DERMATOLOGICA SINICA 32 (2014) 183–186

Contents lists available at ScienceDirect

Dermatologica Sinica

journal homepage: http://www.derm-sinica.com

CASE REPORT

Ticlopidine-induced subacute cutaneous lupus erythematosus: A case report and literature review

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ARTICLE INFO

Article history:
Received: Jul 5, 2013
Revised: Dec 30, 2013
Accepted: Jan 2, 2014

Keywords:
lupus erythematosus
ticlopidine

ABSTRACT

Many drugs have been reported to induce lupus in a minority of patients. Ticlopidine hydrochloride inhibits platelet aggregation and is widely used for the prevention of thrombosis. There have been only a few reports of ticlopidine-induced lupus. Here, we review 13 previously reported cases and describe the case of a 71-year-old man with ticlopidine-induced subacute cutaneous lupus erythematosus. His diagnosis was supported by the appearance of papulosquamous skin lesions on sun-exposed areas and detectable anti-Ro/SS-A antibodies, shortly after drug initiation as well as the gradual resolution of these symptoms after the discontinuation of ticlopidine. Our case highlights that when a patient presents with subacute cutaneous lupus erythematosus-like skin lesions, ticlopidine should be considered as a potential causative agent.

Introduction

Since the report of skin reactions to hydrochlorothiazide in conjunction with Ro⁄SS-A autoantibody after the drug was first introduced in 1985,[1] more than 40 types of drugs have been reported to induce subacute cutaneous lupus erythematosus (SCLE).[2–4] Ticlopidine hydrochloride is a platelet aggregation inhibitor used as a substitute for aspirin in patients who cannot tolerate the side effects of aspirin.[5] It is commonly prescribed for stroke prevention[6] or after coronary artery stenting to prevent thrombosis based on Food and Drug Administration-labeled indications. Common adverse drug reactions of ticlopidine are diarrhea, exanthematus eruptions, and rarely neutropenia or bone marrow aplasia.[7] Ticlopidine-induced SCLE is extremely rare. Here, we describe the case of a patient with ticlopidine-induced SCLE who was diagnosed based on his clinical medication history, and the clinical, histological, and immunopathological results.

Case report

A 71-year-old man suffered from multiple skin rashes on his trunk and limbs for 2 months. The rashes did not respond to topical steroid treatment. On physical examination, many scaly reddish papules and plaques were observed on the scalp, face, forearms, upper chest, and upper back (Figure 1A–C). He showed no sign of fever, arthralgia, myalgia, pleurisy, or pericarditis. The distribution of the skin rash was mainly on sun-exposed areas, and thus, SCLE or photosensitive lichenoid drug eruption was considered. Blood tests, urine tests, and incisional biopsy for pathology and immunofluorescence were performed.

Based on the medical and medication history, he had suffered from essential hypertension, benign prostate hyperplasia, and type 2 diabetes mellitus for many years. He was persistently treated with losartan, isosorbide dinitrate, propranolol, tamsulosin, desmopressin, bromazepam, acarbose, glimepiride, and sitagliptin without change for more than 1 year. He was diagnosed with cardiovascular disease after coronary artery stenting that occurred 2 years prior to admission. Subsequently, he had taken aspirin for thrombus prevention until 4 months ago when he was prescribed ticlopidine hydrochloride as an aspirin substitute due to gastrointestinal discomfort.

The blood test results revealed anemia (hemoglobin: 9.8 mg/dL) and the urine test results suggested proteinuria. The other test items, including liver and renal functions, were within the normal

Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

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1027-8117/$ – see front matter
http://dx.doi.org/10.1016/j.dsi.2014.01.001

