

## Clopidogrel and Ticlopidine Cross-reactivity–Induced Erythroderma Following Drug-Eluting Stenting

To the Editor:

Erythroderma, a potentially fatal dermatologic emergency, is a scaling erythematous eruption involving 90% or more of the cutaneous surface.<sup>1</sup> Psoriasis, mycosis fungoides, Sézary syndrome, and atopic dermatitis may culminate in the presentation of erythroderma. Several drugs also have been implicated.<sup>1</sup> A thienopyridine derivative, such as clopidogrel or ticlopidine, in combination with aspirin is the gold standard of care after percutaneous coronary intervention (PCI) with stenting.<sup>2</sup> We present a patient who developed erythroderma after undergoing drug-eluting stent (DES) implantation.

A 76-year-old man presented for a coronary angiogram because of a stable angina and a positive exercise test. His medical history included hypertension, dyslipidemia, and myocardial infarction. The patient was on aspirin, carvedilol, enalapril, and atorvastatin. Coronary angiography revealed a critical stenosis in the right coronary artery, and the patient underwent PCI with DES implantation. He was given a loading dose of 600 mg of clopidogrel before PCI followed by clopidogrel 75 mg once daily.

Twenty days after clopidogrel administration, the patient developed a limited itching rash on his abdomen and chest that gradually spread to the back, neck, and face. Our initial diagnosis was a drug-induced rash due to clopidogrel. Clopidogrel was switched to ticlopidine 250 mg twice daily and oral methylprednisolone 4 mg once daily (with gradual dose tapering) was started with rash recession. One and a half months later, the patient was readmitted with a diffuse, erythematous, pruritic exfoliative rash. He reported malaise and chills. On physical examination he had a fever (temperature, 38.5°C),

hypotension (95/60 mm Hg), and ankle edema. The laboratory tests showed an elevated white blood cell count of 11,000/ $\mu$ L (reference range, 4500–11,000/ $\mu$ L) with neutrophils (74.8%); an erythrocyte sedimentation rate of 68 mm/h (reference range, 0–20 mm/h); C-reactive protein level of 2.79 mg/L (reference range, 0.08–3.1 mg/L); blood urea nitrogen level of 57 mg/dL (reference range, 8–23 mg/dL); creatinine level of 1.47 mg/dL (reference range, 0.6–1.2 mg/dL); and decreased total proteins (5.6 g/dL [reference range, 6.0–8.0 g/dL]) and albumin (2.93 g/dL [reference range, 3.5–5.0 g/dL]). Our diagnosis was drug-induced erythroderma due to ticlopidine. Ticlopidine was withdrawn, and intravenous fluid, methylprednisolone, and oral antihistamine were administered. His aspirin intake was increased from 100 mg to 325 mg once daily, and low-molecular-weight heparin was started.

Routine laboratory and immunologic tests were performed, including serum and urine albumin immunoelectrophoresis; tumor marker detection; serologic tests for hepatitis B, hepatitis C, and human immunodeficiency viruses; IgE, IgA, IgG, and IgM serum immunoglobulins; thyroid function tests; antithyroid antibodies; antinuclear antibodies; determination of complement components; CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes; and blood, urine, and sputum cultures, which were all normal. Skin biopsy showed nonspecific dermatitis findings with perivascular and interstitial distribution of lymphocytes, histiocytes, and neutrophils.

One week later the patient was afebrile and hemodynamically stable with rash remission. Blood tests on discharge were within reference range. Our final diagnosis was cross-reactivity to orally administered clopidogrel and ticlopidine.

Dual antiplatelet therapy with aspirin and a thienopyridine derivative after stent implantation is essential to prevent stent thrombosis. Thienopyridine derivatives ticlopidine and clopidogrel are platelet adenosine diphosphate receptor antagonists that share the same chemical structure and present the same function. Clopidogrel 75 mg once daily is equivalent to ticlopidine 250 mg twice daily.<sup>2</sup> Clopidogrel is currently the thienopyridine of choice, offering

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better safety with lower incidence of rash and neutropenia.<sup>2</sup> However, adverse reactions to clopidogrel are not uncommon and affected patients must switch to ticlopidine.

Erythroderma is a rare skin disorder characterized by generalized erythema with varying degrees and types of scaling, pruritus, and often loss of hair and nail dystrophy. This disorder carries an important risk for the patient because of the extended skin involvement. Erythroderma may be idiopathic or the result of preexisting dermatoses, malignancies, cutaneous T-cell lymphoma, drug reactions, or infections.<sup>1</sup> The onset of erythroderma usually is gradual. Approximately 25% of cases in adults are drug induced, and only acute erythroderma is associated with medications. However, drug-induced cases, with the exception of erythroderma evolving to toxic epidermal necrolysis, have the best prognosis.<sup>1</sup>

Our patient presented with abrupt onset of erythroderma, fever with chills and malaise, hemodynamic instability, pruritus, and skin edema. A preexisting dermatosis was excluded by his medical history, while blood, biochemical, and immunologic tests ruled out infectious, immunologic, and paraneoplastic causes. The acute onset, the exclusion of other possible causes, and the recent clopidogrel initiation followed by ticlopidine replacement led us to a clopidogrel- and ticlopidine-induced erythroderma diagnosis that was supported by the skin biopsy and the rash recession after discontinuation of the 2 suspicious drugs. A biopsy is important to rule out some specific malignant causes such as cutaneous T-cell lymphoma. However, it is impossible to correlate clinical presentation with histologic findings because the specific cutaneous changes of a dermatosis or a drug reaction are obscured by nonspecific changes induced by erythroderma. Indeed, biopsy identifies the cause of erythroderma in up to 50% of cases, particularly after multiple skin biopsies.<sup>3</sup>

Clopidogrel and ticlopidine are both thienopyridine derivatives; therefore, a cross-reaction between them can explain our patient's condition. Makkar et al<sup>4</sup> reported 2 cases of maculopapular pruritic rash following successive oral administration of clopidogrel and ticlopidine. The reaction was attributed to a cross-reactivity between clopidogrel and ticlopidine.<sup>4</sup> Camara and Almeda<sup>5</sup> presented 2 more cases of the same cross-reaction appearing as a rash. Nebeker et al<sup>6</sup> studied 5783 patients after DES implantation and traced hypersensitivity reactions in 262 cases including rash. These reactions can be caused either

by the DES itself or the antiplatelet treatment. Prasugrel, a new and more potent thienopyridine derivative,<sup>7</sup> has been administered without any signs of allergic reaction in one patient with a history of hypersensitivity reaction to clopidogrel.<sup>8</sup> However, no data are available regarding the frequency of cross-reactivity between clopidogrel and prasugrel.<sup>9</sup>

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