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Prikaz slučaja /
Case report

CUTANEOUS VASCULITIS AS ADVERSE EFFECT OF METOPROLOL - *Case report*

KOŽNI VASKULITIS KAO NEŽELJENO DEJSTVO METOPROLOL-a – *Prikaz slučaja*

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Abstract

Cutaneous vasculitis (CV) can be idiopathic, but myriad heterogeneous agents may also induce it. Among numerous triggers, drugs are stipulated to cause approximately 15% of CV cases. Medications commonly used in cardiology, including warfarin, aspirin, amiodarone and various β-blockers, e.g. propranolol, acebutolol, sotalol, oxprenolol, atenolol, practolol, alprenolol and carvedilol are very potent to induce CV. **Objective**: This case report is related to cutaneous vasculitis as a probable metoprolol - related adverse effect, with none of the cases described in the available literature. **Case report**: A 61-year-old man was admitted to our hospital due to symptoms related to overdose of oral anticoagulant therapy, expressed as anemic syndrome and worsening lower extremity rash. Physical and pathological examinations confirmed the diagnose of cutaneous vasculitis which was in a possible causal relationship between some of the prescribed drugs. After recommended metoprolol discontinuation, symptoms and signs of CV have been withdrawn. **Conclusion**: A literature search has revealed only a few documented cases of possible beta-blockers induced leukocytoclastic vasculitis. Therefore, metoprolol and bisoprolol should be added to the list of beta-blocker medications that may induce leukocytoclastic (or hypersensitivity) vasculitis.

Key words

metoprolol, adverse effects, cutaneous vasculitis

Ključne reči

metoprolol, neželjena reakcija na lek, metoprolol

INTRODUCTION

Cutaneous vasculitis (CV) relates to vasculitis that affects small- or medium- sized vessels of the skin and/or subcutaneous tissue, but not to the systemic disease. A subcategory of CV, leukocytoclastic or hypersensitivity vasculitis (LCV) refers to a small-vessel vasculitis caused by deposition of immune complexes. Subsequent activation of complement system leads to the vascular injury and extravasation of erythrocytes (Merkel PA 2001). CV has multiple causes: drug intake accounts for 10%–15% of the cases, infection 15%–20%, 15%–20% of cases are related to inflammatory diseases such are collagen vascular disorders. Almost half of the all cases are without known causes (idiopathic) and less than 5% cases are associated with malignancy (Fiorentino DF 2003).

Numerous drugs are marked as potentially causative agents for LCV onset, which occurs usually 7 – 10 days after the drug ingestion. The most common trigger medications are antibiotics (penicillin, sulfonamides, quinolones), analgesics, diuretics (thiazides and furosemide), anticonvulsants, phenothiazines, allopurinol, and granulocyte colony-stimulating factor (GCSF) (Carlson JA 2005). Among other medications, drugs used in cardiology can cause LCV, including warfarin (Hsu CY 2012, Jumean K 2016), aspirin (Al-Nesf

MA 2013), amiodarone (Dootson G 1994) and various β-blockers, e.g. propranolol, acebutolol, sotalol, oxprenolol, atenolol (Wolf R), practolol, alprenolol and carvedilol (Pavlović MD).

Concerning the data from the eHealthMe service, until now, there were 37 cases recorded due to metoprolol intake of all drug-induced vasculitis cases. Among them, CV accounted for 6 cases (eHealthMe.com). But, according to the current literature research, none of these cases are described and published. We present a case of 61-year-old male, who developed LCV within 2 months of initiation of metoprolol.

CASE REPORT

A 61-year-old man was admitted to our hospital due to overdose symptoms related to oral anticoagulant therapy, expressed as anemic syndrome and worsening lower extremity rash, as shown in Figure 1. According to the patients statement, rash was already present during the last month. At the examination, a blistering and oozing sore was noted with burning sensation, and it seemed to be getting worse. Patient denies existence of major problems.

