RASH, FEVER AND PROTEINURIA AFTER AMOXICILLIN IN A SLE PATIENT

M. Couto,[*] C. Duarte,[**] A. Geraldes,[***] Colleen Medeiros,[****] L. Inês,[****] A. Malcata[*****]

Abstract

We report a case of severe type IV hypersensitivity reaction to amoxicillin, which occurred in a person with a 12-year history of SLE. The present case illustrates the wide differential diagnosis in a SLE patient who presents with an allergic drug reaction. The attribution of the presenting symptoms to the underlying SLE and/or to the drugs used to treat SLE and coexisting conditions is a major challenge.

Keywords: Systemic Lupus Erythematosus; Drug Hypersensitivity; Amoxicillin; Simvastatin; Rhabdomyolysis.

Introduction

Allergic drug reactions may be increased in Systemic Lupus Erythematosus (SLE) patients. Some studies show that drug allergies (DA) are similar in SLE and controls,[1,2] others suggest that SLE patients have an increased risk of DA.[3-7] One explanation for discrepancies between these studies is the choice of controls and whether they are normal individuals or disease controls. SLE patients are more frequently exposed to drugs, which, "per se" represents a risk factor for DA[8] and thus normal control would be inappropriate. Pope *et al*[5] studied DA in SLE patients using self-report data from age and sex matched controls with inflammatory arthritis. It was found that, with the exception of skin rash for sulfonamides other DA were not more frequent in SLE. The other possibilities for the reported differences would be differences in the ethnicity of control groups and the means of ascertaining allergic manifestations,[5] with medical record review[1] reporting lower frequencies than self-reported.[5] Finally, making the attribution of any allergic manifestation must deal with the fact that drug[2,3] may exacerbate or even induce SLE.[9] For instance, sulfonamides may cause flares in SLE patients.[9] In addition some manifestations, such as fever, rash and oral ulcers, might be attributed to DA but in fact may be a feature of SLE exacerbation.

Case report

A 30-year-old Portuguese female law student presented to our emergency room with a 3-day history of a progressive maculopapular rash that started over her legs, odynophagia, minimally productive cough and non-bloody diarrhoea 5-6 times a day. Three days before her admission, she had consulted her dentist for dental pain and was given the combination of amoxicillin 875 mg and clavulanic acid 125 mg bid. She had a history of a rash to penicillin. After taking the second tablet, she developed chills, malaise, myalgia and a rash over lower extremities.

The patient had a 12-year history of SLE manifested by malar rash, photosensitivity, oral ulcers and alopecia, leukopenia, polyarthritis and WHO class IV diffuse membranoproliferative nephritis. When she was seen 2 months before, her SLE disease activity measured by SLAM-R was 3 (Table I) with stable doses of prednisone 20 mg qd and azathioprine 50 mg bid. She was also on captopril 50 mg

*Rheumatology Fellow at the Department of Rheumatology, Coimbra University Hospital and Assistant Professor of Physiology, Coimbra University School of Medicine, Coimbra, Portugal
**Rheumatology Fellow at the Department of Rheumatology, Coimbra University Hospital, Coimbra, Portugal
***Immuno-Allergology Fellow at the Department of Immunology and Allergy, Coimbra University Hospital, Coimbra, Portugal
**** Clinical Medicine Pharmacist, Boston Medical Centre, Boston, Massachusetts USA
*****Consultant Rheumatologist at Department of Rheumatology, Coimbra University Hospital and Assistant Professor of Rheumatology at Health Sciences School of Medicine, Beira Interior University, Covilhã Portugal
******Head of the Department of Rheumatology, Coimbra University Hospital and Assistant Professor of Rheumatology at Coimbra University School of Medicine, Coimbra, Portugal

Table I. Comparison of laboratorial values at baseline and on admission

		Baseline values	Admission values	Reference values
Blood	Hgb	11.9	13.0	11.5–16.5 g/dl
	WBC	3.5	8.4	4–11 x10^3/µL
	Lymphocytes	0.7	1.1	1.5-4.95 x10^3/µL
	Platelets	118	57	150–400x10^3/µL
	C3 / C4	not available	0.78 / 0.2	0.9–1.8 / 0.1–0.4 g/L
Urine	Anti-dsDNA	not available	34.2	<4.2 U/ml
	Protein	10	193	0–20 mg/dl
	Leucocytes	7.4	29.4	1.0–36.0/µL
	Red blood cells	2.0	28.3	1.0–43.0/µL
	SLAM-R	3	9	0–81

Hgb- haemoglobin; WBC- White blood cells; SLAM-R: SLE Activity Measure-Revised

bid, simvastatin 20 mg qd, furosemide 20 mg qd and folic acid 5 mg qd.

