Akutni koronarni sindrom uzrokovan liječenjem kapecitabinom u bolesnice s adenokarcinomom gušterače

Capecitabine-induced Acute Coronary Syndrome in a Patient with Pancreatic Adenocarcinoma

Karla Savić[1]*, Mira Stipčević[1,2,3], Jogen Patrk[1,3], Dražen Zekanović[1,3] Marin Bištirlić[1],

[1]Opća bolnica Zadar, Zadar, Hrvatska
[2]Sveučilište u Osijeku, Fakultet za dentalnu medicinu i zdravstvo Osijek, Osijek, Hrvatska
[3]Sveučilište u Zadru, Odjel za zdravstvene studije, Zadar, Hrvatska

[1]Zadar General Hospital, Zadar, Croatia
[2]University of Osijek, Faculty of Dental Medicine and Health, Osijek, Croatia
[3]University of Zadar, Department of Health Studies, Zadar, Croatia

RECEIVED: November 11, 2023
UPDATED: February 7, 2024
ACCEPTED: March 18, 2024

SAŽETAK: *Cilj*: naglasiti teške nuspojave kapecitabina i spriječiti pogrešnu dijagnozu u bolesnika s akutnim koronarnim sindromom (AKS). *Metode*: prikazujemo slučaj 74-godišnje bolesnice s adenokarcinomom gušterače koja je u bolnicu primljena s kliničkom slikom AKS-a induciranim uporabom kapecitabina. Primljena je u hitnu službu zbog epizode pritiska u prsima. Liječenje oralnim kapecitabinom (2500 mg na dan) započeto je 72 sata prije prijema. Imala je elektrokardiografske (EKG) promjene i pozitivne biokemijske markere miokardne ishemije (uključujući visokoosjetljivi kardijalni troponin T; hs-cTnT) te je premještena u Koronarnu jedinicu. Hitna kateterizacija srca i koronarna angiografija dokazale su odsutnost koronarne bolesti srca (KBS). Trideset sati nakon otpusta bolesnica se vratila u hitnu službu s istim simptomima dva sata nakon uzimanja 1000 mg kapecitabina. Razrješenje boli nakon primjene nitrata, normalizacija EKG-a i razina hs-cTnT zajedno s dokazanom odsutnošću KBS-a isključili su AKS. *Zaključak*: prikazana je bolesnica imala vazospazam koronarnih arterija induciran liječenjem kapecitabinom u odsutnosti prethodnog KBS-a. Daljnja primjena kapecitabina mora biti prekinuta kako bi se izbjegao rizik od njegovih kardiotoksičnih nuspojava.

SUMMARY: *Aim*: To emphasize the severe adverse effects of capecitabine and prevent misdiagnosis in patients with acute coronary syndrome. *Methods*: We present the case of a 74-year-old woman with pancreatic adenocarcinoma who presented to the hospital with capecitabine-induced acute coronary syndrome. She was admitted to the Emergency Department (ED) because of a squeezing chest pain episode. Treatment with oral capecitabine (2500 mg daily) was initiated 72 hours before admission. The patient had electrocardiographic (ECG) changes and positive biochemical markers for myocardial ischemia (including HS-troponin T) and was transferred to the coronary intensive care unit. Urgent cardiac catheterization was performed and showed no coronary artery disease (CAD). Thirty hours after discharge, the patient presented to the ED with the same symptoms arising two hours after taking 1000 mg of capecitabine. The resolution of chest pain after using nitrates, normalization of ECG, and HS troponin T levels combined with the proven absence of CAD ruled out acute coronary syndrome in our patient. *Conclusion*: Our patient had capecitabine-induced coronary vasospasm in the absence of pre-existing CAD. Further use of capecitabine had to be discontinued to avoid the risk of cardiotoxicity.

KLJUČNE RIJEČI: kapecitabin, akutni koronarni sindrom, vazospazam koronarnih arterija, kardiotoksičnost, adenokarcinom gušterače.

