CASE REPORT

DRUG-INDUCED VASCULITIS WITH MULTI-ORGAN INJURY IN A SPLENECTOMISED PATIENT AND MYCOPHENOLATE MOFETIL THERAPY – A CASE REPORT

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Abstract

We present a case with p-ANCA positive general vasculitis and severe multi-organ injury in a splenectomised patient, which developed during ceftriaxone and metamizole administration for treatment of upper respiratory infection. Case report: A middle-aged woman with 400C fever and sore throat got a treatment with IV metamizole and ceftriaxone in a local hospital. She had a post- traumatic splenectomy 5 years ago. After metamizole, during ceftriaxone administration she felt burning in her face, developing red rush which spread over the face and darkened, later extended to her palms and feet. After visiting several clinics, she was referred finally to the University Clinic for Toxicology in Skopje. On admission, she had hypotension, hypoxemia, livid oro-pharynx, necrotic vasculitis with predominant facial distribution and unpalpable purpura on the extremities. The examinations revealed high levels of inflammatory biomarkers, anaemia, polyserositis, acute pancreatitis, hepatomegaly, acute kidney injury, disseminated intravascular coagulation, right eye vitreous haemorrhage and rhabdomyolysis. Microbiological investigations were negative. Immuno-serology showed positive p-ANCA. The acute renal failure and polyserositis resolved under methylprednisolone, meropenem, furosemide, low molecular weight heparin, fresh frozen plasma, and other symptomatic therapy, which decreased the inflammatory biomarkers, but DIC with thrombocytopenia persisted. A skin biopsy finding was inconclusive. After 25 days, the rheumatologist recommended mycophenolate mofetil with prednisolone peroral therapy during two years that resulted in stabilizing the vasculitis. The patient maintained stable after therapy discontinuation. Conclusions: Drug-induced vasculitis has the potential to induce a severe multi-organ injury with life-threatening complications. Mycophenolate mofetil procured a safe and successful treatment of drug-induced vasculitis. Splenectomy may be a potential risk factor for immunomodulated response to drugs and drugs interactions, especially during infections.

ПРИКАЗ НА СЛУЧАЈ

МЕДИКАМЕТОЗНО-ИНДУЦИРАН ВАСКУЛИТИС СО МУЛТИОРГАНСКА ПОВРЕДА КАЈ СПЛЕНЕКТОМИРАН ПАЦИЕНТ И ТЕРАПИЈА СО МИКОФЕНОЛАТ МОФЕТИЛ - ПРИКАЗ НА СЛУЧАЈ

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Извадок

Цел на трудот е приказ на случај со p-ANCA позитивен генерализиран васкулитис и тешка повеќесистемска слабост кај спленектомизиран пациент кој се развил при администрација на цефтриаксон и метамизол за третман на горнореспираторна инфекција. Приказ на случај: Средовечна жена со треска од 400С и болки во грлото била третирана со IV метамизол и цефтриаксон во локална болница. Таа имала пост-травматска спленектомија пред 5 години. Примила метамизол, но за време на администрацијата на цефтриаксон таа почувствувала печење во лицето, развивајќи црвен осип кој се проширил по лицето и потемнувал, подоцна се проширил на дланките и стапалата. По посетата на неколку клиники, конечно била упатена на Универзитетската клиника за токсикологија во Скопје. При приемот имала хипотензија, хипоксемија, ливиден оро-фаринкс, некротичен васкулитис со доминантна дистрибуција на лицето и непалпабилна пурпура на екстремитетите. Испитувањата откриja високи воспалителни биомаркери, анемија, полисерозитис, акутен панкреатитис, хепатомегалија, акутна бубрежна повреда, дисеминирана интраваскуларна коагулација, хеморагија на стаклестото тело на десното око и рабдомиолиза. Микробиолошките наоди беа негативни. Имуносерологијата покажа p-ANCA позитивитет. Акутната бубрежна инсуфициенција и полисерозитисот се повлекоа со метилпреднизолон, меропенем, фуросемид, хепарин со ниска молекуларна тежина, свежо замрзната плазма и друга симптоматска терапија, кои ги намалија нивоата на воспалителните биомаркери, но DIC со тромбоцитопенија опстојуваше. Наодот од биопсија на кожата беше неубедлив. По 25 дена, ревматологот препорача микофенолат мофетил со преднизолон перорална терапија во текот на две години со што се стабилизираше васкулитисот. Пациентката останаа стабилни по прекинувањето на терапијата. Заклучок: Васкулитисот предизвикан од лекови има потенцијал да предизвика тешка повреда на повеќе органи со компликации опасни по живот. Микофенолат мофетил овозможи безбеден и успешен третман на васкулитисот предизвикан со лекови. Спленектомијата може да биде потенцијален ризик-фактор за имуномодулиран одговор на лекови и нивните интеракциите, особено за време на инфекции.