Four months ago, patient had suffered from an anterior STEMI, complicated by cardiogenic shock, ventricular fibrillation, and paroxysmal atrial fibrillation. Percutaneous coronary intervention with a drug eluting stent (DES) insertion in left main/left descending artery (LM/LAD) has been performed. Double antiplatelet therapy (aspirin and ticagrelor), as well as antithrombotic agent warfarin, have been prescribed to the patient, but he used only aspirin and warfarin.

In his medical record were noted paroxysmal atrial fibrillation, arterial hypertension, chronic cardiomyopathy and chronic renal failure.

After a month, patient experienced stent thrombosis. Recoronarography was performed and bare metal stent (BMS) has been placed. His condition was complicated by cardiogenic shock and left heart failure. Ejection fraction (EF) was 20%. Since then, he regularly was taking numerous prescription medications: dual antiplatelet therapy (aspirin, ticagrelor), warfarin, amiodarone, furosemide, spironolactone, metoprolol, trimetazidine, atorvastatin, pantoprazole, and nitroglycerin.

After two months, in August, purpuric lesions appeared onto the patient's trunk and extremities. Outpatient dermatological exam suggested the diagnosis of hypersensitive vasculitis and the patient was hospitalized in the Clinic for Dermatology. A biopsy of purpuric lesions was performed and according to the histopathological findings, cutaneous vasculitis was diagnosed. Patient was treated with prednisone and levocetirizine. Patient had negative ANCA, ANA-Hep2, and rheumatoid factor, he was also hepatitis and human immunodeficiency virus negative. Specific serum proteins (IgG, IgM, IgA, C3, C4, β-2- microglobulin, ASTO) were within normal range. Tumor markers CYFRA (21-1) 4 (<3.3) μg/L, AFP, CA 19-9, CA72-4, CEA NSE, tPSA, fPSA were within the normal range.

Patient was hospitalized again at the beginning of September, due to petechial rash onto abdomen, arms and legs with the signs of skin necrosis at the front of left lower leg. Complete blood count analysis verified anemia (Hg 93, Ht 0.28) with thrombocythosis (Tr 467) and international normalized ratio (INR) 4.51. Due to suspected adverse drug reaction, metoprolol was withdrawn from therapy, and replaced by bisoprolol. Dual antiplatelet therapy has not been changed or withdrawn, because of the high risk of restenosis occurrence.

Less than 24 h after the first dose of bisoprolol, skin changes have worsened. This reaction could be attributed to the adverse effect of beta-blockers, therefore bisoprolol was also withdrawn from the therapy.

Repeated biopsy of purpuric papule showed presence of moderate epidermal atrophy, with fibrinoid necrosis of two small blood vessels and perivascular neutrophilic infiltration, which conforms to an early stage of leukocytoclastic vasculitis (Figure 2).

Besides drugs, possible causes of LCV include hepatitis, human immunodeficiency virus, upper respiratory infections, collagen-vascular disease, inflammatory bowel disease, and rarely, malignancy (Grau RG 2015). According to the all medical findings, our patient didn't have hepatitis and human immunodeficiency virus, he was rheumatoid factor negative, and anti-neutrophil cytoplasmic antibody negative. He denied having inflammatory bowel disease, upper respiratory infections or joint symptoms.

Patient's complete pharmacotherapy, other than aspirin and ticagrelor, was withdrawn and the eruptions began to subside. Dapsone was introduced into the therapy due to slow withdrawal of the changes. Subsequently examination revealed that in less than 5 days after the suspension of therapy and introduction of dapsone, the rash disappeared leaving behind only hyperpigmented macules.

Patient was discharged from hospital and suggested to perform regular medical checkups every 3 – 6 months.

All data were sufficient to perform two causality assessments using different methods, Naranjo scale (Table 1) and WHO system (WHO-UMC) (The use of the WHO-UMC). According to the both methods, the causality of adverse events association with metoprolol was evaluated as probable, i.e. there was high causal association and justified discontinuation metoprolol from the therapy.

DISCUSSION

Leukocytoclastic vasculitis is a rare disease, with annual incidence of 10-30 cases per million persons (Eastham B 2016). Drug-induced vasculitis is a cause of only 10% of cases (Xiao X 2014). There are no published cases of metoprolol induced cutaneous vasculitis, so far, therefore, it could be easily overseen during daily clinical practice and cause of prolongation the period of diagnose establishing.