KEYWORDS: capecitabine, acute coronary syndrome, coronary vasospasm, cardiotoxicity, pancreatic cancer.

CITATION: Cardiol Croat. 2024;19(5-6):236-40. | https://doi.org/10.15836/ccar2024.236

***ADDRESS FOR CORRESPONDENCE**: Karla Savić, Opća bolnica Zadar, Bože Peričića 5, HR-23000, Zadar, Croatia. / Phone: +385-91-1301-991 / E-mail: savickarlaa@gmail.com

ORCID: Karla Savić, https://orcid.org/0000-0002-1339-8922 • Mira Stipčević, https://orcid.org/0000-0003-4351-1102 Jogen Patrk, https://orcid.org/0000-0002-8165-692X • Dražen Zekanović, https://orcid.org/0000-0002-8147-6574 Marin Bištirlić, https://orcid.org/0000-0002-9213-4174

TO CITE THIS ARTICLE: Savić K, Stipčević M, Patrk J, Zekanović D, Bištirlić M. Capecitabine-induced Acute Coronary Syndrome in a Patient with Pancreatic Adenocarcinoma. Cardiol Croat. 2024;19(5-6):236-40. | https://doi.org/10.15836/ccar2024.236

TO LINK TO THIS ARTICLE: https://doi.org/10.15836/ccar2024.236

Uvod

Prema podatcima Hrvatskog registra za rak, karcinom gušterače bio je osmi najčešći maligni tumor u muškaraca i deveti u žena u Hrvatskoj 2013. godine. Čini 3 % ukupnoga broja novootkri-

Introduction

According to the data from the Croatian Cancer Registry, pancreatic cancer was the eighth most common malignant tumor in men and the ninth in women in Croatia in 2013. It constitutes 3% of

venih malignih tumora. Adenokarcinomi čine 95 % svih karcinoma gušterače[1]. Radikalna kirurška resekcija jedina je kurativna metoda liječenja, rezervirana za mali broj bolesnika s lokaliziranom bolešću. U bolesnika podvrgnutih kirurškoj resekciji petogodišnja stopa preživljenja iznosi oko 20 %, uz naznake da adjuvantno liječenje može utjecati na taj postotak[2]. Za većinu bolesnika s lokalno uznapredovalom ili metastatskom bolesti dostupne su palijativne opcije ograničene na kemoterapiju i radioterapiju. Trenutačne terapijske strategije koje koriste se ovim metodama liječenja u uznapredovaloj fazi bolesti pokazale su ograničenu učinkovitost.

Bolesnici liječeni kombiniranom terapijom nakon kirurške resekcije imali su poboljšano preživljenje u usporedbi s onima koji prolaze kroz isključivo kirurško liječenje[3,4]. Neoadjuvantna kemoterapija ili kemoradioterapija preporučuju se bolesnicima s granično operabilnom bolesti[2-4]. Uporaba radioterapije istodobno s 5-fluorouracilom (5-FU) globalno je prihvaćen pristup liječenju adenokarcinoma gušterače. 5-fluorouracil je antimetabolit učinkovit protiv različitih tumora, poput tumora dojke, jednjaka, grkljana, gastrointestinalnih i genitourinarnih karcinoma. Njegova neselektivna citotoksičnost uzrokuje sistemsku toksičnost, najčešće izazivajući neutropeniju, stomatitis i proljev[5].

Kapecitabin, predlijek 5-fluorouracila, proizveden je sa svrhom poboljšanja podnošljivosti i porasta koncentracije lijeka unutar tumora, gdje se konvertira u aktivni oblik. Iako bolesnici mogu uzimati lijek oralno u udobnosti vlastita doma, postoje ozbiljne, ali rijetke nuspojave na koje treba obratiti pažnju, uključujući vazospazam koronarnih arterija induciran liječenjem 5-FU[6,7]. Prikazujemo slučaj 74-godišnje bolesnice s adenokarcinomom gušterače koja se javila u bolnicu s akutnim koronarnim sindromom (AKS) izazvanim uporabom kapecitabina.