Introduction

Almost all drug classes have the potential to induce vasculitis which can result in tissue and organ injury. Drug-induced vasculitis (DIV) is more often associated with certain medicines, however, new drugs or sometimes their combinations have also been presented as culprit agents for vasculitis[1]. Drug-induced vasculitis (DIV) was considered as a distinct form of vasculitis and it was categorized in the group of vasculitis with probable etiology under the Chapel Hill Consensus Conference 2012 definitions for vasculitis[2] . DIV had fivefold increased incidence in the last 30 years3, and one of the assumed reasons for increased diagnosing DIV was the improved availability of immunological tests.

Small-vessel vasculitis (SVV) is the most common type of drug-induced vascular injury. Leukocytoclastic vasculitis is dominantly caused by antibiotics (including beta-lactams) and NSAID, antithyroid drugs and cocaine/levamisole [1,4], localized to skin, although renal, joint and gastrointestinal injury may also be involved. In some cases, they have been associated with antibodies, including antinuclear (ANA), rheumatoid factor and antineutrophil cytoplasmic antibodies (ANCA). Their presentation involves skin manifestations with multi-organ injuries such as interstitial lung disease, alveolar haemorrhage, interstitial nephritis and crescentic glomerulonephritis, gastrointestinal tract, retinal haemorrhage, polyserositis and ANCA against proteinase 3 (c-ANCA) or myeloperoxidase (p-ANCA), or both. ANCAs against other proteins have also been detected, but their presence is associated with other conditions beside vasculitis. Other subtypes of SVV are small vessel IgA vasculitis usually associated with drugs targeting TNF-α, then cryoglobulinaemic vasculitis and vasculitis associated with connective tissue diseases and malignancies5. Medium vessel vasculitis is usually associated with tetracycline antibiotics, while large vessel is not very typical for DIV. Treatment includes immediate drug discontinuation in mild clinical presentation, but in cases with multiorgan failure a treatment with immunosuppression is necessary with administration of cyclosporine as a first- line therapy[6].

We present a case with a general vasculitis and severe multi-organ failure in a splenectomised patient, which developed after ceftriaxone and metamizole administration and upper respiratory tract infection. The complete remission of DIC was achieved after inclusion of mycophenolate mofetil.

Case report

A middle-aged woman presented at the local hospital after a two-day fever (39.8C), sore throat, chills, general weakness. She was given crystalloids, parenteral metamizole of 2.5 gr and IV. ceftriaxone of 2 gr. During the intravenous infusion with ceftriaxone, she felt a warmth, burning and itching in her face. The symptoms first appeared on the tip of the nose and then spread to the cheeks, forehead, chin, covering the entire face. Over the next hour, the rash on her face began to turn black. At the same time, a rash began to appear on the skin of her feet and legs, arms and trunk in the form of pink-red

coloured spots. She received an additional 4 mg dexamethasone IV, 80 mg prednisolone IV and 20 mg chloropyramine IM, and was referred to the University Clinic for Infectious Diseases; afterwards they referred her to the dermatology, haematology and rheumatology clinics. After consultations with all of these specialties, due to the severity of the patient's general condition and suspicion for drug-induced vasculitis, she was referred to the University Clinic for Toxicology.

On admission, she had necrotic facial vasculitis (Picture 1), livid mucosa of oro-pharynx, non-palpable purpura on the trunk and extremities, especially gluteal region with discrete periorbital, perioral, pretibial, palmar and feet bilateral oedema with macular rush and few hematomas on the trunk and gluteus.

