

KARDIOTOKSIČNOST VISOKE DOZE METILPREDNIZOLONA KOD BOLESNIKA SA HRONIČNOM LIMFOCITNOM LEUKEMIJOM – PRIKAZ SLUČAJA

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CASE REPORT

CARDIOTOXICITY OF HIGH-DOSE METHYLPREDNISOLONE IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA – A CASE REPORT

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SAŽETAK

Uvod: Nekoliko klasa lekova mogu izazvati atrijsku fibrilaciju (AF) kod bolesnika koji nemaju oboljenje srca, kao i pojavu atrijske fibrilacije kod postojećeg srčanog oboljenja. AF izazvana lekovima se najčešće klinički manifestuje u vidu paroksizma. Visoke doze intravenskog metilprednizolona (VDMP) u lečenju hronične limfocitne leukemije (HLL) povezane su sa pojavom različitih neželjenih efekata, uključujući i pojavu atrijske fibrilacije. Tačan mehanizam atrijske fibrilacije indukovane VDMP-om nije poznat.

Prikaz slučaja: Prikazujemo slučaj bolesnika sa HLL-om, kod koga je, nakon primene visoke doze intravenskog metilprednizolona, došlo do pojave atrijske fibrilacije.

Zaključak: Lekari bi trebalo da budu upoznati sa posebnim okolnostima u lečenju hronične limfocitne leukemije, jer AF izazvana lekom može biti neželjeni efekat koji ograničava dalju terapiju.

Ključne reči: hronična limfocitna leukemija, atrijska fibrilacija izazvana lekovima, visoke doze metilprednizolona

ABSTRACT

Introduction: Several classes of drugs can cause atrial fibrillation (AF) in patients without heart disease, as well as the occurrence of AF in pre-existing heart disease. Drug-induced AF is most often clinically manifested in the form of paroxysms. High doses of intravenous methylprednisolone (HDMP) in the treatment of chronic lymphocytic leukemia (CLL) have been associated with the occurrence of various adverse effects, including AF. The exact mechanism of HDMP-induced AF is unknown.

Case presentation: We present the case of a patient with CLL in whom AF occurred after the administration of a high dose of intravenous methylprednisolone.

Conclusion: Physicians should be aware of the special circumstances in the treatment of CLL, because drug-induced AF can be a side effect that limits further therapy.

Key words: chronic lymphocytic leukemia, drug-induced atrial fibrillation, high doses of methylprednisolone

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UVOD

Atrijalna fibrilacija (AF) predstavlja najčešći poremećaj srčanog ritma u kliničkoj praksi i najčešće je udružena sa koronarnom bolešću i hipertenzijom. Iz literature je poznato da nekoliko klasa lekova (simpatikomimetici, parasimpatikomimetici i njihovi inhibitori) mogu da izazovu atrijalnu fibrilaciju kod bolesnika koji nemaju oboljenje srca [1–3]. AF izazvana lekovima povećava broj hospitalizacija i incidenciju ishemijskog moždanog udara.

Visoka doza intravenskog metilprednizolona (VDMP) predstavlja standardnu terapiju kod velikog broja autoimunih i hematoloških oboljenja (autoimuna trombocitopenija, hronična limfocitna leukemija (HLL) i druge bolesti) [4–7].

Pojava atrijalne fibrilacije indukovane metilprednizonom opisana je u literaturi kod nekoliko različitih bolesti (multipla skleroza, reumatoidni artritis, membranozni proliferativni glomerulonefritis). Upotreba kortikosteroida udružena je sa pojavom različitih neželjenih efekata. Takođe, zabeleženi su i primeri pojave atrijalne fibrilacije [8–14]. Kao najčešća neželjena dejstva visokih doza kortikosteroida, zabeležene su sledeće pojave: izmenjeno čulo ukusa (61%), crvenilo lica (61%), nesanica (44%) i poremećaj raspoloženja (36%) [15].

