Skin Eruption and Thrombocytopaenia in a Woman with Glaucoma

A Case Report

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ABSTRACT

Antibiotic and non-antibiotic sulphonamides are often prescribed. Although chemical differences make cross-reactivity rare, reactions may be severe in patients allergic to sulphur. Adverse reactions are common with sulphonamides but low platelets and skin changes are rarely associated with eye-drops for glaucoma. A woman treated with dorzolamide and timolol presented with disseminated eruption. On admission, her physical examination was unremarkable except for the skin changes and severe thrombocytopaenia was detected. Skin biopsy showed hyperkeratosis, acanthosis, perivascular and periadnexal infiltrates with no vasculitis. After discontinuation of eye-drops, the eruption improved but low platelets persisted. Skin changes reappeared with use of dapsone which suggested sulphonamide cross-reactivity.

Keywords: Glaucoma; Skin eruption; Sulphonamide side effect; Thrombocytopaenia.

Erupción Cutánea y Trombocitopenia en una Mujer con Glaucoma

Reporte de un Caso

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RESUMEN

A menudo se prescriben sulfonamidas antibióticas y no-antibióticas. Aunque las diferencias químicas hacen que la reactividad cruzada sea algo raro, las reacciones pueden ser severas en los pacientes alérgicos al azufre. Las reacciones adversas son comunes con las sulfonamidas pero las plaquetas bajas y los cambios en la piel raramente se asocian con las gotas oculares para el glaucoma. A una mujer a quien se le hizo un tratamiento con dorzolamida y timolol, se le presentó una erupción diseminada. En el momento del ingreso, su examen físico fue común y corriente excepto por los cambios en la piel. Además se le detectó una trombocitopenia severa. La biopsia de la piel reveló hiperqueratosis, acanthosis, infiltrados perivasculares y periadnexales sin vasculitis. Tras descontinuar las gotas oculares, la erupción mejoró pero las plaquetas bajas persistieron. Los cambios de la piel reaparecieron con el uso de dapsona, lo que hizo pensar en una reactividad cruzada de la sulfonamida.

Palabras claves. Glaucoma, erupción cutánea, sulfonamida, efecto secundario, trombocitopenia

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INTRODUCTION

Glaucoma occurs with high prevalence among individuals of African descent in Brazil and the Caribbean and may often go undiagnosed and untreated (1). Moreover, data from the Barbados Eye Study suggest excess of cardiovascular mortality believed to be related to timolol (2). Dorzolamide and timolol are often used for glaucoma. Skin changes or low platelets are rarely described in association with these medications (3–5). Coexistent skin eruption and thrombocytopaenia during the treatment of glaucoma is reported.

CASE REPORT

A 63-year old Brazilian woman was admitted in March 2007 with scattered skin lesions that appeared over the previous four months. She reported dizziness and severe loss of vision due to chronic glaucoma which was treated with dorzolamide plus timolol maleate eye-drops. She denied fever, weight

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loss or atopic tendency. She did not use alcohol, tobacco or illicit drugs and did not have animal pets. There was family history of hypertension, diabetes mellitus, uterine cancer and glaucoma (sister and daughter). She reported treatment for syphilis in 1995 and in 2005 she was administered a new course of penicillin in another hospital, allegedly to treat similar skin lesions.

The slightly painful and non-pruritic reddish papules first appeared on her face and upper extremities; and, except for the scalp, palms and soles of the feet, there was a wide dissemination of the skin lesions. The papules evolved to serous-containing ulcerative lesions followed by crusts which healed leaving hyper-and hypo-pigmented maculae and with varicella-like scars. Co-existent lesions were observed in different phases of evolution (Fig. 1) and some had an iris-like feature.