Picture 1. Necrotic facial vasculitis on admission

She had a history of post-traumatic splenectomy 5 years ago. Laboratory tests (Table 1) presented hypoglycaemia, rhabdomyolysis, acute kidney injury with oliguria (400 ml/24 h), and urine analysis with haematuria and disseminated intravascular coagulation (DIC) (Platelets 51x10^9/l, Di-dimer 4427 ng/ml, prolonged PT 58sec, aPTT 120 sec and TT 120 sec (ref. values PT 9.8-14.2 sec, aPTT 27.9-37.7 sec, TT 16.1-24.1 sec). C-reactive protein (CRP) increased up to 129 ng/ml and she had normal thyroid gland status (Table 1). Gas analysis from arterial blood showed metabolic acidosis compensated with respiratory alkalosis. Treatment included crystalloids up to 2000 ml/24 hours, prednisolone of 1.5 mg/kg (80 mg) IV for 1 week then 1 mg/kg, amp. Meropenem 3 gr/24 hours, amp ranitidine IV twice a day, enoxaparin 40mg s.c. twice a day and isogroup plasma 440 ml on the first day with 10 units of cryoprecipitates. During the next few days, purpura gradually intensified, acute kidney injury well responded to administration of furosemide (60 mg/day for three days

and 10 mg /day for the next five days); sodium bicarbonate was calculated by a standard formula and rehydration was controlled. Diuresis started to increase from day 3 (2000 ml /24 hours) and soon continued to polyuria during recovery of the kidney function with max diuresis of 6000 ml/24 hours. Blood urea and creatinine levels rose to maximum levels on the 5th day of hospitalisation, normalized on the 10th day and remained in reference range until the end of hospital stay (Table 1).

Day of hosp. / Parameter	1	2	3	4	5	8	9	10	11	18	25
WBC (x10^9/l) (4-9)	7	9.3	17.8	27	35	17	10	11.5	11	7.6	7.3
Er (x10^12/l) (3.6-5.2)	3.56	2.79	2.6	3.60	3.6	4.2	4.1	4.06	3.8	3.5	2.8
Hgb (g/l) (120-160)	116	92	88	123	115	139	129	128	127	118	94
PLT (x10^9/l) (150-450)	51	59	86	52	23	55	56	77	94	62	47
BUN (mmol/l) (2.7-7.8)	11.6	14.9	28	36.5	47	46	35	28	27	7.3	5.5
Creatinine (µmol/l)(45-109)	265.6	308.1	463	484	528	215	155	112	92	52	49
CK (U/l) (<173)	333	318	428						47	22	
CK-MB (U/l) (<25)	118	87		1672					13		
LDH (U/l) (<248)	1867	1726	1865	1672	894	473	470	499	450	297	232
Amylase (U/l) (30-110)	187	136	163	254		1048	855	859	733	159	142
Lipase (U/l) (30-60)						881				106	111
Troponin-I (ng/l) (<25)				325	107				22.9		12
CRP (mg/l) (<6)		129		247	130	27	19	15	14	4.6	2

Day of hosp., day of hospitalization; WBC, white blood count; Er, erythrocyte; PLT, platelet; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatinine phosphokinase; CK-MB creatinine phosphokinase-myocardial band; CRP, C-reactive protein.

Chest radiography presented dominantly right-sided pleural effusion, confirmed by an ultrasound, but pleural biopsy was not performed due to thrombocytopenia, which persisted during hospitalization.

The patient complained of abdominal pain from day 3 accompanied with rose of amylase(s) levels reaching the highest values on day 8 associated with an increase in lipases levels up to 881 U/l. Abdominal ultrasound (3rd day) detected ascites, congestive liver, dilated hepatic veins and inferior vena cava with a diameter of 28-30 mm with maintained blood flow, cholecystolithiasis. Ultrasound examination could not visualize the pancreas because of the increased intestinal gas collections. The kidneys were enlarged with reduced parenchymal echogenicity, with no signs of hydronephrosis. Splenectomy with accessory spleen and diameter of 20-21 mm were detected. Aminotransferase concentrations decreased after the 4th day along with normalization of

diuresis, while lipases levels reduced slowly remaining at double values of the reference range until the end of hospitalisation (Table 1). The abdomen CT on the third day of hospitalisation confirmed the ultrasound findings. Troponin increased on day 3 to 327 ng/ml and decreased on day 11 down to 22.9 ng/ml and 12.5 ng/ml on day 25. Echocardiography revealed acute pericarditis without signs of cardiac tamponade with normal ejection fraction (71%) and first degree of mitral regurgitation.