In the emergency room, her physical examination showed an alert but ill woman, bilateral conjunctival haemorrhages, generalized purpuric rash, and a temperature of 39.5º C. Her pulse was 111/min, her blood pressure was 103/70 mm Hg; the rest of her physical examination was normal.

Laboratory tests showed high values of serum creatinine (4.6 mg/L) and C-reactive protein (29.8 mg/dL), hypoalbuminemia (2.9 g/dL), elevated SGOT (311 U/L), SGPT (86 U/L) and CPK (24220 U/L). Her lymphocytes (1.1x10^3/µl) and platelets (57x10^3/µL) were low (Table II). There was no eosinophilia. Her urine dipstick showed 3+ proteinuria and hematuria. Her arterial blood gases showed pH=7.39 [7.35-7.45]; paO_2=118 mm Hg [85-108]; pCO_2=21.2 mm Hg [35-45] and HCO_3= 12.7 mmol/L [21-29]. The chest X-ray showed diffuse bilateral lung interstitial infiltrates.

Table II. Laboratorial values on admission

	Value	Reference values
Creatinine	4.6	0.6-1 mg/dl
CRP	29.8	0-0.82 mg/l
Albumine	2.9	3.5-5 g/dl
SGOT	311	5-34 U/L
SGPT	86	5-34 U/L
CK	24220	29-168 U/L
Hgb	13.0	11.5-16.5 g/dl
Leukocytes	8.4x10^3	4-11x10^3/µL
Lymphocytes	1.1x10^3	>1.5x10^3/µL
Platelets	57x10^3	150-400x10^3/µL

The presumptive diagnoses at emergency room were sepsis, drug allergic reaction to the antibiotic, rhabdomyolysis with secondary acute renal failure and a SLE flare. She received intravenous fluids, paracetamol, bicarbonate, imipenem, a 250 mg iv bolus of methylprednisolone followed by oral prednisone 60 mg qd, intramuscular clemastin and supportive care.

After admission to the rheumatology ward, prednisone was tapered from 60 mg qd to 20 mg over 13 days and she was given hydroxyzine 25 mg qd, furosemide 20 mg bid and albumin 1 g tid. Her skin lesions were treated with topical 0.1% betamethasone. By the third day she became afebrile, without constitutional symptoms, skin lesions became vesicular and epidermolysis occurred. Antibiotherapy was stopped at the 8th hospital day. Laboratory values normalized as she recovered (Figures 1 and 2). Sputum was unobtainable and a subsequent chest film showed clearing of the infiltrates present at admission.

Blood, urine and stool cultures, serology for EBV, CMV, parvovirus B19 and coxsackie were negative. Anti-dsDNA antibody was 34.2 U/ml [<4.2 U/ml], C3 0.78 g/L [0.9-1.8] and C4 0.2 g/L [0.1-0.4]. She had a proteinuria of 2.88 g/day, which persisted after creatinine and CPK normalization. Except for proteinuria, urinalysis did not show abnormalities (Table I); myoglobin, red cell casts and dysmorphic red blood cells were absent. Her disease activity measured by SLAM-R was 9. A repeat renal biopsy showed WHO class IV-C diffuse prolipherative glomerulonephritis, with diffuse and segmen-

tal sclerosis without active lesions (Figures 3 and 4). Intradermal skin tests confirmed type IV hypersensitivity to amoxicillin, ampicilin and dicloxacillin.

The patient was discharged at the 28th hospital day treated with prednisolone 10 mg qid, furosemide 40 mg bid, enalapril 5 mg qid and azathioprine 50 mg bid. After discharge, the Nephrologist decided to change azathioprine for mycophenolate mofetil 1 g bid, stopped after one year due to lack of benefit. She continues her follow-up at the Rheumatology and Nephrology Outpatient Clinics. She maintains mild chronic renal insufficiency with a SLAM-R score of 3 (low disease activity) at last visit.

Discussion

In this patient several diagnoses had to be considered. These were in order of likelihood: 1) amoxicillin hypersensitivity; 2) sepsis; 3) rhabdomyolysis from simvastatin precipitated by amoxicillin hepatotoxicity; 4) sepsis causing a lupus flare; 5) amoxicillin- induced lupus flare or 6) some combination of the above.