Prikaz bolesnice

Sedamdesetčetverogodišnja bolesnica primljena je u Hitnu službu zbog epizode pritiska u prsima sat vremena prije prijema. Tegobe su trajale otprilike 40 minuta, dok nije primila 0,8 mg nitroglicerina pod jezik i 300 mg acetilsalicilatne kiseline oralno. Bolesnica je napomenula da je dvaput povratila i obilno se oznojila. U osobnoj anamnezi, osim arterijske hipertenzije, nije imala drugih bolesti srca, ni poremećaja zgrušavanja krvi, pušenja ili zloupotrebe droga. Njezin indeks tjelesne mase i vrijednosti lipidnog profila bili su unutar referentnih vrijednosti, a bila je umjereno tjelesno aktivna. Od lijekova je uzimala samo antagonist angiotenzina II u kombinaciji s tijazidnim diuretikom. Bolesnica je prije dva mjeseca podvrgnuta Whippleovu postupku zbog adenokarcinoma gušterače. Liječenje oralnim kapecitabinom (2500 mg na dan) započelo je 72 sata prije prijema.

Dvanaestokanalni_elektrokardiogram (EKG) snimljen u hitnoj službi pokazao je sinusni ritam s frekvencijom od 73/minuti sa supraventrikularnim ekstrasistolama i diskretnom depresijom ST-segmenta u odvodima D1, avL, V5 i V6. Imala je pozitivne biokemijske markere za miokardnu ishemiju (visokoosjetljivi kardijalni troponin T; hs-cTnT 36,90 ng/L) i premještena je u Koronarnu jedinicu. Učinjena je hitna koronarna kateterizacija kojom je isključena koronarna bolest srca (KBS) (**slika 1**). Ultrazvuk srca, učinjen kad je pacijentica bila bez boli, pokazao je normalnu veličinu uz blago zadebljanje stijenki lijeve klijetke, bez regionalnih ispada kontraktilnosti

the total number of newly discovered malignant tumors. Adenocarcinomas make up 95% of all pancreatic cancers[1]. Radical surgical resection is the only curative treatment method, reserved for a small number of patients with localized disease. Among those who undergo surgical resection, the 5-year survival rate is around 20%, with some indications that adjuvant treatment may impact this survival[2]. For the majority of patients facing locally advanced or metastatic disease, available palliative options are confined to chemotherapy and radiation treatment. Current therapeutic strategies utilizing these methods in advanced disease have, at most, shown limited effectiveness.

Patients treated with combined modality therapy (CMT) after surgical resection have demonstrated improved survival compared to those undergoing surgery alone[3,4]. Neoadjuvant chemotherapy or chemoradiotherapy is recommended for patients with marginally resectable disease[2-4]. The use of radiation therapy concurrently with 5-fluorouracil (5-FU) is an approach that has been widely adopted globally for the treatment of pancreatic adenocarcinoma. 5-fluorouracil (FU) is an antimetabolite effective against various neoplasms, such as breast, esophagus, larynx, gastrointestinal, and genitourinary cancers. Its nonselective cytotoxicity leads to systemic toxicity, most commonly causing neutropenia, stomatitis, and diarrhea[5].

Capecitabine, designed as a 5-FU prodrug, aims to enhance tolerability and intratumor drug concentrations by converting specifically to the active drug within tumors. Although patients may receive the drug orally in the convenience of their own homes, there are severe but rare adverse effects clinicians and patients should be aware of, including 5-FU-induced coronary vasospasm[6,7]. Herein, we present the case of a 74-year-old woman with pancreatic adenocarcinoma who presented to the hospital with capecitabine-induced acute coronary syndrome.

Case report

A 74-year-old woman was admitted to the Emergency Department because of a squeezing chest pain episode an hour before admission that lasted approximately 40 minutes, until she received 0.8 mg of sublingual nitroglycerine and 300 mg of aspirin. The patient reported she had vomited twice and sweated profusely. She had no prior history of cardiac disease, coagulation disorders, smoking, or drug abuse. Her BMI and lipid panel values were normal, and she was moderately physically active. The patient was only taking an angiotensin II receptor antagonist combined with a thiazide diuretic for arterial hypertension. The patient had undergone the Whipple procedure due to pancreatic adenocarcinoma two months ago. Treatment with oral capecitabine (2500 mg daily) was initiated 72 hours before admission.