Elektrofiziološki efekti u pretkomori koji dovode do atrijalne fibrilacije mogu biti uzrokovani ili pokrenuti fiziološkim procesima, kao što su adrenergička ili vagalna stimulacija, metaboličkim ili elektrolitnim poremećajima, kao i efektima određenih lekova ili agenasa [16]. Patofiziološki, lekovi koji povećavaju ili smanjuju adrenergičku ili vagalnu aktivnost, kao što su simpatikomimetici, parasimpatikomimetici i njihovi inhibitori, mogu da izazovu atrijalnu fibrilaciju, posebno kod kardiovaskularnih pacijenata (bolest je supstrat, lek je pokretač), ali i kod, naizgled, zdravih pacijenata [3]. Mehanizam atrijalne fibrilacije izazvane lekovima nije tačno poznat. Fujimoto i saradnici su pronašli da efluks kalijuma iz ćelije, koji je uzrokovan direktnim dejstvom metilprednizolona na ćelijsku membranu, može dovesti do poremećaja srčanog ritma [12].

Prikazujemo slučaj bolesnika sa HLL-om, kod koga je, nakon primene visoke doze intravenskog metilprednizolona, došlo do pojave AF.

PRIKAZ SLUČAJA

Bolesnik, starosti 69 godina, imao je dijagnozu hronične limfocitne leukemije, koja je postavljena 1992. godine, u kliničkom stadijumu (engl. *clinical stage* – CS) 0. Anamneza je bila bez drugih hroničnih bolesti. Redovno je kontrolisan, bez terapije do februara 2019. godine, kada dolazi do progresije bolesti, sa pojavom opštih simptoma i splenomegalije. Laboratorijske

INTRODUCTION

Atrial fibrillation (AF) is the most frequent cardiac rhythm disturbance in clinical practice and is most commonly associated with coronary disease and hypertension. It is known, from relevant literature, that several classes of drugs (sympathomimetics, parasympathomimetics, and their inhibitors) may cause atrial fibrillation in patients who do not suffer from heart disease [1–3]. Drug-induced AF increases the number of hospitalizations and the incidence of ischemic stroke.

High-dose intravenous methylprednisolone therapy (HDMT) is the standard therapy in a large number of autoimmune and hematological diseases (autoimmune thrombocytopenia, chronic lymphocytic leukemia (CLL), and other diseases) [4–7].

The occurrence of methylprednisolone-induced atrial fibrillation has been described in literature in several different diseases (multiple sclerosis, rheumatoid arthritis, membranoproliferative glomerulonephritis). The use of corticosteroids is associated with different adverse effects. Cases of atrial fibrillation have also been documented [8–14]. The following have been registered as the most frequently occurring adverse effects of high doses of corticosteroids: altered sense of taste (61%), facial redness (61%), insomnia (44%), and mood disorders (36%) [15].

Electrophysiological effects in the atrium, leading to atrial fibrillation, may be induced or triggered by physiological processes, such as adrenergic or vagus nerve stimulation, by metabolic or electrolyte disorders, as well as by the effects of certain drugs or agents [16]. Pathophysiologically, drugs increasing or decreasing adrenergic or vagal activity, such as sympathomimetics, parasympathomimetics, and their inhibitors, may cause atrial fibrillation, especially in cardiovascular patients (the disease is the substrate, the drug is the trigger), but also in seemingly healthy patients. [3]. The mechanism of drug-induced atrial fibrillation is not precisely known. Fujimoto et al. found that the efflux of potassium from the cell, caused by the direct action of methylprednisolone on the cell membrane, may lead to cardiac rhythm disturbance [12].

We present the case of a patient with CLL, in whom, after the administering of high-dose intravenous methylprednisolone, AF occurred.

CASE REPORT

A 69-year-old patient had the diagnosis of chronic lymphocytic leukemia, established in 1992 – clinical stage (CS) 0. Anamnesis showed no other chronic diseases. The patient had regular follow-up; he received no treatment until February 2019, when the disease started to progress and general symptoms, as well as splenomegaly,

analize krvi su pokazale: leukocitozu ($47,1 \times 10^9/l$) sa 80% limfocita, anemiju sa hemoglobinom od 115 g/l, trombocitopeniju ($132 \times 10^9/l$), te normalne vrednosti laktat dehidrogenaze (194 IJ/L), parametara bubrežne funkcije i hepatograma. Citogenetska analiza – fluorescentna *in situ* hibridizacija (FISH) otkrila je deleciju 13q u 80% jedara i deleciju 17p u 20% jedara.