Drug allergy (DA) to amoxicillin was the most probable precipitating event considering the patient's previous history, the temporal sequence of events and because allergic reactions to β-lactamic drugs are common. Our patient presented a type IV hypersensitivity reaction, which can occur from one hour to several days after re-exposure to the drug, more commonly 48-72 hours after.[10] This reaction differs from an immediate hypersensitivity reaction, which generally appears within 12 minutes and no longer than one hour of an antigen challenge with urticaria with or without angioedema or anaphilaxis.[1] There is evidence that the longer the interval between drug intake and appearance of the reaction the less the probability of being IgE mediated. The patient had no family or personal history of atopy, which has been associated with an increased risk of DA.[2] The onset of maculopapular lesions occurring after the re-exposure to antibiotics is typical of Type IV hypersensitivity reactions.[3] As the mechanism is not IgE-mediated, measuring IgE specific to amoxicillin would not help confirm the diagnosis. The use of skin testing, such as in-

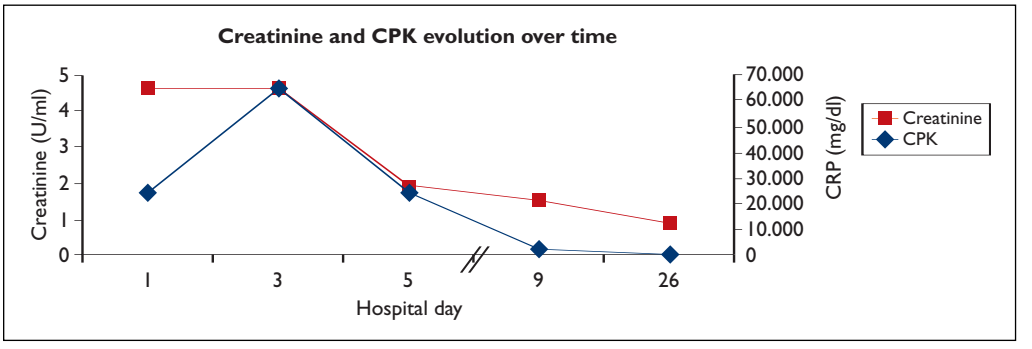

Figure 1. Evolution of creatinine and CPK over time

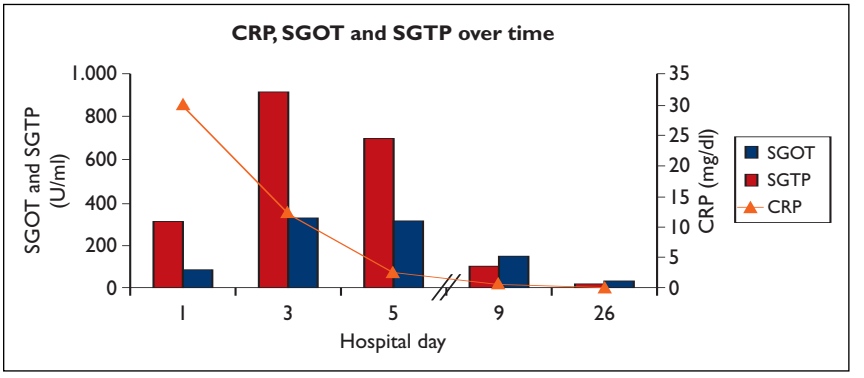

Figure 2. Evolution of creatinine and CPK over time

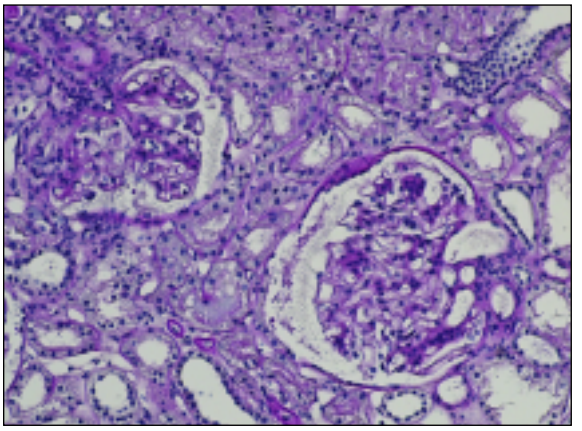

Figure 3. Two hyaline glomeruli with global sclerosis; chronic interstitial nephritis with fibrosis (PAS staining; magnification: 20x)

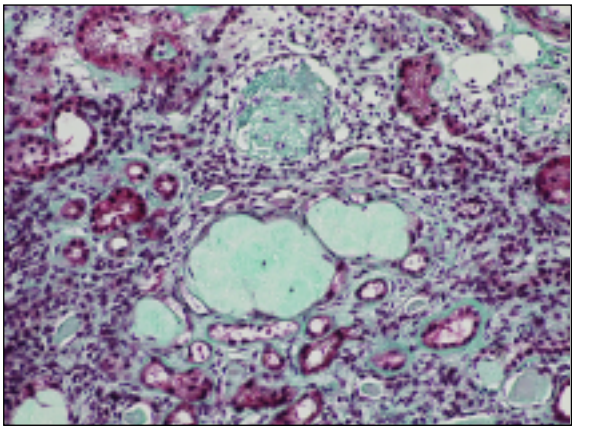

Figure 4. Two hyaline glomeruli and peritubular sclerosis with epithelial atrophy (Masson tricromic staining; magnification: 20x)

tradermal or patch testing is somewhat controversial and some contend that is particularly not helpful in autoimmune diseases like SLE.[3]

Oral challenge test with amoxicillin is the diagnostic gold standard test,[4] but in this patient it was contraindicated because she had a severe event and testing was potentially dangerous or even fatal. In this case, the positive intradermal test to amoxicillin helped to confirm the diagnosis.