The electrocardiogram (ECG) taken in the emergency room showed a sinus rhythm with a heart rate of about 73 beats per minute (bpm), with supraventricular premature beats and discrete ST segment depression in leads V5, V6, I, and avL. The patient had positive biochemical markers for myocardial ischemia (hs-cTnT 36.90 ng/L) and was transferred to the Coronary Intensive Care Unit (CICU). Urgent cardiac catheterization was performed and showed no coronary artery disease (CAD) (**Figure 1**). The echocardiogram, which was performed when the patient was pain-free, revealed normal left ventricular volume, slightly

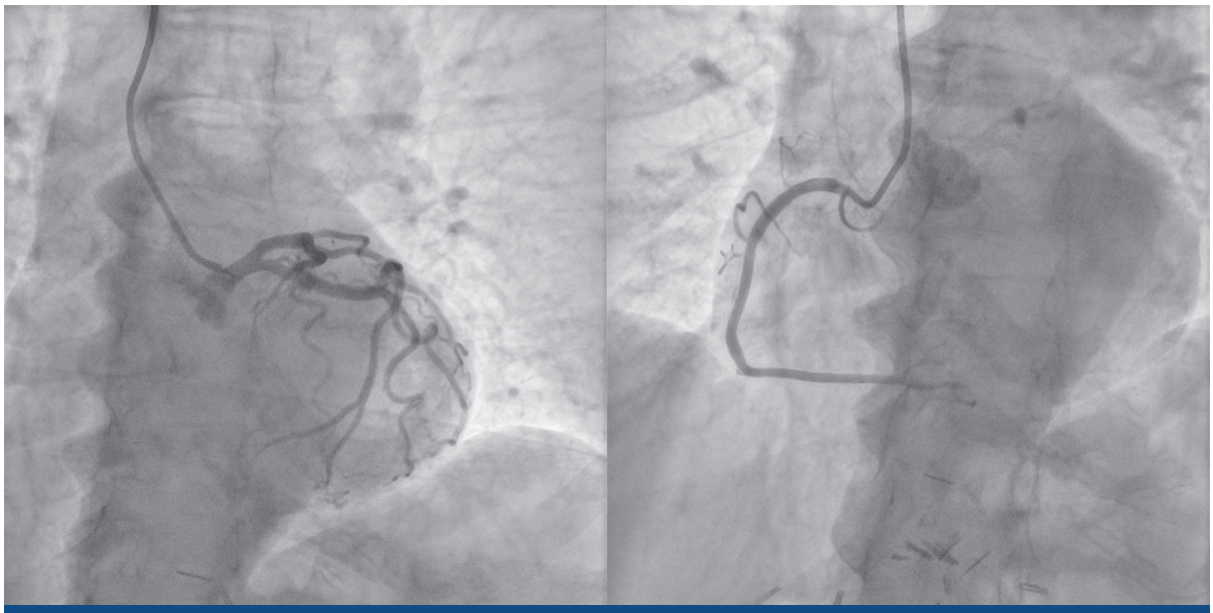

FIGURE 1. Coronary angiography showing no obstructive coronary artery disease.

s ejekcijskom frakcijom lijeve klijetke od 60 %, dijastoličkom disfunkcijom prvoga stupnja, normalnim protokom kroz zalistke i odsutnost perikardijalnog izljeva. Početno je liječena acetilsalicilatnom kiselinom od 100 mg, atorvastatinom od 80 mg, enoksaparinom od 5500 IU (40 mg) primijenjenim supkutano dvaputa na dan, intravenskim gliceriltrinitratom od 10 mcg/min sporom infuzijom i diazepamom od 5 mg. Tijekom sljedeća 24 sata razine su hs-cTnT padale, a uzastopna EKG očitanja pokazivala su normalizaciju ST-segmenta. Nakon dva dana otpuštena je iz bolnice s dijagnozom akutnog infarkta miokarda s neopstruktivnom koronarnom bolesti[8]. Postavljena je čvrsta sumnja na kardiotoksičnost prouzročenu liječenjem kapecitabinom.