Lečenje je započeto primenom VDMP-a (1.500 mg dnevno, IV, tokom 5 dana, u ciklusima od 4 nedelje). Trećeg dana drugog ciklusa, nakon primene VDMP-a, bolesnik prijavljuje osećaj lupanja srca. Na elektrokardiogramu (EKG) registrovane su pojedinačne ekstrasistole, a zatim i pojava atrijske fibrilacije, sa komorskom frekvencom od oko 140/min, bez promena u ST segmentu. Bolesnik je bio normotenzivan. Troponin (engl. *high sensitivity troponin I assay* – *hsTnI*), kreatin-kinaza (engl. *creatine kinase* – CK), kreatin-kinaza izoenzim (engl. *creatine kinase isoenzyme* – CK-MB), proBNP (engl. *pro b-type natriuretic peptide*) (100 pg/ml) i tiroidni status (engl. *thyroid stimulating hormone* – TSH) (1,66 mU/l) bili su u referentnom opsegu (*hsTnI* < 34 ng/L; CK = 29 - 168 IJ/L; CK-MB = 7 - 25 IJ/L; proBNP < 450 pg/ml; TSH = 0,35 - 4,94 mU/L). Ehokardiografski, leva pretkomora je bila normalnih dimenzija, bez spontanog eho kontrasta i trombnih masa; registrovana je normalna sistolna i dijastolna funkcija leve komore (ejekciona frakcija = 55%). Koronarografijom nije utvrđeno postojanje koronarne bolesti srca.

Nakon 48 sati terapije antiaritmikom klase III (amiodaron), došlo je do konverzije u sinusni ritam, koji se održavao, što je potvrđeno i 24-časovnim Holter EKG-om. Bolesnik je, pored amiodarona, bio i na niskoj dozi beta-blokatora, kada je primenjen sledeći ciklus VDMP-a, a po čijem završetku, tokom 48-časovnog Holter-EKG-a, nije registrovan paroksizam atrijske fibrilacije.

DISKUSIJA

Atrijska fibrilacija izazvana lekovima javlja se kod pacijenata bez prethodne pojave atrijske fibrilacije ili strukturnih srčanih oboljenja. Očekivani rizik od pojave atrijske fibrilacije izazvane lekovima povećan je kod starijih osoba i pacijenata sa kardiovaskularnim komorbiditetima [3,17]. Mehanizam nastanka aritmija nakon visokih doza kortikosteroida nije jasan. Predloženo je nekoliko mehanizama: direktno povećanje efliksa kalijuma, efekat mineralokortikosteroida, koji dovodi do zadržavanja natrijuma i tečnosti, povećanja leve pretkomore i kongestivne srčane insuficijencije, kao i razvoj kasnih potencijala i izražen periferni vazodilatatorni odgovor [3,12,18,19].

U literaturi je opisano nekoliko slučajeva atrijske fibrilacije nakon terapije visokim dozama kortikosteroida [10,11,13,19-22]. Studija van der Hufta i saradnika

developed. Laboratory blood test results showed the following: leukocytosis ($47.1 \times 10^9/l$) with 80% of lymphocytes, anemia with a hemoglobin level of 115 g/l, thrombocytopenia ($132 \times 10^9/l$), as well as normal levels of lactate dehydrogenase (194 IJ/L), renal function parameters, and hepatogram. Cytogenetic analysis – fluorescence *in situ* hybridization (FISH) discovered 3q deletion in 80% of nuclei and 17p deletion in 20% of nuclei.

Treatment started with the application of HDMP (1,500 mg per day, IV, for 5 days, in four-week cycles). On the third day of the second cycle, after the application of HDMP, the patient reported feeling palpitations. The electrocardiogram (ECG) registered individual extrasystoles, and then the occurrence of atrial fibrillation, with a ventricular frequency of around 140/min, without changes in the ST segment. The patient was normotensive. Troponin (high sensitivity troponin I assay – *hsTnI*), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), pro b-type natriuretic peptide (proBNP) (100 pg/ml), and thyroid status (thyroid stimulating hormone – TSH) (1.66 mU/l) were within the reference range (*hsTnI* < 34 ng/L; CK = 29 - 168 IJ/L; CK-MB = 7 - 25 IJ/L; proBNP < 450 pg/ml; TSH = 0.35 - 4.94 mU/L). Echocardiographically, the left atrium had normal dimensions, without spontaneous echo contrast or thrombotic masses; normal systolic and diastolic function of the left ventricle (ejection fraction = 55%) was registered. Coronarography did not establish the presence of coronary heart disease.