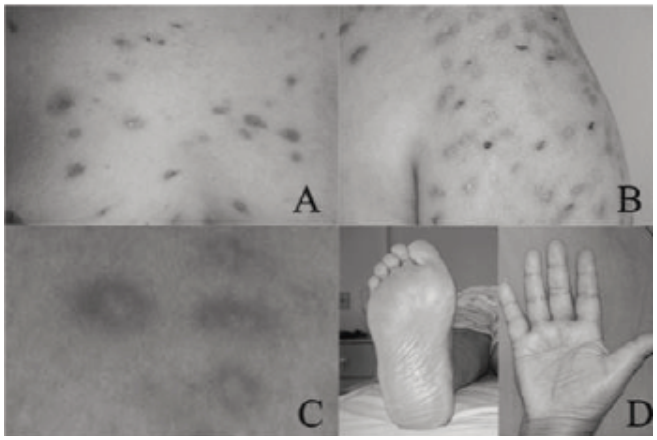

Fig. A to 1C. Diffuse papules, healed ulcers, hyper-and hypopigmented maculae and few varioliform scars. The lesions appear in various stages of evolution, some with iris-like appearance.

Fig. 1D. Absence of lesions in the palm and sole areas.

On admission, her Body mass index (BMI) was 36.9 kg/m^2. Laboratory results showed severe thrombocytopaenia (Table 1), not responsive to platelet transfusions. In addition, Venereal Disease Research Laboratory (VDRL) test was reactive (1:2), FTA-ABS-positive IgG, Herpes virus 1 and 2 IgM and HIV 1 and 2- negative, antinuclear factor: negative, cancer antigen 19–9 (8 U/mL) and carcinoembryonic antigen (0.4 ng/mL) were unremarkable. The skin biopsy sample was negative for spirochaetes (Warthin) and acid-fast bacilli (Fite-Faraco) and showed superficial and deeper perivascular dermatitis with post-inflammatory pigmented changes. The epidermis showed focal areas of hyperkeratosis and acanthosis, angiectasis, hyperaemia, perivascular and peri-adnexal lymphocyte infiltrates and mild fibrosis were observed in the superficial dermis (Fig. 2A and 2B). Worthy of note, keratinocyte apoptosis, exocytose, plasmocytosis, vasculitis or CD30$^+$ cells were not found. Immunohistochemical studies of the lymphocytes were positive utilizing the following clones: CD3 (F7.2.38), CD4 (1F6+4B12), CD8 (C8/144B) and CD20 (L26). The tests disclosed predominant CD3$^+$ lymphocytes around the vessels (Fig. 2C), in addition to CD8$^+$ and CD4$^+$ lymphocyte populations, while CD20$^+$ cells were seen rarely. Bone marrow smears showed no abnormalities, except for an increased number of mature and young megakaryocytes and the search for IgM and IgG specific anti-platelet antibodies were negative.

Table 1: Admission blood tests and controls from a woman with pityriasis lichenoides-like eruption and low platelets associated with chronic use of dorzolamide eye-drops.

Test	Day 1	Day 23	Reference range and units
White blood cells	7.2	9.9	4.5–11 (x 10^9/L)
Red blood cells	5.19	4.54	4.3–5.7 (x 10^{12}/L)
Hematocrit	45.8	40.0	39–49 (%)
Haemoglobin	15.1	13.9	13.5–17.5 (g/dL)
MCV	88.0	87.0	80–100 (fL)
MCHC	33.0	35.0	31–37 (%)
Platelets	32.0*	34.0*	150–450 (x 10^9/L)
Urea	22.0	32.0	10–50 (mg/dL)
Creatinine	1.0	0.9	< 1.3 (mg/dL)
Uric acid	3.1	4.0	2.0–5.0 (mg/dL)
Albumin	4.8	4.2	3.5–5.0 (g/dL)
Globulin	2.8	2.5	< 4.0 (g/dL)
Glucose	100.0		70–100 (mg/dL)
AST	30.0		< 33 (U/L)
ALT	23.0		< 32 (U/L)
GGT	73.0		7–32 (U/L)
AP	133.0		65–300 (U/L)
Free T4	1.1		0.7–1.48 (ng/dL)
TSH	1.5		0.35–4.94 (μU/mL)
Fibrinogen	329.0		200–400 (mg/dL)
CRP	1.3	0.8	< 0.3 (mg/dL)
ESR	29.0	57	< 20 (mm/hour)
Amylase	67.0		< 125 (U/L)
Lipase	50.2		5–60 (U/L)
Total cholesterol	196.0		< 240 (mg/dL)
LDL	119.0		< 160 (mg/dL)
HDL	49.0		35–85 (mg/dL)
Triglycerides	137.8		< 150 (mg/dL)
PA	84.0	91.0	70–100 (%)
APTT	31.9	29.8	25–40 (second)
Bleeding time	2.0		1–5 (minute)
Coagulation time	8.0		2–10 (minute)
Clot retraction	Complete		Complete
Capillary fragility test	Negative		Negative