Trideset sati nakon otpusta, bolesnica se ponovno javila u hitnu službu s istim simptomima dva sata nakon uzimanja 1000 mg kapecitabina. Novi 12-kanalni EKG pokazao je sinusnu tahikardiju (110/min) s difuznom elevacijom ST-segmenta (**slika 2**), što je upućivalo na globalnu ishemiju. Serumski markeri opet su bili pozitivni za ishemiju miokarda (hs-cTnT 77,30 ng/L). Zaprimljena je u Koronarnu jedinicu i primila je gliceriltrinitrat od 10 mcg/min sporom infuzijom. Bol je ubrzo nakon parenteralne infuzije nitrata regredirala. U EKG-u 45 minuta kasnije, registriran je progresivni oporavak abnormalne repolarizacije ventrikula, a naknadne su se razine hs-cTnT-a snizivale. Tim kardiologa, gastroenterologa i onkologa procijenio je ovakvo stanje i, zajedničkom odlukom, liječenje kapecitabinom je prekinuto. Bolesnica je pažljivo opservirana i otpuštena iz bolnice nakon pet dana s trimetazidinom 2 x 35 mg, rosuvastatinom 1 x 20 mg, izosorbid mononitratom 2 x 20 mg i diazepamom 5 mg. Gastroenterolozi su joj propisali pankreatinske kapsule 3 x 25 000 i. j. uz tri glavna obroka, kapsulu ursodeoksiholne kiseline 1 x 250 mg, oralni nutritivni dodatak prehrani visokoga kalorijskog sadržaja 1 x na dan i otilonijev bromid 3 x 40 mg. Onkolozi su naručili kontrolni MSCT toraksa, trbuha i zdjelice koji nije pokazao znakove diseminacije bolesti. Bolesnica trenutačno prima suportivnu i simptomatsku terapiju te se redovito kontrolira kod nadležnog onkologa.

increased left ventricular wall thickness, no regional wall motion abnormalities with a left ventricular ejection fraction of 60%, grade I diastolic dysfunction, normal valve flow, and absence of pericardial effusion. The patient was initially treated with aspirin 100 mg, atorvastatin 80 mg, enoxaparin 5500 IU (40 mg) administered subcutaneously twice daily, glyceryltrinitrate 10 mcg/min via slow infusion, and diazepam 5 mg. During the next 24 hours, hs-cTnT levels were in decline, and consecutive ECG readings showed normalization of the ST segment. After two days, the patient was discharged from the hospital and diagnosed with myocardial infarction with non-obstructive coronary arteries[8] with solid suspicions of capecitabine-induced cardiac toxicity.

Thirty hours after discharge, the patient presented to the Emergency Department with the same symptoms arising two hours after taking 1000 mg of capecitabin. A new 12-lead ECG was immediately performed and revealed sinus tachycardia (110 bpm) with widespread ST-segment elevation (**Figure 2**), suggestive of global ischemia. Serum cardiac markers were again positive for myocardial ischemia (hs-cTnT 77.30 ng/L). The patient was transferred to the CICU and was given glyceryltrinitrate 10 mcg/min via slow infusion. The pain subsided shortly after parenteral nitrate infusion. A subsequent ECG performed 45 minutes afterward showed progressive recovery of ventricular repolarization abnormalities. Additionally, hs-cTnT values were declining. A team of cardiologists, gastroenterologists, and oncologists evaluated this case, and capecitabine treatment was ceased. The patient was carefully observed and released from the hospital after five days with trimetazidine 2x1, rosuvastatin 1x20 mg, isosorbide mononitrate 2x20 mg, and diazepam 5 mg. Gastroenterologists prescribed pancrelipase 3x25000 IJ with three main meals, ursodeoxycholic acid capsules 1x250 mg, high caloric oral nutritional supplement 1x daily, and otilonium bromide 3x40 mg. Oncologists ordered a control MSCT scan of the thorax, abdomen, and pelvis, which showed no signs of disease dissemination. The patient is currently receiving supportive and symptomatic treatment and is receiving regular check-ups with an oncologist.