After 48 hours of treatment with a class III antiarrhythmic (amiodarone), conversion into normal sinus rhythm occurred; the normal sinus rhythm persisted, which was confirmed with 24-hour Holter ECG. In addition to amiodarone, the patient was also on a low dose of beta-blockers when the next cycle of HDMP was administered, upon whose completion, after 48-hour Holter monitoring, paroxysmal atrial fibrillation was not registered.

DISCUSSION

Drug-induced atrial fibrillation occurs in patients without previous episodes of atrial fibrillation or structural heart disease. The expected risk of drug-induced atrial fibrillation is increased in elderly patients and patients with cardiovascular comorbidities [3,17]. The mechanism of the development of arrhythmias after high doses of corticosteroids is not clear. Several possible mechanisms have been proposed: direct increase in the efflux of potassium, the effect of mineralocorticoids, which leads to the retention of sodium and fluids, increase of the left atrium and congestive heart failure, as well as the development of late potentials and pronounced peripheral vasodilator response [3,12,18,19].

je pokazala da je upotreba visokih doza kortikosteroida povezana sa povećanim rizikom od razvoja atrijske fibrilacije [18].

U nekim radovima, kortikosteroidi su dovodeni u vezu sa pojavom atrijske fibrilacije, nezavisno od puta primene leka. Pojava atrijske fibrilacije je zabeležena tokom primene visokih pulsniha doza metilprednizolona [5–9,14], kod primene nižih doza intravenske terapije metilprednizolonom, kao i nakon primene inhalatornih oblika kortikosteroida [5,23,24].

U literaturi je opisano da se atrijska fibrilacija javila tokom ili ubrzo nakon završetka infuzije VDMP-a [11] ili u roku od 24 – 48 sati od završetka terapije VDMP-om [5,21,22]. Takođe, nekoliko objavljenih slučajeva je pokazalo da je pojava atrijske fibrilacije registrovana u roku od 24 do 48 sati od završetka terapije VDMP-om. Kod našeg bolesnika vreme pojave atrijske fibrilacije je bilo u skladu sa prethodnim zapažanjima.

Moreti i saradnici su opisali slučaj pedesetdevetogodišnjeg muškarca sa dijagnozom primarno progresivne multiple skleroze, koji je lečen visokim dozama metilprednizolona. Posle treće doze metilprednizolona (1 g, IV, tokom 2 h) na EKG-u je viđena AF. Nakon što je dva dana lečen digoksinom i propafenonom, AF je medikamentozno konvertovana u sinusni ritam [9].

Početak atrijske fibrilacije indukovane lekovima je prilično varijabilan, u zavisnosti od leka, u rasponu od nekoliko sekundi/minuta nakon intravenozne primene leka kratkog poluvremena, do nekoliko dana, u slučaju nekih hemoterapijskih agenasa. Ponekad se AF indukovana lekovima pojavljuje, ne tokom prvog, već nakon ponovljenog izlaganja leku. Trajanje atrijske fibrilacije izazvane lekovima je takođe promenljivo – opisano je trajanje od nekoliko sekundi do nekoliko sati [25].

Naš bolesnik nije imao istoriju prethodnog moždanog udara, niti istoriju hipertireoze, koronarne bolesti, kao ni implantirane srčane uređaje, prethodne operacije na otvorenom srcu ili prethodno zabeleženu pojavu atrijske fibrilacije. EKG, pre primene VDMP-a, pokazao je normalni srčani ritam. Kao i u većini slučajeva, i u našem slučaju, AF je bila paroksizmalna i završila se nakon nekoliko sati.

Do danas nisu identifikovani nikakvi faktori pomoću kojih bi se mogla predvideti pojava atrijske fibrilacije. U prethodno objavljenim studijama, tzv. *global strain* i *strain rate* leve pretkomore bili su značajno smanjeni kod pacijenata sa paroksizmalnom atrijskom fibrilacijom, u poređenju sa normalnim vrednostima u kontrolnoj grupi [26,27,28,29].