AP = alkaline phosphatase, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, PA = prothrombin activity, INR = international normalized ratio, APTT = activated partial thromboplastin time. *Indicates abnormal values.

After cessation of dorzolamide and administration of fexofenadine, all the active cutaneous changes rapidly disappeared. With a diagnosis of skin eruption associated with eye-drops, the patient was sent for haematological evaluation to better clarify the origin of her low platelets. In May 2007, as the platelet count persisted at a very low level (31 x 10^9/L), she received Diamino Diphenyl Sulphone (DDS) [100 mg/day] and, one month later, the platelet count improved to 152 x 10^9/L which was considered a good therapeutic response. Nevertheless, concomitantly with the use of DDS, a flare-up of the skin lesions recurred (Fig. 2D). There was no lymph node enlargement or fever but the cutaneous eruption

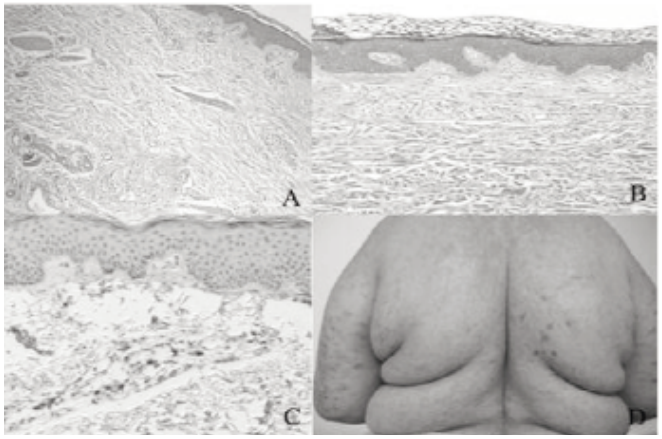

Fig: 2A and 2B. Epidermic focal area of acanthosis and hypergranulosis, in addition to superficial and deep dermal lymphocytic infiltrate in perivascular and periadnexial areas (Haematoxylin and eosin).

Fig: 2C. Immunohistochemistry positive reaction for CD3 T-lymphocytes mainly distributed in the dermal perivascular areas and scarcely found in the basal epidermis. (Biotin-streptavidin-peroxydase).

Fig: 2D. Acute lichenoid eruption observed after the dapsone utilization.

developed in association with moderate liver changes (AST 89 U/mL, ALT 97 U/mL, GGT 205 U/mL, and AP 115 U/mL) as typically described in the early phase of dapsone hypersensitivity syndrome (6) and this drug was discontinued.

DISCUSSION

After the use of topical dorzolamide plus timolol maleate to treat glaucoma, this Brazilian woman was admitted with co-existent asymptomatic thrombocytopaenia and widespread skin eruption.