Causality assessment of adverse drug reactions (ADRs) is a method used for estimating the strength of relationship between drug exposure and occurrence of adverse reaction. One of the most widely used causality assessment tools is the Naranjo ADRs probability scale (Naranjo CA) (Table 1), a questionnaire consists of 10 items and classifies the likelihood that an adverse event is related to a drug. Each element contains specific clauses which are weighted, such are timing, evidence, de-challenge and re-challenge/previous exposure to the medication. Total score is used to grade

the adverse event as definite, probable, possible and doubtful. In order to confirm obtained result, we used, also practical and useful, WHO causality assessment system (WHO-UMC) (The use of the WHO-UMC). Concerning the existence of 6 registered but not published cases of cutaneous vasculitis due to metoprolol intake (eHealthMe.com), we treated such cases as previous conclusive reports on this reaction.

Patient with LCV has to be completely anamnestic, physically and laboratory examined, in order to eliminate concomitant diseases and assess the other organs invasion. Signs and symptoms within anamnesis could rule out the systemic disease or possible malignancy and identify possible underlying causes. Time relationship between drug intake and onset of symptoms could indicate eventually the presence of LCV. Physical examination could reveal some pathological signs, indicating that additional diagnostic tools are needed. Basic or first-line tests include complete blood cell count with differential, C-reactive protein level and/or sedimentation rate, serum creatinine and BUN levels, liver enzymes, urinalysis (with microscopic review), faecal occult blood test, antistreptolysin O titer test (AST-O), antistaphylolysin (Asta) level, antineutrophil cytoplasmic antibodies (cANCA), perinuclear antineutrofil cytoplasmic antibodies (pANCA), rheumatoid factor (RF), complement tests (C3, C4), serum protein electrophoresis, cryoglobulins test, antibodies against hepatitis B, C and HIV. For those patients with suspected malignancy, tumor markers analysis should be performed. A chest-X ray imaging (heart, lungs) should be performed to all patients with vasculitis. A skin biopsy is gold standard for the diagnosis of LCV. (Holl-Ulrich K 2009, Carlson JA 2010).

Patient was admitted to our hospital due to symptoms related to overdose of oral anticoagulant therapy, expressed as anemic syndrome and worsening vasculitis-like lower extremity rash. His medical documentation showed that he already had formerly confirmed LCV, diagnosed at Clinic for dermatovenerology, few months ago, when all the other laboratory and physical findings showed the absence of systemic disease or malignancy. Considering present symptoms, in order to clarify his health condition, repeated skin biopsy was performed, as dermatologist suggested. Diagnose of LCV was again confirmed; therefore it was an objective evidence, according to the Naranjo scale. Value of INR was within reference range, so it could be concluded that the bleeding and anemic syndrome were due to vasculitis complications, without involving other organs.

Beta-blocker drug metoprolol was marked as the most

Table 1. *Naranjo algorithm*

Information	**Question**	**Answer**		
		Yes	**No**	**Do not know or not done**
1. Previous recorded ADRs	Are there previous conclusive reports on this reaction?	**+1**	0	0
2. Temporal association of drug administration and event occurrence	Did the adverse event occur after the suspected drug was administered?	**+2**	-1	0
3. *Dechallenge*	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	**+1**	0	0
4. *Rechallenge*	Did the adverse reaction reappear when the drug was readministered?	+2	-1	**0**
5. Alternative causes	Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	**+2**	0
6. Placebo effect	Did the reaction reappear when a placebo was given?	-1	+1	**0**
7. Overdose	Was the drug detected in any body fluid in toxic concentrations?	+1	0	**0**
8. Dose dependence	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	**0**
9. Previous patient experience with the medication	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	**0**	0
10. Objective evidence	Was the adverse event confirmed by any objective evidence?	**+1**	0	0
	Total score		**+7**	

Scoring:
Definite ADR (≥9)
Probable ADR (5 - 8)
Possible ADR (1 - 4)
Doubtful ADR (≤0)

probable cause of LCV, so it was discontinued from therapy and replaced with bisoprolol, because of the necessity of beta-blockers therapy. Immediately after bisoprolol induction therapy, changes related to LCV worsened, and after its discontinuation, improvement was noticed.

