

Therapy Side Effects in Systemic Lupus Erythematosus

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ABSTRACT: Glucocorticoids (GS) are widely used drugs for various inflammatory pathologies (Nephrotic syndrome, Proliferative glomerulonephritis, Extramembrane glomerulonephritis, Nephropathy of the Nodous Poliarterita (PAN), Nephropathy from purple Henoch-Schonlein, lupus nephropathy (LN), Acute adrenal insufficiency Waterhouse-Friederichsen, Chronic adrenal insufficiency Addison, Systemic Lupus Erythematosus (SLE), Polymyositis and dermatomyositis, Chronic granulomatosis, Crohn's disease, Hemorrhagic rectocolitis, Hemolytic anemias, Acute leukemias and chronic lymphocytic leukemia, Hodgkin's lymphoma). Although they are prescribed for their anti-inflammatory and immunosuppressive properties, they also have many side effects, hyperglycemia being one of the most common and representative, which is why these drugs need careful monitoring when administered over the long term. This paper presents the case of a 39 year old patient diagnosed with systemic lupus erythematosus (SLE) with class IV lupus nephropathy (LN) who developed numerous complications due to the pathogenic side effects: diabetes, amenorrhea, recurrent infections, and depression.

KEYWORDS: Corticotherapy, systemic erythematosus lupus, cortico-induced diabetes

Introduction

SLE is an autoimmune disease in the collagenosis group with systemic pathogenesis which, besides the immune imbalance, involves a whole series of genetic, environmental and hormonal factors.

Autoimmune diseases are defined as conditions in which the immune response to certain autoantigens is the cause of tissue damage.

SLE affects predominantly female sex (80-90%), suggesting an involvement of

estrogenic hormones in the pathogenesis of the disease.

The evolution of the disease is marked by periods of exacerbation and remission [1,2] but also by a whole series of complications: carbohydrate metabolism, protein, lipid metabolism, hydro-electrolyte disorders and disorders of endocrine, ophthalmic, dermatological, neuropsychiatric [1,3], LN occurs in 40-75% of the patients and is one of the most serious lesions of organ from SLE [4].

GS are widely used drugs in acute or chronic inflammatory pathology seen in Table 1

Table 1. Indication of glucocorticoids in various pathologies

Renal affections	Cortico adrenal affections	Collagenosis	Pulmonary affections	Digestive affections	Hematological affections
Nephrotic syndrome	Acute adrenal insufficiency Waterhouse-Friederichsen	SLE	Chronic Bronchitis intense	Crohn's disease	Acute leukemias and chronic lymphocytic leukemia

Proliferative glomerulonephritis	Chronic adrenal insufficiency Addison	PAN	Bronchial asthma	Hemorrhagic rectocolitis	Thrombocytopenic purpura
Extramembrane glomerulonephritis		Polymyositis and dermatomyositis			Hemolytic anemias
Nephropathy from purple Henoch-Schonlein		Chronic granulomatosis			Hodgkin's lymphoma
Nephropathy of the Nodous Poliarterita (PAN)					
LN					

GS reduce the synthesis of proinflammatory cytokines, Fc receptor antibody expression, T cell function, which activate anti-inflammatory and immunosuppressive processes, thus laying the foundations of SLE treatment [1].

Despite their effectiveness, their use is limited by the variety of associated side effects, and close monitoring is required (Table 2) [5].

Table 2. Side effects of the glucocorticoids [5]

SIDE EFFECT of Prednisone	TIME DEPENDENT	DOSE DEPENDENT	THE MINIMUM DOSE RESPONSIBLE FOR THE OCCURRENCE OF THE EFFECTS. ADVERSE (mg)
Osteoporosis	Yes	Yes	5
Hyperglycemia	Yes	Yes	2.5
Cushing's Syndrome	Yes	Yes	5
Cardiovascular disease	Yes	Yes	7.5
Increasing the risk of infection	Yes	Yes	5-7,5
Dermatology	Yes	Yes	Undefined
Glaucoma	Yes	Yes	7.5
Cataract	Yes	Yes	6
Psychological and behavioral	Yes	Yes	Undefined

Corticoid-induced diabetes, one of the most common adverse effects of glucocorticoids, is defined as an abnormal increase in serum glucose associated with their use in a patient with or without a history of Diabetes Mellitus (DM) [6].

Some of the risk factors for DM corticoinduced could be the dose and duration of action of the drug, but also traditional factors such as: patient age, heredo-collateral history, glucose tolerance, body mass index (BMI) [7].