Zanimljiva je činjenica da su trajanje P talasa i disperzija P talasa takođe povezani sa povećanim rizikom za pojavu atrijske fibrilacije i mogu se koristiti kao elektrokardiografski markeri [30]. Takođe, natriuretski

Several cases of atrial fibrillation developing after high-dose corticosteroid treatment have been described in literature [10,11,13,19–22]. A study by van der Hooft et al. has shown that the application of high doses of corticosteroids is connected with increased risk of atrial fibrillation development [18].

In some studies, corticosteroids have been connected to the occurrence of atrial fibrillation, independently of the method of drug administration. The occurrence of atrial fibrillation was recorded during the application of high-dose methylprednisolone pulse therapy [5–9,14], in the application of lower doses of intravenous methylprednisolone therapy, as well as after the application of inhalation corticosteroids [5,23,24].

Reports of atrial fibrillation occurring during or soon after IV administration of HDMP [11] or within 24 – 48 hours of the completion of HDMP therapy [5,21,22] can be found in literature. Also, several published cases have shown that the occurrence of atrial fibrillation was registered within 24 to 48 hours since the completion of HDMP therapy. In our patient, the time of atrial fibrillation occurrence was in keeping with previous reports.

Moretti et al. described the case of a fifty-nine-year-old man diagnosed with primary progressive multiple sclerosis, who was treated with high doses of methylprednisolone. After the third dose of methylprednisolone (1 g, IV, for 2 hours) ECG showed AF. After being treated for two days with digoxin and propafenone, AF was converted to normal sinus rhythm with medication [9].

The onset of drug-induced atrial fibrillation is rather variable, depending on the drug, ranging from several seconds/minutes after intravenous application of a drug with a short half-life, to several days after application, in the case of some chemotherapeutic agents. Sometimes, drug-induced AF occurs, not during the first, but after repeated exposure to a drug. The duration of drug-induced atrial fibrillation is also variable – the duration of several seconds to several hours has been described [25].

Our patient did not have a history of previous stroke, or a history of hyperthyreosis, coronary disease, nor implanted cardiac devices, previous open-heart surgeries or previously registered episodes of atrial fibrillation. The ECG, before HDMP application, showed normal cardiac rhythm. As in most cases, in the case of our patient as well, AF was paroxysmal and ended after a few hours.

To date, no factors have been identified that would help predict the occurrence of atrial fibrillation. In previously published studies, the so-called global strain and strain rate of the left atrium were significantly decreased in patients with paroxysmal atrial fibrillation, as compared to the normal values found in the control group [26,27,28,29].

peptidi su statistički značajno povezani sa incidentnom atrijskom fibrilacijom [31]. Kod našeg bolesnika *proBNP* je bio u referentnom opsegu.

Pojava atrijske fibrilacije je takođe opisana i kod primene inhibitora tirozin kinaze (ibrutinib) kod bolesnika sa HLL-om, u 6 – 16% slučajeva [32,33].

ZAKLJUČAK

Atrijska fibrilacija indukovana lekovima predstavlja neželjeni efekat terapije, koji može biti ograničavajući faktor za nastavak lečenja osnovne bolesti. Klinički pregled i elektrokardiografsko praćenje, tokom i nakon terapije visokim dozama kortikosteroida, mogu povećati šanse za raniju dijagnozu atrijske fibrilacije. Neophodna su dalja istraživanja radi otkrivanja prediktivnih faktora za pojavu atrijske fibrilacije, pre davanja specifične terapije.

Sukob interesa: Nije prijavljen.

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It is interesting that P-wave duration and P-wave dispersion are also connected with the increased risk of atrial fibrillation occurrence, and they can be used as electrocardiographic markers [30]. Also, natriuretic peptides are statistically significantly connected with incident AF [31]. In our patient, *proBNP* was within the reference range.

The occurrence of atrial fibrillation has also been reported in the application of tyrosine kinase inhibitors (ibrutinib) in patients with CLL, in 6 – 16% cases [32,33].

CONCLUSION

Drug-induced atrial fibrillation is a side effect of treatment, which may be a limiting factor for the continuation of underlying disease treatment. Clinical examination and electrocardiographic monitoring, during and after high-dose corticosteroid treatment, may increase the chances of earlier diagnosis of atrial fibrillation. Further research and investigation are necessary in order to discover the predictive factors for the occurrence of atrial fibrillation, before the administration of specific therapy.

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