In order to find actual cause of patients LCV, we had to eliminate other possible drugs. Alternative medications, described in the literature, could be marked as causative agents of our patients LCV, like aspirin, ticagrelol and warfarin. Additional complications within his health condition were stent restenosis and paroxysmal atrial fibrillation, therefore the discontinuation of such medications could lead to fatal outcome. When symptoms were withdrawn after beta-blockers discontinuation, there was no need to eliminate other essential medications from therapy.

We couldn't conclude the definite causality, as the highest strength of causal relationship, neither using Naranjo scale nor WHO-UMC system, because re-challenge was not performed and not recorded in previous medical records. However, probably causality was assessed regarding metoprolol and bisoprolol medication and LCV occurrence.

CONCLUSION

The example of our patient showed that leucocytoclastic vasculitis could be caused by beta-blockers, especially metoprolol and bisoprolol. Therefore, metoprolol and bisoprolol should be added to the list of beta-blocker medications that may induce LCV, in spite of the lack of literature data and only a few documented such cases, so far. This condition is reversible and withdraws after discontinuation of drug.

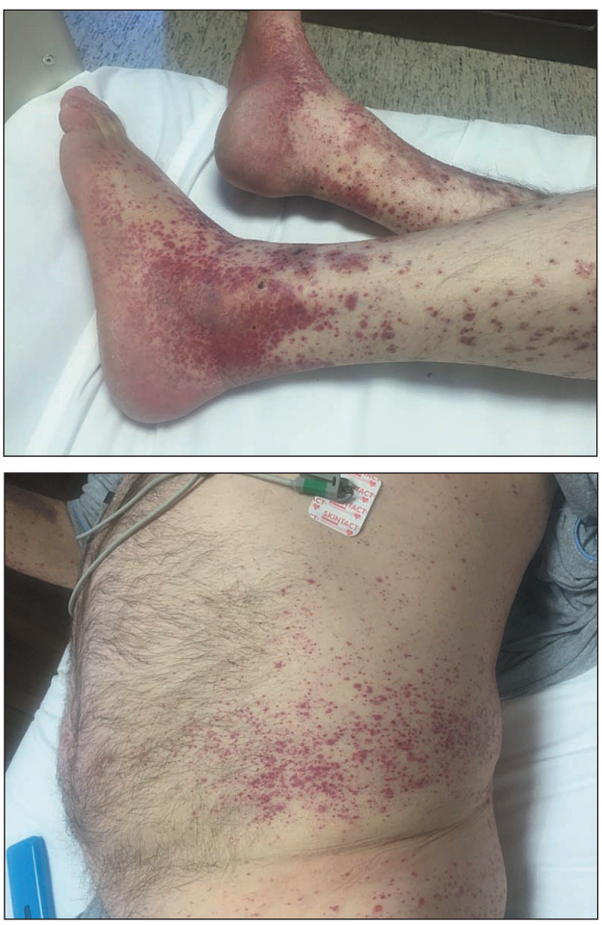


Figure 1. *Lower extremity rush, blistering and oozing sore during patients admittance to the hospital.*