From the pathophysiological point of view GS administration leads to increased gluconeogenesis and glycogen synthesis, eventually leading to the development of DM [8].

The diagnostic criteria of DM developed by the American Diabetes Association take into account:

-the glycemic value of jeun ≥ 7.0 mmol/L (126mg/dl), 2 hours after the oral glucose tolerance test (OGTT) ≥ 11.1 mmol/200mg/dl),

-glycosylated hemoglobin (HbA 1c) $\geq 6,5\%$ or patients with value of serum glycemia at any time of the day $> 11,1$ mmol/l (200mg/dl) [5].

HbA1c is useful in diagnosing DM in patients treated with corticosteroids for a period of 2 to 3 months, but not for patients whose treatment has been recently initiated.

Recently, Japanese researchers have developed an algorithm for cortico induced DM diagnosis suggesting that HbA1c level monitoring is of real importance. Patients who may be false elevated with HbA1c are those with hemoglobinopathy, renal insufficiency or anemia/recent blood transfusions or those with Hb1Ac within normal limits when initiating corticosteroid therapy, therefore measuring serum fructosamine value would be a better alternative [7].

Fructosamine is a marker of glycemic control over the past 2-3 weeks. Fructosamine has not gained popularity as Hb1Ac for DM control, the reasons being still unclear [9].

Therefore, the most useful criterion for the diagnosis of corticosteroid diabetes in most patients is serum glucose level > 200 mg/dl at any time of the day [1].

Case Report

The present paper presents the case of a 30-year-old rural smoker who presented herself in January 2016 at the Carol Davila Bucharest Nephrology Hospital with elevated TA (190/100mmHg), lower limb edema, arthralgia of the elbow and knee.

The clinical examination revealed the general altered condition of the patient, high blood pressure (TA=190/100mmHg), palpebral and sural edema and polyarthralgia, the rest of the clinical picture being within normal limits.

Laboratory data revealed the modified immunological profile, with elevated immune circulating complexes (CIC) values, low complement C3, high perinuclear Anti-Neutrophil Cytoplasmic Antibodies (pANCA), increased anti-ADN antibody, nephrotic proteinuria 3.6g/24h, dysmorphic red blood cells in the urine summary.

Table 3. Biological immunological balance

No	Investigation	Result
1	CIC	79,5 R.U/ml
2	IgG	1284mg/dl
3	IgA	234,2mg/dl
4	IgM	149mg/dl
5	complement 3	38,49g/L
	complement 4	7,28
6	cANCA	<0,2u/ml
7	pANCA	35u/ml
8	lupic anticoagulant	Positive
9	anticardiolipin antibody	>80GPL/ml

Table 4. Evolving inflammatory syndrome

No		Result	Result after GS initiation
1	VSH	124mm/ 1h	27mm/1h
2	Fibrinogen	807,7mg/dl	329mg/dl
3	PCR	16,7	4,6mg/l
4	Ferritin	275,3ng/ml	ng/ml

Corroborating the outcome of clinical and paraclinical data, suspicion of SLE with renal impairment was raised. In order to confirm the diagnosis, renal biopsy puncture was done, which established the diagnosis of glomerulonephritis lupus class IV with extra capillary proliferation, required initiation of corticosteroid therapy (methylprednisolone 1g for 3 days, then prednisone 1mg/kg for 30 days with gradual dose reduction, 10mg/day every 2 weeks up to a dose of 40mg/kg, cyclophosphamide 600mg intravenous/ 2 weeks, 3 pulses).

After about 2 weeks, renal function improvement and proteinuria reduction were obtained.

After about 7 months of remission, the patient discontinues immunosuppressive therapy on her own initiative, returning after 12 months with a creatinine value of 11.86g/dl, proteinuria/ 24h=6.9g/dl, serum albumin=2.2g/dl, for which reasons it was decided to admit to the Nephrology Clinic of the County Emergency Clinical Hospital from Craiova for further investigations and adequate therapeutic behavior.

