izazvalo sumnju na drugi uzročnik koji bi potencijalno mogao biti odgovoran za tešku disfunkciju miokarda. Liječenje je u ovom slučaju bilo multidisciplinarno, uz sudjelovanje kardiologa, onkologa i kardijalnih kirurga. Brzo zaustavljanje terapije kapecitabinom i liječenje svih kardiovaskularnih komplikacija dovelo je do uspješna oporavka funkcije lijeve klijetke i do kliničke stabilizacije.

Kemoterapijom inducirana Takotsubo kardiomiopatija jedan je od mogućih uzročnih mehanizama u bolesnika s novonastalom disfunkcijom srca, no u našem slučaju ehokardiografski nalazi nisu slijedili tipičan obrazac – apikalna akineza i baloniranje s hiperdinamičnom bazom. S obzirom na potpun oporavak funkcije miokarda unutar devet dana od nastupa simptoma, smatramo da je u našem slučaju potencijalni toksični miokarditis bio najvjerojatniji uzročni mehanizam koji je doveo do izražene depresije miokarda. Na temelju istraživanja na životinjskim modelima, mogućim se uzročnim mehanizmima smatraju izravni toksični učinak na koronarni endotel ili toksični miokarditis s vazospazmom. Izravan toksični učinak na miokard, koji se pripisuje antimetaboličkom djelovanju lijeka, može izazvati kliničku sliku toksične kardiomiopatije[14].

Konačno, individualna osjetljivost na kardiotoksičnost mogla bi biti rezultat nasljednih varijacija u enzimskim putevima koji sudjeluju u katabolizmu fluoropirimidina, što dovodi do različitih razina kardiotoksičnih produkata nastalih razgradnjom[15]. U bolesnika s nedostatkom dihidropirimidin dehidrogenaze (DPD) i s kolorektalnim karcinomom te u onih koji imaju povećan rizik od kardiotoksičnosti, toksičnost inducirana 5-FU-om obično se pojavljuje brzo, pokatkad čak i

concerns about a possible fatal outcome in some of the patients. McAndrew *et al.* reported a case series of patients with HF leading to cardiogenic shock shortly after exposure to capecitabine[9]. Published case reports reveal that symptoms usually occur within two to three days after the initiation of capecitabine therapy[10]. Risk markers for potential cardiotoxic effects have been examined in many studies. Kwakmall *et al.* performed a retrospective analysis and discovered that ischemic heart disease was a risk marker for cardiotoxicity in patients who received capecitabine[11].

The present case report highlights several key points that need to be taken into consideration in patients with suspected capecitabine cardiotoxicity. First, the initial presentation of the patient with chest pain, ECG changes, and significantly elevated cardiac markers are highly suggestive of ACS. Although vasospasm is the most common mechanism that causes this clinical scenario, few cases in the literature point out that, apart from vasospasm, coronary thrombosis could be observed after capecitabine treatment as a possible direct effect of this drug[12,13]. Considering the fact that coronary vasospasm is not always the underlying mechanism, patients under capecitabine treatment presenting with ACS should be referred for primary percutaneous coronary intervention in order to prevent potential catastrophic events.

In our case, echocardiography demonstrated reduced LV ejection fraction and global hypokinesia, which did not correspond to the segmental distribution of the major coronary arteries. LAD stenting did not lead to improvement of the clinical condition of the patient, and once he was transferred to the ICU, he developed refractory shock despite the successful stenting. This raised the suspicion of another mechanism that was potentially responsible for the severe myocardial dysfunction. The treatment in this case was multidisciplinary, with the inclusion of cardiologists, oncologists, and cardiac surgeons. Prompt exclusion of capecitabine therapy and treatment of all cardiovascular complications lead to successful recovery of LV function and clinical stabilization of the patient.

Chemotherapy-induced Takotsubo cardiomyopathy is one of the potential causative mechanisms in patients with newly-developed cardiac dysfunction, but in our case the echocardiographic findings did not reveal the typical pattern-apical akinesia and ballooning with hyperdynamic base. Considering the full recovery of the myocardial function in nine days from the initial presentation, we believe that in our case the most probable mechanism of such severe myocardial depression is potential toxic myocarditis. Based animal models, a direct toxic effect on the coronary endothelium, or toxic myocarditis with vasospasm, have been proposed as possible mechanisms. A direct myocardial toxic effect attributed to the antimetabolite effects of the drug may provoke a toxic cardiomyopathic clinical picture[14].