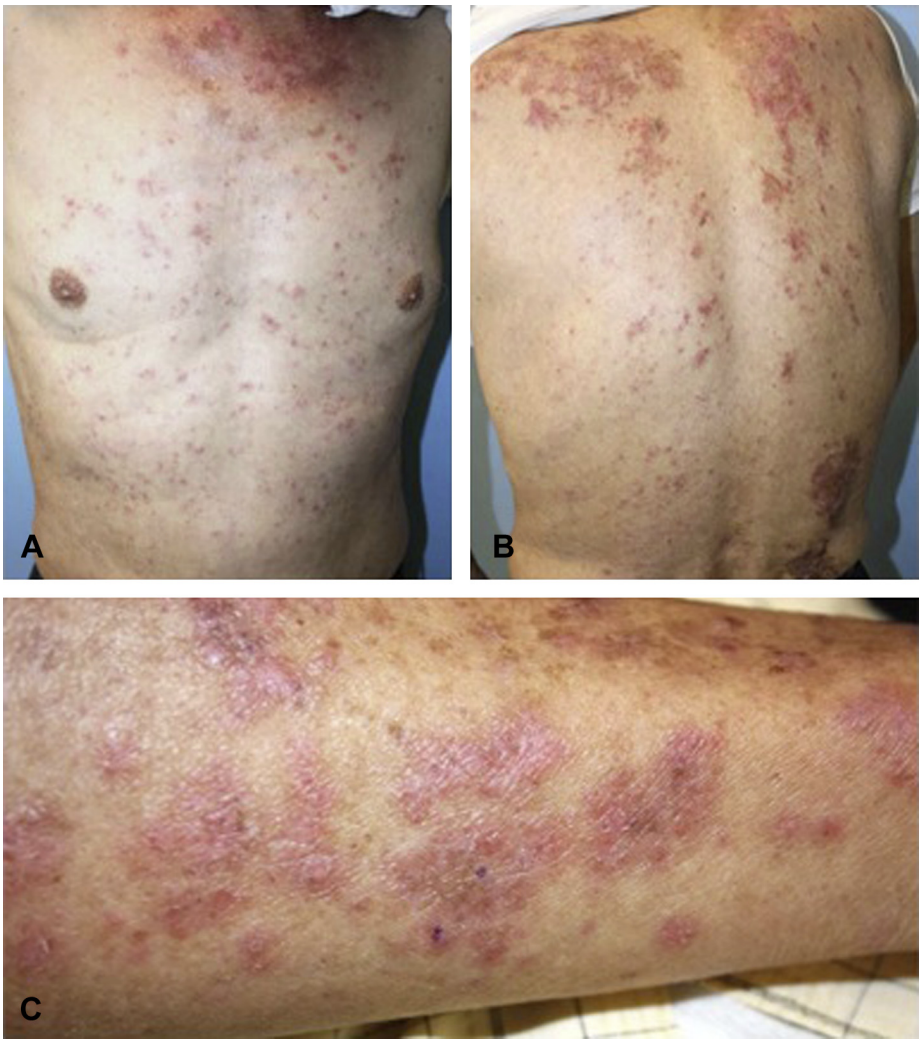

Figure 1 Multiple scaly erythematous plaques on the (A) upper chest and (B) upper back. (C) A close view of the reddish papulosquamous papuloplaques on the extensor side of the right forearm.

range. Circulating antinuclear antibodies (ANAs) were detected (antinuclear factor 40X; speckled/centromere) and identified as anti-Ro antibodies (anti-Ro 347 AU/mL; normal range: <120 AU/mL). Other tests to survey for connective tissue disease were within normal limits, including C3, C4, and anti-double-stranded DNA.

Histological examination revealed diffuse vacuolar degeneration of the basal layers of keratinocytes (Figure 2A and B) and mild to moderate lymphocytic perivascular infiltrates in the upper dermis. There was focal parakeratosis and lymphocytic exocytosis in the epidermis, but neither an increase in dermal mucin deposition nor basement membrane thickening was observed. Eosinophils were rare. Direct immunofluorescent tests of the involved skin showed deposition of cytoid bodies that expressed immunoglobulins (Ig), including IgA, IgG, and IgM (Figure 2C and D). There was also fibrinogen deposition along the dermal–epidermal junction. The overall features represented interface dermatitis and were consistent with a connective tissue disorder such as lupus erythematosus or dermatomyositis.