Table 5. Biological balance in evolution

No	Investigation	Admission result	Result after initiation of GS and HD
1	Hb	10,1g/dl	8,2g/dl
2	Leukocytes	6450mm ³	12410mm ³
3	Platelets	235000mm ³	111240mm ³
4	Urea	173mg/dl	207mg/dl
5	Creatinine	11,8mg/dl	12,5
6	eRFG	4ml/min/1,73m ²	<4ml/min/1,73m ²
7	alkaline reserve	17mEq/l	20mEq/l
8	uric acide	6,33mg/dl	
9	Cholesterol	220mg/dl	
10	Triglycerides	121mg/dl	
11	Glycemia	97mg/dl	150mg/dl 6 o clock 169-97mg/dl 18 o clock
12	Hb1Ac	4,8%	
13	Calcium	7,1mg/dl	8,3mg/dl
14	Phosphorus	10,9 mg/dl	
15	IPTH	227,8pg/l	
16	Total proteins	4,6 g/dl	5g/dl
17	Seric albumin	2,6g/dl	2,8g/dl
18	Urinal summary exam	Proteinuria-2,5g/24h; 8,7g/24h, numerous red blood cell	
32	sputa BK, bacteriological		MRSA
33	Seric ionogram	Na 132mEq/l K 5,4mEq/l	124mEq/l 6,5-3,6mEq/l

Clinical examination has shown a general condition of an influenced patient, pale mucous, dehydrated, irregular skin lesions, exfoliated at the face and upper limbs level, massive sural edema and palpebral, stethacoustic pulmonary, no over added rales, TA=180/100mmHg, AV=40b/min (sinus bradycardia), rhythmic cardiac noises, pulsating peripheral arteries.

Urine summary: confirmed nephrotic serum, proteinuria/24h=8.94g, important inflammatory syndrome was shown in Table 3 and 4.

Electrocardiogram (EKG): does not reveal any special changes.

Abdominal-pelvic ultrasound: hepatosplenomegaly with homogeneous ecostructure, medium ascites fluid, VCI=21mm, both long-sleeved kidneys about 12.5cm, IP=1.5cm with hyperechogenic parenchyma, well differentiated pyramids, deleting differentiation cortico-medullary, without dilation of the urinary tract.

The following diagnoses have been made: systemic lupus erythematosus with lupus apophytis class IV with extracapillary proliferation, Corticoinduced diabetes mellitus, pANCA vasculitis, Antiphospholipid syndrome, Aggravated chronic kidney disease, treated by hemodialysis, secondary nephrotic syndrome, Hypoproteinemia with hypoalbuminemia, Moderate hypercholesterolemia, Secondary hypertension, Moderate secondary anemia, Mild hyperuricemia Secondary hyperparathyroidism, Moderate hypocalcaemia, Severe hyperphosphatemia, Metabolic acidosis.

In the therapy of the patient, targets were aimed at reducing systemic inflammation, decreasing disease activity, achieving remission of the disease, resuming diuresis and renal function, preventing relapse, counteracting the risk of complications, comorbidities and side effects associated with corticotherapy.

Non-pharmacological treatment was chosen to avoid cold, dampness, intense physical effort and exposure to the sun, and contraindications such as: smoking, alcohol consumption, water intake greater than 500ml. The diet should be hyperproteic, hypocarbohydrate, hypo-sodium, hypolipidic, with low purine intake.

The pharmacological treatment of SLE and vascular pANCA was related to the systemic and renal activity which required the initiation of pulse-therapy with methylprednisolone 1g iv for 3 days, then Prednisone 1mg/kg 30 with a decrease of 10mg/day from the dose to 2 weeks, until the dose is 40mg/day, then the dose will decrease by 5mg/day until you have a dose of

10mg/day and cyclophosphamide 600mg IV at 2 weeks 3 pulses.

For antiphospholipid syndrome, we have received antiaggregant, anticoagulant treatment as the anti-cardiolipin antibody titer was increased, the activated thromboplastin time is low, thus presenting a high risk of thromboembolic events.

The treatment of cardiovascular complications included loop diuretics, calcium receptor blockers, and statins. Low heart rate did not allow the administration of beta blockers.

For the complications of phosphocalcic metabolism were admitted: lactic calcium, phosphorus chelators.

Repeated clinical and paraclinical balance after initiation of corticotherapy was revealed in Table 5.

Considering the important nitrate retention (creatinine=12mg/dl, urea=207mg/dl), acid-base and hydro-electrolyte imbalance, oligoanuria and clinical evolution of the patient, it was decided to initiate renal replacement therapy by hemodialysis on CVC, is obtaining partial correction of hypoalbuminemia: 2.6→2.9mg/dl. The increase in glycemia (67mg/dl→140mg/dl) secondary to immunosuppressive therapy led to the diagnosis of secondary corticosteroid DM and hypoglycid diet with 250g carbohydrates in 5 meals was recommended. The Psychological and Psychiatric Examination established the diagnosis of corticosteroid-induced anxiety adjustment disorder.