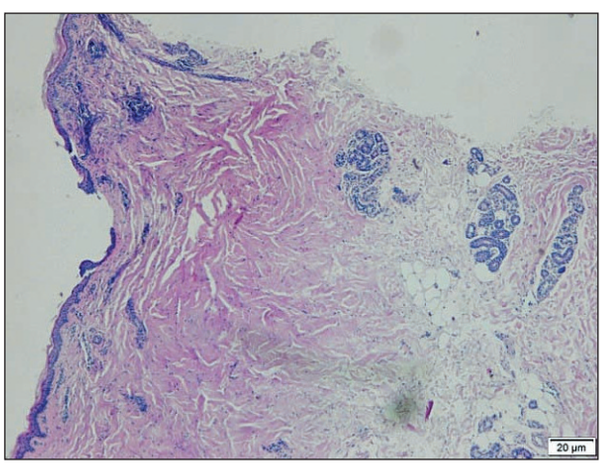
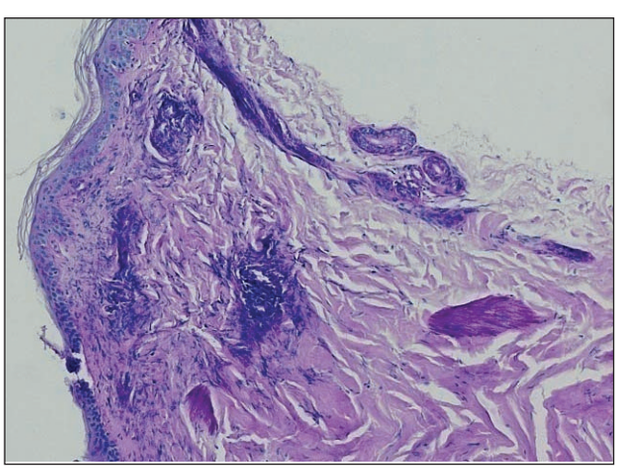
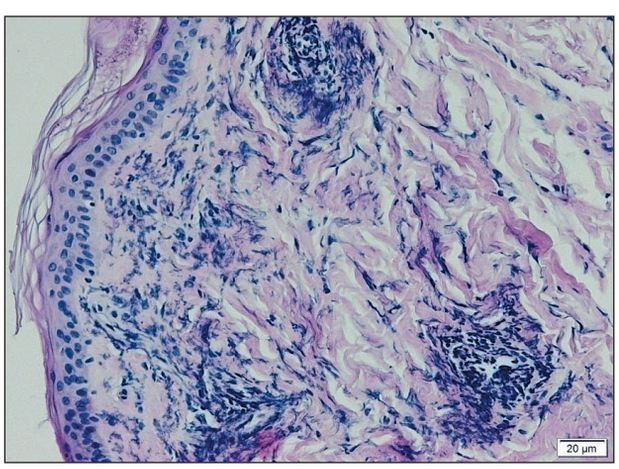


Figure 2. *Biopsy of purpuric papule showing presence of moderate epidermal atrophy, with fibrinoid necrosis of two small blood vessels and perivascular neutrophilic infiltration, which conforms to an early stage of leukocytoclastic vasculitis.*





Sažetak

Kožni vaskulitis (CV) može biti idiopatski, ali ga može izazvati i mnoštvo heterogenih agenasa. Među brojnim okidačima, navodi se da lekovi izazivaju oko 15% slučajeva CV. Lekovi koji se obično koriste u kardiologiji, uključujući varfarin, aspirin, amiodaron i razne b-blokatore, npr. propranolol, acebutolol, sotalol, okprenolol, atenolol, praktolol, alprenolol i karvedilol su veoma potentni da indukuju CV. Cilj: Ovaj prikaz slučaja se odnosi na kožni vaskulitis kao mogući neželjeni efekat povezan sa metoprololom, pri čemu nijedan slučaj nije opisan u dostupnoj literaturi. Prikaz slučaja: Muškarac, star 61 godinu, primljen je u našu bolnicu zbog simptoma u vezi sa predoziranjem oralnim antikoagulansima, izraženih kao anemični sindrom i pogoršanje osipa na donjim ekstremitetima.

Fizikalnim i patološkim pregledima potvrđena je dijagnoza kožnog vaskulitisa koji je u mogućoj uzročno-posledičnoj vezi između nekih od propisanih lekova. Nakon preporučenog prekida uzimanja metoprolola, simptomi i znaci CV se povlače. Zaključak: Pretraživanje literature otkrilo je samo nekoliko dokumentovanih slučajeva mogućeg leukocitoklastičnog vaskulitisa izazvanog beta-blokatorima. Stoga, metoprolol i bisoprolol treba dodati na listu beta-blokatora koji mogu izazvati leukocitoklastični (ili preosetljivi) vaskulitis

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