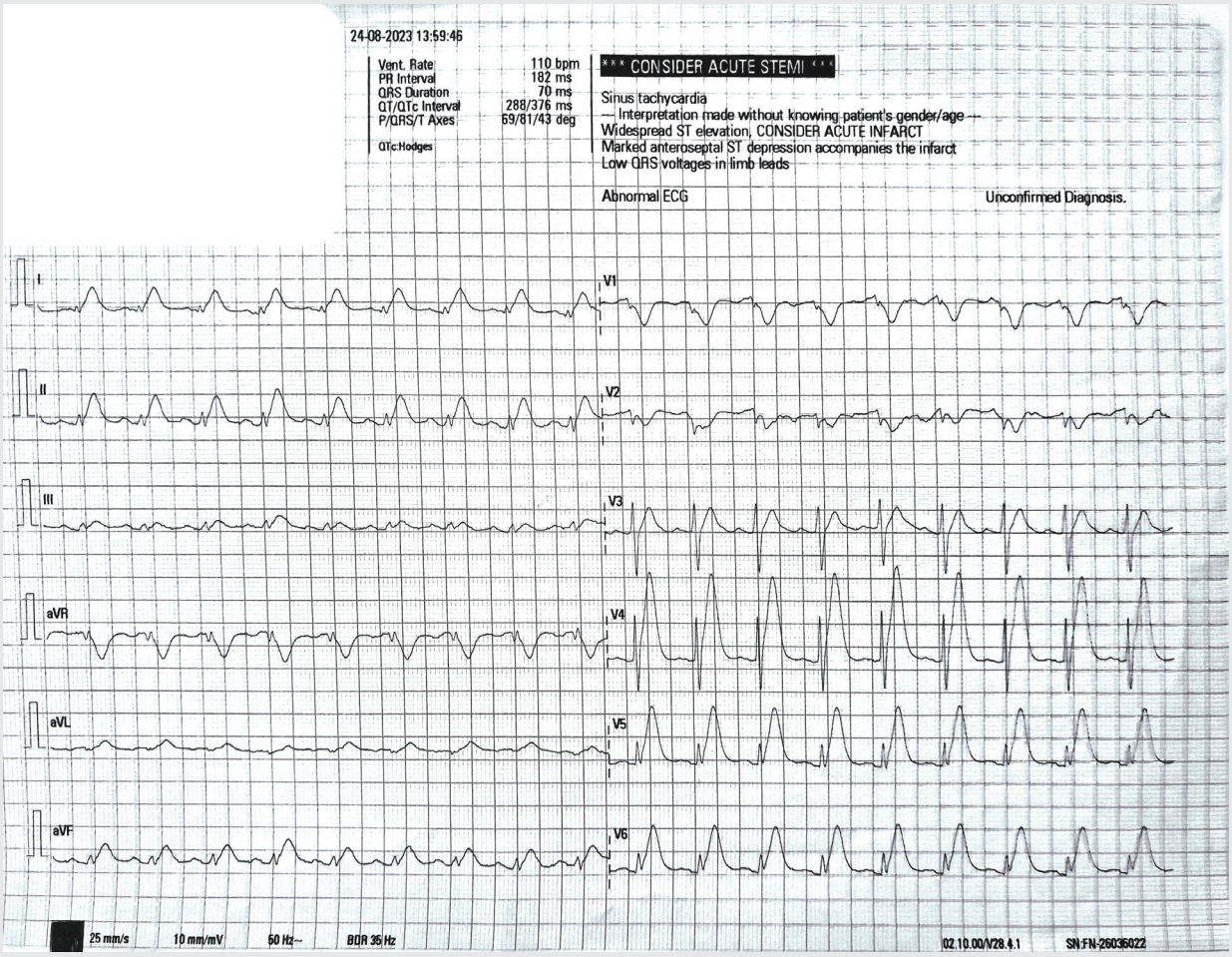

FIGURE 2. An electrocardiogram suggesting global myocardial ischemia.