Finally, individual sensitivity to cardiotoxicity could be a result of inherited variations in the enzyme pathways involved in the catabolism of fluoropyrimidines, leading to variable levels of cardiotoxic degradation products[15]. In patients with dihydropyrimidine dehydrogenase (DPD) deficiency and colorectal cancer who have increased risk of cardiotoxicity, the onset of 5-FU toxicity usually happens rapidly, sometimes even within hours of the first dose. In such cases, an antidote, uridine triacetate, may be considered, and pretreatment DPD unutar nekoliko sati nakon prve doze. U takvim se slučajevima može razmotriti primjena uridin triacetata kao antidota, a također bi trebalo uzeti u obzir i procjenu DPD aktivnosti prije liječenja[15,16]. S obzirom na učestalost kardiotoksičnosti uzrokovane kapecitabinom, bolesnike treba pomno pratiti od prvog ciklusa liječenja do završetka terapije. Praćenje bi trebalo uključivati elektrokardiografiju, a prema kliničkim simptomima i ehokardiografiju, što omogućuje otkrivanje supkliničke kardiotoksičnosti. Bolesnici s prethodnim bolestima srca zahtijevaju osobito pomno praćenje.

Jedno od ograničenja bio je izostanak primjene magnetne rezonancije srca, koja nije inicijalno provedena zbog nagloga hemodinamskog pogoršanja koje je zahtijevalo primjenu liječenja ECMO-om zbog kardiogenog šoka refraktarnog na optimalnu inotropsku i vazopresorsku terapiju. Biopsija miokarda također je mogla pružiti korisne podatke, no provođenje tako invazivnog postupka u hemodinamski nestabilnog bolesnika veoma je zahtjevno te stvara dodatne rizike.

Liječenje akutnoga kardiogenog šoka uzrokovana kardiotoksičnim učinkom kapecitabina i 5-FU-a zahtijeva primjenu inotropne i vazopresorske terapije te hitan prekid primjene lijeka. Oporavak od kardiomiopatije obično se očekuje unutar nekoliko dana, kao što je opisano u ovom slučaju. Nakon tako teške kardiotoksičnosti, ponovno izlaganje 5-FU-u ne bi trebalo pokušavati te se smatra kontraindiciranim.

Zaključak

Ovaj prikaz bolesnika naglašava važnost brze dijagnostike i uzimanja u obzir potencijalne kardiotoksičnosti uzrokovane kapecitabinom te uključivanje multidisciplinarnog tima u liječenje ozbiljnih kardiovaskularnih komplikacija. Akutno ZS koje dovodi do kardiogenog šoka rijedak je oblik kardiotoksičnosti, ali ga treba uzeti u obzir kao moguću komplikaciju. U takvim slučajevima primjenu kapecitabina treba odmah prekinuti. Bolesnici s kardiotoksičnošću povezanom s kemoterapijskim lijekovima trebali bi biti upućeni specijalistima iz područja kardioonkologije kako bi primili optimalno liječenje bez rizika od potencijalnih kardiotoksičnih komplikacija, čime se u konačnici poboljšavaju onkološki ishodi. Onkolozi i kardiolozi trebali bi održavati visoku razinu sumnje na rjeđe kliničke slike te usko surađivati, jer neki od ovih događaja mogu imati smrtonosan ishod.

activity may be considered as well[15,16]. Having in mind that capecitabine cardiotoxicity is common, patients should be closely followed up from the first cycle throughout the treatment. The follow-up should include electrocardiography and, according to the clinical symptoms, echocardiography as well, which allows the detection of subclinical cardiotoxicity. Patients with previous heart diseases should be monitored more closely.

One of the limitations in our case is the lack of CMR, which was not initially performed because of the rapid hemodynamic deterioration which necessitated the use of ECMO due to cardiogenic shock refractory to optimal inotropic and vasopressor support. Finally, the patient's rapid recovery with complete return of the LV function in a few days and successful weaning of inotropic stimulation confirmed the initial suspicion of possible direct toxic myocardial injury. A myocardial biopsy may have also provided useful information, but performing such an invasive procedure in a hemodynamically unstable patient is extremely difficult and creates an additional risk.

The management of acute cardiogenic shock due to the cardiotoxic effect of capecitabine and 5-FU requires supportive inotropic and vasopressor therapy and immediate discontinuation of the drug. Reversal of cardiomyopathy over several days is usually expected, as has been described in this case. After such severe cardiac toxicity, rechallenge with 5-FU should not be attempted and is considered contraindicated.

Conclusion

This case highlights the importance of rapid diagnostics and considering potential capecitabine cardiotoxicity, with the inclusion of a multidisciplinary team in the management of serious cardiovascular complications. Acute HF leading to cardiogenic shock is a rare form of cardiotoxicity that should be considered as a possible complication. In such cases, capecitabine should be promptly discontinued. Patients who experience cardiotoxicity related to chemotherapeutic agents should be referred to cardio-oncology specialists in order to receive the best possible treatment without the risk of potential cardiotoxic complications, ultimately resulting in improved oncologic outcomes. Oncologists and cardiologists must maintain a high index of suspicion for less common presentations and should collaborate closely, as some of these events may cause a fatal outcome.

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