Because of the antecedent syphilis, which had been treated with courses of penicillin, she presented weakly positive VDRL and FTA-ABS tests. Although a possible concern could be secondary syphilis, the papular rash spared the scalp, palms and soles of feet and the search for *Treponema pallidum* was negative in tissue samples. The polymorphism of the lesions, some with an iris-like aspect, favoured the hypothesis of drug-induced erythema multiforme, a diagnosis that was consistent with the biopsy findings. Notwithstanding, as several lesions appeared with lichenoid features, the differential diagnosis of her skin changes also included psoriasis guttata, pityriasis rosea, lichen planus, vasculitis, lymphomatoid papulosis and pityriasis lichenoides (PL). Except for PL, the clinical data, the laboratory tests and the biopsy findings ruled out other differential diagnoses. Pityriasis lichenoides may develop as an acute, subacute or chronic eruption of erythematous papules which evolve to multiple polymorphic lesions with hyper/hypopigmentation and varicella-like sequels (7). Classical histopathological features of chronic PL include dermal perivascular and periadnexal lymphocytic infiltration extending to the deep reticular dermis, similar to the present case (7). The epidermis usually shows parakeratosis, with $CD3^+$, $CD4^+$ and $CD8^+$ lymphocyte infiltrates around the vessels, the adnexal epithelia and the hair follicles. Moreover, co-existent PL and idiopathic thrombocytopaenic purpura were reported (8). Based on these data, and because of a possible association with adverse drug-reactions (7), the hypothesis of PL was a major initial concern. Another concern in the present case was the possibility of glaucoma worsening after eventual corticosteroid utilization for skin changes, but the symptoms were successfully controlled after the use of fexofenadine.

Her bone marrow biopsy disclosed a large number of megakaryocytes and the platelet counts did not rise after eye-drops were discontinued, a phenomenon strongly suggestive of consumption or peripheral destruction. Drug-induced thrombocytopaenia includes bone marrow suppression and increased peripheral destruction by non-immune or immune mechanisms (9). The median time to the platelet count normalization is about seven days after drug withdrawal, and if the time to recovery is prolonged (> 60 days) or recurrent thrombocytopaenia occurs, the hypothesis of idiopathic thrombocytopaenic purpura (ITP) must be ruled out (10, 11). Unlike ITP, auto-antibodies reacting with platelet-specific antigens were not detected in the patient while the tests for drug-dependent antiplatelet antibodies were not performed (10). Patients with a suspicion of drug-induced thrombocytopaenia have been treated like ITP, with corticosteroids or dapsone (DDS) because of the usual difficulties in differentiating these conditions. Notwithstanding, in addition to the concern about glaucoma, no difference in recovery between corticosteroid-treated and untreated patients has been found (11). Therefore, she started a course of dapsone (100 mg/day) aiming to normalize the platelet count. However, this drug had to be discontinued because of the reappearance of the skin eruption and abnormal serum liver enzymes. These changes occurred just after the subsequent receipt of another kind of sulphonamide which indicates drug cross-reactivity (CR). Dorzolamide ($C_{10}H_{16}N_2O_4S_3$) is 4-ethylamino-6-methyl-7, 7-dioxo-5, 6-dihydro-4H-thieno[5, 4-b]thiopyran-2-sulfonamide while DDS ($C_{12}H_{12}N_2O_2S$) is 4-[(4-Aminophenyl) sulphonyl]aniline. Due to stereo-specificity of T-cell responses, the CR between sulphonamide antibiotics and non-antibiotics is considered unlikely and due to multiple allergies rather than hypersensitivities (12); however, CR has been described between DDS and sulphonamide antibiotics (13).

As far as the authors are aware, there is no previous report about co-existent skin eruption and low platelets associated with anti-glaucoma eye-drops. In some Latin American countries, published research or systematic studies on drug reactions have been rare, although the Drug Surveillance Centres have played an important role in pharmacovigilance (14). Additionally, post-marketing reports of suspected drug reactions and the resurgence of severe events like thalidomide embriopathy may not follow a formal surveillance system (15). More recent reports about adverse effects of dorzolamide eye-drops have included local

changes, more extensive allergic contact dermatitis and life-threatening erythema multiforme (16–18).

Despite the inherent limitations of a single case description, the aim of this report is to alert physicians to possible systemic adverse effects of anti-glaucoma eye-drops.

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