Rasprava

Kapecitabin je potencijalno kardiotoksičan lijek, što se može manifestirati kao vazospazam koronarnih arterija, hipertenzija, ventrikularne aritmije, kardiogeni šok, pa čak i srčani zastoj[6,9], ovisno o kardiovaskularnim komorbiditetima, dozi i rasporedu primanja kemoterapije[10]. Smatra se da kapecitabinom inducirana kardiotoksičnost proizlazi iz utjecaja 5-FU na endotel, što dovodi do stvaranja endotelina-1 i posljedičnoga koronarnog vazospazma[10]. Sukladno navedenom, bolesnici mogu imati simptome slične varijantnoj angini, uključujući bol u prsima koja se pojavljuje čak i u mirovanju. Ti simptomi mogu postojati u prisutnosti i odsutnosti promjena u EKG-u, te upućivati na ishemiju miokarda[11]. U preglednom radu Američkog udruženja za srce (AHA) o lijekovima povezanima sa srčanim zatajivanjem, Page *i sur.* pokazuju da je kapecitabin poznat kardiotoksičan lijek[12]. Što se tiče pojave boli u prsima tijekom terapije kapecitabinom, Wijesinghe *i sur.* izvijestili su o AKS-u u bolesnika koji je uzimao kapecitabin samo dva dana[13]. Ovisno o dozi, kardiološke nuspojave mogu se pojaviti unutar 24 sata nakon uzimanja lijeka[14]. U retrospektivnom istraživanju Jensena *i sur.*, simptomi su nestali primjenom nitroglicerina[15]. Ova se bolesnica javila u hitnu službu s bolima u prsima tri dana nakon prve primjene kapecitabina i dva

Discussion

Capecitabine may induce cardiotoxicity that can manifest as vasospasm, hypertension, ventricular arrhythmias, cardiogenic shock, and even cardiac arrest[6,9], depending on cardiac comorbidity, dose, and the chemotherapy schedule[10]. Capecitabine-induced cardiotoxicity is believed to result from the influence of 5-FU on the endothelium, leading to the production of endothelin-1 and subsequent coronary vasospasm[10]. As a consequence, patients may exhibit symptoms resembling variant angina, including chest pain occurring even at rest. These symptoms can occur with or without ECG changes, indicating myocardial ischemia[11]. In an American Heart Association (AHA) review of drugs associated with heart failure, Page *et al.* indicated that capecitabine is a known cardiotoxic drug[12]. With regard to the onset of chest pain with capecitabine therapy, Wijesinghe *et al.*[13] reported an acute coronary syndrome in a patient who had been on capecitabine for only two days. Depending on the dose, cardiac side effects can occur within 24 hours after taking the drug[14]. In a retrospective study by Jensen et al., symptoms were abolished by nitroglycerine[15]. Our patient presented with chest pain three days after taking capecitabine for the first time and 2 hours after taking it the second time. The resolution of chest pain after using ni-

sata nakon druge primjene. Potpuna regresija boli nakon primjene nitroglicerina, normalizacija EKG-a i hs-cTnT razina uz dokazanu odsutnost KBS-a u ove se bolesnice isključili AKS.

Zaključak

Prikazana je bolesnica imala koronarni vazospazam prouzročen liječenjem kapecitabinom bez prethodnog KBS-a. Daljnja uporaba kapecitabina treba biti prekinuta kako bi se izbjegao rizik od njegovih kardiotoksičnih nuspojava. Naglašavamo važnost pridržavanja plana liječenja, prevenciju nuspojava i pravodobno prepoznavanje potencijalnih toksičnosti povezanih s uporabom ovog lijeka.

trates and normalization of ECG and hs-cTnT levels combined with the proven absence of CAD ruled out acute coronary syndrome in our patient.