The patient presented secondary under fever to a respiratory interference (productive cough, pulmonary stethacoustic, bronchial rallies) radiologically-increased vascular drawing, enlarged hills in the projection area. Bacteriological sputum revealed methicillin resistant *Staphylococcus aureus* (MRSA) thus allowing the formulation of the diagnosis of acute MRSA pneumopathy, subsequently treated with Clarithromycin 500mg 2 tablets/day 7 days (according to the antibiogram).

Discussion

GS played an important role in the pathogenic therapy of SLE, but their management also brought a whole series of adverse effects, especially those that were administrated in the long term, but can occurred in the short term. These were endocrine side effects (amenorrhea, azoospermia, Corticosuprarenale hypoplasia), metabolic (DM, hyperglycemia), bone, dermatological (purpura, acne, hirsutism), ophthalmology (cataract,

reversible glaucoma, myopia) psychological and psychiatric (psychoses, depressions nervousness, euphoria) [3,10,11]. These were mainly linked to the mechanism of genomic action and were dose-dependent and therapy duration-dependent [1].

At the metabolic level, glucocorticoids increased the risk of hyperglycemia in both DM and non-DM patients [1], as was the case with this patient displaying elevated blood glucose levels approximately 3 days after initiation of corticotherapy.

The patient was being monitored glycemic at the time of admission, but also during GS therapy, because nearly 94% of cases of hyperglycemia developed within 1-2 days of initiating steroid therapy in non-diabetic patients. If you maintained your blood sugar <140mg/dl without having insulin about 24-48 hours, glycemic monitoring may be interrupted [5], according to specialized publications.

The GS effect is usually transient and reversible. As steroid doses were reduced, their effect on endocrine metabolism returned to initial value, and GS-induced diabetes will be remitted; however, this was not a general rule [1,4].

Another apparent side effect after GS in this case was Pneumonia with MRSA, because these drugs had an immunosuppressive effect, resulting in a decrease in the number of elements responsible for the immune process, so there is a decrease in anti-infectious protection [3], being a cause the importance of morbidity and mortality in many inflammatory pathologies. This adverse effect were dose-dependent and treatment duration-dependent, although the literature was not accurate if there was a limit threshold below which glucocorticoid therapy was safe [5]. However, lung infections also occurred in clinical manifestations of SLE is dry or wet pleurisies (40 to 60%); lupus pneumonia and pulmonary fibrosis are rare [2]. no additional investigations were required in view of the favorable progression of the patient from the pulmonary point of view.

Another apparent adverse effect of GS administration was amenorrhea being affirmed anamnesis, not being investigated endocrinologically and gynecologically during admission.

According to GS, at high doses it lowers estrogen and testosterone levels, but infertility or decreased libido has not been established, but may also be a secondary premature ovarian failure SLE [9].

Glucocorticoids could have caused psychological and behavioral disorders, including mood disorders, sleep and psychosis, as has been seen in the patient's case. The most common side effects of glucocorticoid treatment are short-term euphoria and hypomania, while long-term therapy could induce depressive symptoms. These disorders were dose related and may occurred immediately after initiation of treatment, sometimes requiring association of GS with neurosedatives [12], but considering the patient's mild symptomatology, no medical treatment was required.

The prognosis and progression of the patient after approximately 6 months was favorable in terms of systemic SLE activity and secondary side effects of GS therapy, but it was not favorable for lupus nephritis because nitrate retention and anuria was counter-sparing for discontinuation of renal substitution therapy through hemodialysis. This case accounts for 25-30% of patients who do not respond to treatment is associated with worse renal outcomes [13].

Conclusion

The widespread use of GS in the medical field requires careful monitoring of patients in order to diagnose and correct the adverse effects of these therapeutic agents. Early detection of adverse events associated with corticotherapy is required by careful monitoring of biological constants to prevent the development of diabetes, infections, glaucoma, cataracts, cardiovascular disease, osteoporosis, major depression.

Immunosuppressive medication is a challenge for the clinician by dosing and continuously adjusting doses according to the clinical-biological status of the patient with the objective of reducing the activity of the disease and minimizing adverse effects.

Abbreviations

Glucosteroids (GS), systemic lupus erythematosus (SLE), lupus nephropathy (LN), Nodous Poliarterita (PAN), Diabetes mellitus (DM), Body mass index (BMI), glycosylated hemoglobin (HbA 1c), blood pressure (TA), immune circulating complexes (CIC), anti-neutrophil cytoplasmic antibodies (p-ANCA), Cytoplasmatic antineutrophil cytoplasmic antibodies (c-ANCA) renal biopsy puncture (PBR), methicillin resistant Staphylococcus aureus (MRSA).

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