On the second day of hospitalisation, the temperature started to decrease to subfebrile (37.6 ºC) and the patient was afebrile from the third day. The treatment with amp Meropenem of 3gr / 24 hours was continued for 14 days, with maximal CRP levels on the fourth day (247 mg/l) and normalization on the 15th day of stay. Microbiology analysis (haemoculture - three times, urine culture – 2 times, nasal and pharyngeal swap, Hantaan virus test, HIV, anti HCV, HBs Ag, virus panel) were negative. Immuno-serology was positive only for p-ANCA. The lactate dehydrogenase concentration, as a nonspecific marker of inflammation, was increased until the 25th day of hospitalization with maximum values of 1865 U/l, presenting prolonged tissue damage (Table 1).

During the hospital stay, platelets did not rise more than 100x 10^9/l, the lowest values being 19 x10^9/l, interpreted as a part of DIC and microvasculitis. Peripheral blood smear showed thrombocytopenia (32x10^9/l), neutrophilia 83% with “toxic granulation”, interpreted as a result of infection, fragmented erythrocytes and rare acanthocytes.

The patient was treated with enoxaparin of 0.4 mg s.c 2x1 and FFP once a day. She received 28 units of 220 ml FFP and 35 units of cryoprecipitates during the hospital stay which normalized the coagulation test (PT, aPTT and TT), corrected fibrinogen levels while DD remained increased during the whole hospitalization period (maximal concentration 7658 ng/ml to lowest concentration 2530 ng/ml). The control blood smear on the 20th day of hospitalization presented absence of toxic neutrophil granulation with increased reticulocytes 9.6x10^9/l (reference 05.- 2.5 x10^9/l). Skin biopsy was performed on the 10th day but it was inconclusive. On the 20th day, a vitreous haemorrhage on the right eye appeared although the patient was treated with LMWH and FFP. The ophthalmologist recommended continuation of the already included therapy with consecutive resorption of the haemorrhage after 2 weeks.

During the hospital stay, immunosuppressive therapy was initiated with a higher dosage of corticosteroids (methylprednisolone 1.5 mg/kg) for one week, then 1 mg/kg, without improving the platelet count, DIC and microvasculitis. The treatment of DIC included 80 mg/kg TT enoxaparin/24 hours, 8 units/50ml thrombocyte concentrates, 33 units fresh frozen plasma (220 ml/unit), 80 units of cryoprecipitates. Due to the resistance to corticosteroid and antihistaminic therapy, after 4 weeks the rheumatologist recommended mycophenolate mofetil 2 gr/day in the next 9 months and reducing to 1.5 gr/day in the following 1.5 year. Corticosteroid peroral therapy with prednisolone was gradually reduced, starting from 40 mg to 5mg /24 hours

for 10 weeks with maintaining dosage of 5 mg /24 hours. Therapy also included vitamin D, paracetamol and NSAID, and proton pump inhibitor. The patient had discrete residual facial hyperpigmentation. After 2 years, immunosuppression was discontinued and the patient has been maintained in a stable condition for the last 3 years.

Discussion

Herein we have reported a case with a severe clinical presentation of p-ANCA positive vasculitis and multiorgan injury after simultaneous exposure to drugs (ceftriaxone with metamizole) administered for treatment of upper respiratory infection in a splenectomised patient. The aetiology of primary SVV although well researched is not completely understood. However, secondary SVV may be a result of infection, malignancy and drugs including different classes of antibiotics[7]. Detecting the vasculitis aetiology in DIV is the primary goal and provides better prognosis. In cases of mixed infection with drug administration, diagnosis is often challenging. However, the cutaneous form of vasculitis in our patient developed during ceftriaxone administration very soon after she got metamizole intravenously. At the same time, cutaneous presentation progressed to severe extracutaneous manifestations and they persisted even after drug cessation, which implied that the combination of infection with medicines was the potential trigger factor. Ceftriaxone was reported as a culprit agent of DIV[8] presenting as cutaneous form or in some cases with additionally extracutaneous manifestations. Almasoudi *et al.* reviewed a large series of ceftriaxone-induced vasculitis and reported the shortest time for manifesting vasculitis (one day) unlike our case in which vasculitis appeared during ceftriaxone administration[8]. Additionally, the combination of ceftriaxone with metamizole had a nephrotoxic potential for development of AKI. Biopsy with histological confirmation of vasculitis (vascular wall infiltration with neutrophiles with fibrinoid deposition and necrosis) is considered as a gold standard for diagnosis. Nevertheless, there is a short time window of 48 hours when it can be confirmed, because after 2 days the specific findings for vasculitis started to transform. We missed this time window in our case due to prominent thrombocytopenia and could not confirm these changes with the histological examination[9]. Other authors suggest that negative pathohistological findings should not be a criterion of prime importance to exclude SVV in cases with clinical typical presentation and late performed biopsy[10].