Conclusion

This patient had capecitabine-induced coronary vasospasm without pre-existing CAD. Further use of capecitabine had to be discontinued to avoid the risk of cardiotoxicity. We emphasize the importance of adhering to the treatment plan, prevention of adverse effects, and promptly identifying any potential toxicities associated with this medication.

LITERATURE

1. Hrvatski zavod za javno zdravstvo. Bilten Incidencija raka u Hrvatskoj 2015. godine. Available from: https://www.hzjz.hr/wp-content/uploads/2018/03/Bilten_2015_rak_final.pdf (January 8, 2024)
2. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. Ann Surg. 1987 Sep;206(3):358-65. https://doi.org/10.1097/00000658-198709000-00014
3. Yeo CJ, Abrams RA, Grochow LB, Sohn TA, Ord SE, Hruban RH, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. Ann Surg. 1997 May;225(5):621-33. https://doi.org/10.1097/00000658-199705000-00018
4. Klinkenbijl JH, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999 Dec;230(6):776-82. https://doi.org/10.1097/00000658-199912000-00006
5. Walko CM, Lindley C. Capecitabine: a review. Clin Ther. 2005 Jan;27(1):23-44. https://doi.org/10.1016/j.clinthera.2005.01.005
6. Polk A, Vistisen K, Vaage-Nilsen M, Nielsen DL. A systematic review of the pathophysiology of 5-fluorouracil-induced cardiotoxicity. BMC Pharmacol Toxicol. 2014 Sep 4;15:47. https://doi.org/10.1186/2050-6511-15-47
7. Ang C, Kornbluth M, Thirlwell MP, Rajan RD. Capecitabine-induced cardiotoxicity: case report and review of the literature. Curr Oncol. 2010 Feb;17(1):59-63. https://doi.org/10.3747/co.v17i1.437
8. Severino P, D'Amato A, Prosperi S, Myftari V, Colombo L, Tomarelli E, et al. Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA): Focus on Coronary Microvascular Dysfunction and Genetic Susceptibility. J Clin Med. 2023 May 21;12(10):3586. https://doi.org/10.3390/jcm12103586
9. Henry D, Rudzik F, Butts A, Mathew A. Capecitabine-Induced Coronary Vasospasm. Case Rep Oncol. 2016 Oct 17;9(3):629-632. https://doi.org/10.1159/000450544
10. Südhoff T, Enderle MD, Pahlke M, Petz C, Teschendorf C, Graeven U, et al. 5-Fluorouracil induces arterial vasocontractions. Ann Oncol. 2004 Apr;15(4):661-4. https://doi.org/10.1093/annonc/mdh150
11. Camaro C, Danse PW, Bosker HA. Acute chest pain in a patient treated with capecitabine. Neth Heart J. 2009 Aug;17(7-8):288-91. https://doi.org/10.1007/BF03086268
12. Page RL 2nd, O'Bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, et al; American Heart Association Clinical Pharmacology and Heart Failure and Transplantation Committees of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Drugs That May Cause or Exacerbate Heart Failure: A Scientific Statement From the American Heart Association. Circulation. 2016 Aug 9;134(6):e32-69. https://doi.org/10.1161/CIR.0000000000000426
13. Wijesinghe N, Thompson PI, McAlister H. Acute Coronary Syndrome Induced by Capecitabine Therapy. Heart Lung Circ. 2006 Oct;15(5):337-9. https://doi.org/10.1016/j.hlc.2006.03.010
14. Schnetzler B, Popova N, Collao Lamb C, Sappino AP. Coronary spasm induced by capecitabine. Ann Oncol. 2001 May;12(5):723-4. https://doi.org/10.1023/A:1011152931300
15. Jensen SA, Sørensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. Cancer Chemother Pharmacol. 2006 Oct;58(4):487-93. https://doi.org/10.1007/s00280-005-0178-1