The other major differential was sepsis from her dental infection. High fever, hypotension and elevated CRP made sepsis diagnosis very likely and thus the decision to treat her immediately with antibiotic. Knowledge of a previous allergy to Benzyl penicillin could have prevented this hospitalization; penicillin, amoxicillin and, to a lesser extent cephalosporins share extensive cross-reactivity.[5] One might also question the use of imipenem during her hospitalization as it is a β-lactamic and its cross-reactivity is not fully known.[6,7] Rhabdomyolysis is uncommon in amoxicillin DA, but is a known and rare adverse effect of simvastatin and thought to be dose-related. Hepatotoxicity has been described in amoxicillin and liver injury could interfere with the metabolism of simvastatin resulting in higher drug levels leading to muscle necrosis. Acute renal failure develops in 30-40% of patients with rhabdomyolysis. Suggested mechanisms include precipitation of myoglobin and uric acid crystals within renal tubules, decreased glomerular perfusion, and the nephrotoxic effect of ferrihemate (formed upon dissociation of myoglobin in the acidic environment of the renal parenchyma).[8]

Infection[2,7] and drugs,[9] including antibiotics can trigger a systemic lupus flare or the patient could have had a lupus flare not related to these. The presence of chills, neutrophilia, leucocytosis are thought to be markers of infection rather than SLE[11] and our patient had these features. The patient had SLE class IV diffuse glomerulonephritis since ten years before. On this admission, presence of fever, hypocomplementemia, lymphopenia, thrombocytopenia, elevated anti-dsDNA and almost nephrotic-range proteinuria (compared to her baseline) favours a lupus flare. A non-renal lupus flare is likely to have occurred. The reversal of acute renal failure could relate to improvement of the drug reaction but a lupus nephritis flare could also have improved with the increase in steroid therapy. However, the argument for a lupus nephritis flare is weak, since the renal biopsy showed no evidence of active lesions. Furthermore, the trial with mycophenolate mofetil produced no improvement, as expected from the biopsy.

In conclusion, the most likely causal pathway for the most severe manifestations was a type IV hypersensitivity reaction due to amoxicillin causing hepatotoxicity leading to increased simvastatin precipitating rhabdomyolysis and acute renal failure. Also, a non-renal lupus flare and possibly an infection likely occurred in this complex clinical case.

Correspondence to:
Maura Couto
Department of Rheumatology,
Coimbra University Hospital,
Coimbra, Portugal
E-mail: maura_couto@yahoo.com

Acknowledgments
We are extremely grateful to Dr Matthew Liang for his insightful comments that much contributed for the case discussion.

References

1. Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER. Drug Allergy. In Middleton`s Allergy, principles and practice. New York: Mosby Co, 2003: 1679-1694.
2. Pope J. Frequency of adverse drug reactions in patients with sytemic lupus erythematosus. J Rheum 2003; 30: 480-484.
3. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002; 57: 45-51.
4. Aberer W, Bircher A, Romano A et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy 2003; 58: 854-863.
5. Zandman-Goddard G, Shoenfeld Y. Infections and SLE. Autoimmunity 2005; 38: 473-485.
6. Gomez MB, Torres MJ, Mayorga C, Demoly P, DeWeck A. Immediate allergic reactions to betalactams: facts and controversies. Curr Opin Allergy Clin Immunol 2004; 4:261-266.
7. Kishiyama JL, Adelman DC. The cross-reactivity and immunology of beta-lactam antibiotics. Drug Saf 1994; 10:318-327.
8. Craig S. Rhabdomyolysis. eMedicine: Specialties: Emergency Medicine. Updated in 2008.
9. Rubin RL. Drug-induced lupus. In Wallace, D J.; Hahn, BH. Dubois' Lupus Erythematosus. Baltimore: Lippincott Williams & Wilkins, 2007: 874-875.
10. Pichler WJ. Drug Hypersensitivity reactions: Classification and relationship to T-Cell activation. In Drug Hypersensitivity. Basel: Karger, 2007: 168-189.
11. Stahl NI, Klippel JH, Decker JL. Fever in systemic lupus erythematosus. Am J Med 1979; 67:935-940.

V Jornadas de Reumatologia e Medicina Familiar do Algarve

Algarve, Portugal
30 a 31 de Outubro de 2009

4th European Workshop on Immune Mediated Inflammatory Diseases

Cascais, Portugal
18 a 20 de Novembro de 2009