The proposed mechanisms for betalactams and metamizole to induce allergic immune hypersensitivity reactions was through extensive reactions of T-lymphocytes or/and IgE by using hapten formation and p-i – pharmacological interaction with immune cell receptors (HLA - human leukocyte antigen) or T lymphocyte receptors[11]. But the cessation of metamizole and ceftriaxone and high corticosteroid doses in our patient did not correct the laboratory signs and clinical presentation of microvasculitis with DIC. Other group of medicines including vancomycin, NSAID, opioids, cyclosporine, ciprofloxacin, radioiodine contrast, induce DIV by

pseudo-allergic or "non-immune" reaction through activating inflammatory cells without activation of IgE or T lymphocytes[12]. The drug-induced hypersensitivity reactions have severe presentation with exanthem, fever, hematologic and visceral organ reaction. The non-immunological pathways operating by by-passing T cells activation was associated with resistance to standard immunosuppressive therapy (corticosteroids, cyclosporine, antihistamines and NSAID) and this mechanism was proposed as underlying culprit for resistant SVV[13]. The therapy with corticosteroids and anticoagulants mostly succeeded in withdrawing the clinical signs of polyserositis, acute kidney injury, rhabdomyolysis and pancreatitis in our patient, but the vasculitis and DIC did not completely resolve. Kolhie *et al.* detected resistance to corticosteroid therapy in 20% of cases with urticarial vasculitis 7. Nevertheless, adding therapy with mycophenolate mofetil improved the vasculitis parameters and clinical presentation in our patient. Mycophenolate mofetil induces inhibition of B and T cell proliferation and suppresses cell-mediated immune response, which results in stabilizing the inflammatory processes in the small vessels. Our patient received mycophenolate mofetil during the next 25 months simultaneously with gradually lowering the corticosteroid therapy. Low doses of corticosteroid with immunosuppressing agent in newly diagnosed ANCA vasculitis was as efficient as solitary high corticosteroid dose regimen in succeeding remission[14] but longer corticosteroid treatment was associated with reduced relapses as it was in this presented case [15].

Our patient had systemic symptoms and positive immunology tests for p-ANCA, but negative for all other tests in the immunology panel during hospitalization and after 2 years of follow up, considering her condition as a drug-induced vasculitis with multisystem injury. She had a history of post-traumatic splenectomy which was less often associated with infectious and thrombotic complications compared to splenectomy because of other underlying medical conditions. However, in both situations splenectomy was associated with reactions of hypersensitivity. Patients with post-traumatic splenectomy and preserved Th2 leukocyte function have been reported as prone to allergy and reaction of hypersensitivity[16] because splenectomy induces losing lien immunocytes that participate in prevention of auto- immune inflammation[17].

Conclusion

DIV is presented with cutaneous form of vasculitis but it also leads to extracutaneous manifestations with severe multi-organ failure as life-threatening complications. The awareness of DIV and early withdrawal of the culprit drug can help in early recovery and better prognosis. In severe cases, immunosuppression with mycophenolate mofetil has been safe and successful therapy for vasculitis control. Different aetiology factors of SVV affects the skin, which emphasises the importance of identifying SVV with underlying systemic autoimmune disease that need life-time medical attention. Splenectomy might be taken in consideration as a potential risk factor for immunomodulated response to

drugs and drug interactions, especially during infections.

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