Dermatomyositis was less likely because of the absence of muscle weakness and normal blood tests for muscle enzymes. The diagnosis after clinicopathological correlation was SCLE. The presence of anti-Ro antibody and his medication history raised the possibility of drug-induced SCLE. Ticlopidine hydrochloride, the only recent addition to the medical regimen, was highly suspected. He was asked to discontinue oral ticlopidine, and a topical potent steroid (0.05% fluocinonide) was prescribed without oral medication. After discontinuation of ticlopidine, the skin lesions rapidly improved and completely subsided 4 weeks later. Therefore, no further blood test was performed. Lesions did not recur during the 1-year follow-up period.

Discussion

There have been only 12 cases of ticlopidine-induced lupus and only two cases of ticlopidine-induced SCLE reported in the literature (Table 1).[8,15–20] The time from ticlopidine exposure to the onset of drug-induced lupus varied from 1 week to 4 years. Most patients started to feel better after discontinuing ticlopidine for several weeks and completely recovered after several months. ANAs and antihistone antibodies are a common finding in drug-induced lupus and are detected in almost all ticlopidine-induced systemic lupus cases. ANAs and Ro/SS-A autoantibodies were detected in both cases of ticlopidine-induced SCLE. The case of ticlopidine-induced SCLE reported in Poland[8] shares many similar

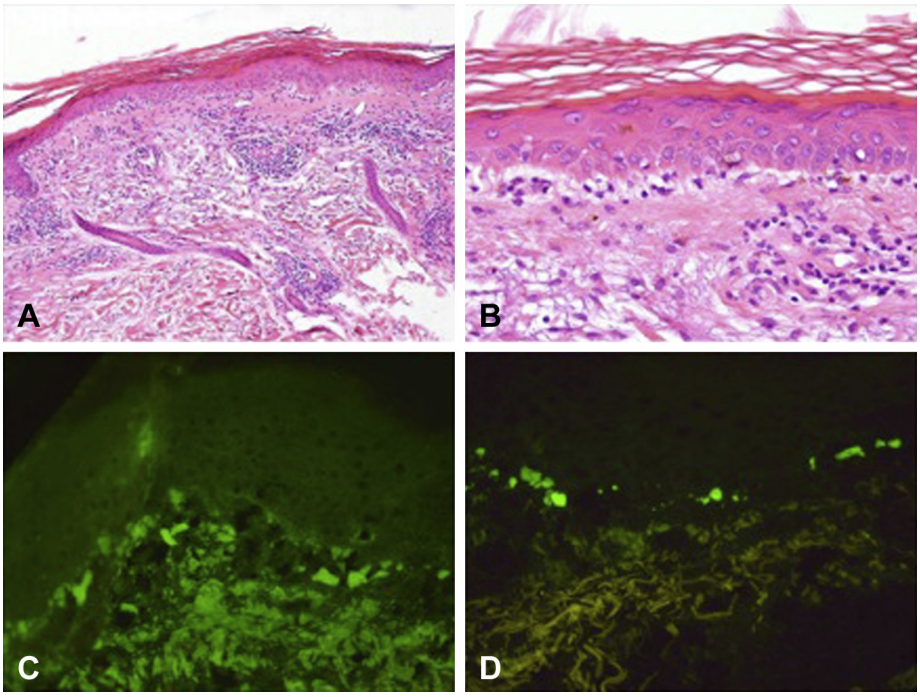

Figure 2 (A) Histopathological analysis (scanning magnification) showed moderate superficial and deep perivascular infiltrates. (B) High-powered images demonstrated diffuse vacuolar degeneration of the basal keratinocytes [hematoxylin and eosin: (A) 100×; (B) 400×]. (C) Many immunoglobulin G (IgG)-deposited ovoid bodies were present at the dermal–epidermal junction and papillary dermis. (D) Scattered IgM-deposited ovoid bodies at the dermal–epidermal junction [direct immunofluorescence test: (C) 400×, (D) 400×].

findings with our patient, including old age (age >70 years), the presence of anti-Ro/SS-A autoantibodies, interface dermatitis, and the resolution of cutaneous lesions soon after discontinuing ticlopidine.

There is no significant difference between drug-induced and non-drug-induced SCLE based on clinical, histopathological, or immunopathological features.[9,10] Both present with annular/papulosquamous lesions occurring mainly in sun-exposed areas, interface dermatitis with perivascular lymphocytes infiltration, and detectable ANA, anti-Ro/SS-A (a positive result is obtained in more than 80% of cases[2]), or occasionally anti-La/SS-B autoantibodies. Attempting to distinguish drug-induced from non-drug-induced SCLE by tissue eosinophilia is not reliable or feasible.[11] One clue for a physician to consider is that drug-induced SCLE often affects

Table 1 Summary of previous reports and present case on ticlopidine-induced lupus erythematosus.

Ref.	Age (y)	Sex	Presentation	Immunological finding	Duration of exposure	Resolution time	Treatment
Japan[15]	81	M	Fever, arthralgia, myalgia, pericardial effusion	ANA (1:640), antihistone	4 y	5 min	Prednisolone 30 mg/d + pulse therapy
	76	M	Fever, pleural effusion, myalgia	ANA (1:2560), antihistone	1 y	4 min	Nil
Japan[16]	71	M	Fever, arthralgia, pleural effusion + mesangial proliferative glomerulonephritis	ANA (1:640), antihistone, anti-dsDNA, anti-ssDNA	2 y	2 min	Prednisolone 15 mg/d
Japan[17]	55	M	Fever, arthralgia, under hemodialysis	ANA, antihistone, anti-dsDNA	7 mo	Weeks	Nil
Japan[18]	62	M	Arthralgia, pleuritis	ANA	9 mo	—	Nil
USA[19]	74	M	Fever, polyarthritis, myalgia	ANA, antihistone	9 mo	2 min	Prednisolone 5 mg/d
	76	F	Polyarthritis, myalgia	ANA, antihistone, anti-dsDNA	<1 y	1 min	Prednisolone 5 mg/d
	73	F	Serositis, arthritis	ANA, antihistone, anti-dsDNA, anticardiolipin	4 y	3 min	Prednisolone 20 mg/d + MTX
	67	F	Pleurisy, polyarthritis	ANA, antihistone, anti-dsDNA	1 y	10 min	Prednisolone 5–10 mg/d, hydroxylchloroquine
Israel[20]	77	M	Polyarthritis, urticaria	ANA, antihistone	2 wk	2–3 min	NSAID
	69	F	Fever, arthritis, proteinuria	ANA, antihistone, anti-dsDNA	2 min	3 min	Prednisone 15–30 mg/d
	53	M	Fever, polyarthritis	ANA, antihistone	2 wk	4 min	Nil
Poland[8]	76	F	Annular SCLE	ANA, anti-Ro	1 wk	4 min	Topical potent steroid
Taiwan	71	M	Annular SCLE	ANA, anti-Ro	4 min	4 wk	Topical potent steroid

ANA = antinuclear antibody; anti-dsDNA = anti-double-stranded DNA; anti-ssDNA = anti-single-stranded DNA; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; SCLE = subacute cutaneous lupus erythematosus.

older individuals presenting with SCLE for the first time, particularly those being treated with antihypertensive or antifungal agents.[2,3,12] Although the golden standard for a definite diagnosis is a rechallenge test, it is not ethical in most situations. Therefore, a diagnosis can also be made if a complete recovery is achieved after halting the suspected medication.

The pathogenesis underlying drug-induced SCLE is unclear, but is probably multifactorial and complex.[10,13] Reed et al[1] proposed possible mechanisms that included enhancing Ro/SS-A antigen expression, enhancing epidermal cytotoxicity through direct phototoxicity, or enhancing anti-Ro/SS-A antibody production. In the review by Lowe et al[3] and the study by Sontheimer et al,[4] many drugs that trigger SCLE were argued to do so by inducing a photosensitivity state. There has been no report that ticlopidine could cause a photosensitive reaction but its chemical analog, the thienopyridine (clopidogrel), has been reported to induce photosensitive lichenoid eruption.[14]

In conclusion, ticlopidine-induced lupus erythematosus is a rare entity. Drug-induced SCLE should be considered when elderly patients present with an SCLE-like skin rash that is confirmed by histological analysis. Physicians should review the complete medication history and identify the possible candidate drug. Discontinuation of the causative drug and sun protection are the best way to treat patients who have drug-induced LE, rather than systemic corticosteroid treatment that may result in complications in these patients.

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