Torasemide-induced Vascular Purpura in the Course of Eosinophilic Granulomatosis with Polyangiitis

Torasemide is a loop diuretic with a molecule that is chemically similar to the sulphonamides described as eosinophilic granulomatosis with polyangiitis (EGPA) triggering drugs. The presented case is probably the first description of torasemide-induced vascular purpura in the course of EGPA. Any diagnosis of vasculitis should be followed by an identification of drugs that may aggravate the disease.

A 74-year-old patient was admitted to the Department of Dermatology with purpura-like skin lesions on the upper, and lower extremities, including the buttocks. The lesions had appeared around the ankles 7 days before admission to the hospital and then started to progress upwards. The patient complained on lower limb paresthesia and pain. Other comorbidities included bronchial asthma, chronic sinusitis, ischemic heart disease, mild aortic stenosis, arterial hypertension, and degenerative thoracic spine disease. The woman had previously undergone nasal polypectomy twice. She was on a constant regimen of oral rosuvastatin 5 mg per day, spironolactone 50 mg per day, metoprolol 150 mg per day, inhaled formoterol 12 µg per day, and ipratropium bromide 20 µg per day. Ten days prior to admission, she was commenced on torasemide at a dose of 50 mg per day prescribed by a general practitioner due to high blood pressure.

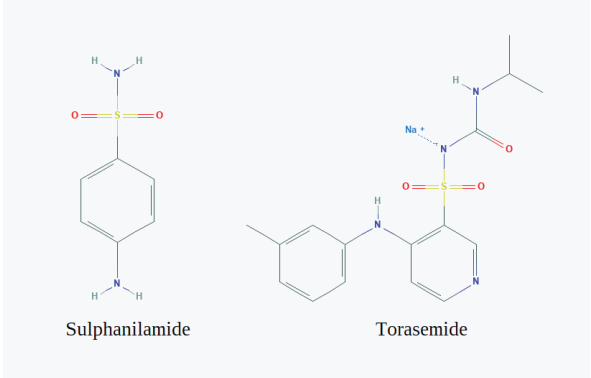

Figure 1. Comparison of the chemical structure of torasemide and sulfanilamide molecules. The sulfonamide group that is common for both molecules is marked in color.

Doppler ultrasound upon admission to the hospital excluded deep venal thrombosis. The laboratory tests revealed leukocytosis (17.1 thousand per mm3) with eosinophilia (38.6%), elevated plasma level of C-reactive protein (119 mg per L) and D-dimers (2657 ng per mm3). Indirect immunofluorescent test identified a low titer (1:80) of antinuclear antibodies, but elevated (1:160) antineutrophil cytoplasmic antibodies (ANCA) in the patient's serum. Immunoblot found them to be aimed against myeloperoxidase (pANCA). A chest X-ray showed increased vascular lung markings, while high-resolution computed tomography revealed peribronchial glass-ground opacities. Microscopic evaluation of skin biopsy taken from the lower limbs showed perivascular infiltrates consisting of eosinophils and neutrophils, fragments of neutrophil nuclei, and fibrinous necrosis of small vessels. Electromyography performed in the lower limbs because of their weakness highlighted a loss of response from both sural nerves, as well as slowed conduction velocity of the right tibial nerve and in both common peroneal nerves. Both clinical characteristics of skin lesions and histopathology suggested a diagnosis of EGPA, which was later confirmed by a consultant in rheumatology. The patient was commenced on prednisone at a dose of 0.5 mg per kg of body weight daily and mycophenolate mofetil at a daily dose of 2 g. The antihypertensive therapy was modified, and torasemide was replaced by spironolactone 25 mg per day. The treatment resulted in a gradual regression of skin lesions within a few weeks.

The first report of EGPA dates back to 1951. Its authors were Jacob Churg and Lotte Strauss. They described a case series of 13 patients who had severe asthma, fever, peripheral blood eosinophilia, and granulomatous vasculitis in microscopic evaluation of the skin. Three histopathological criteria were then proposed, and Churg-Strauss syndrome was recognized when eosinophilic infiltrates in the tissues, necrotizing inflammation of small and medium vessels, and the presence of extravascular granulomas

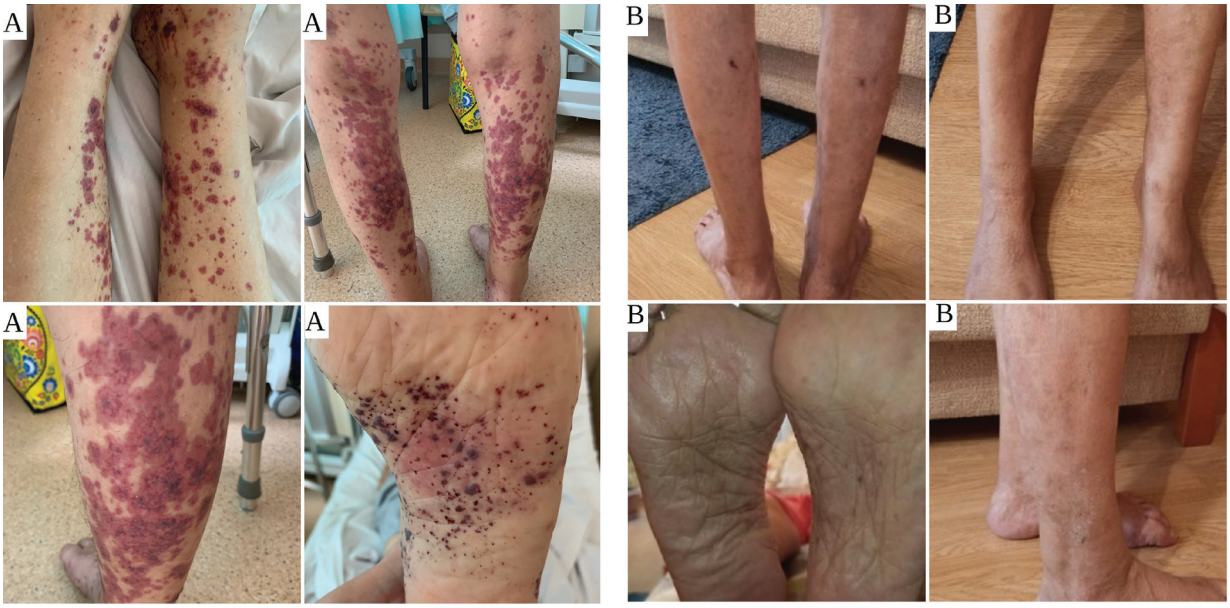

Figure 2. (A) Skin lesions on admission. Petechiae and purpura on the lower limbs due to torasemid-induced vasculitis. (B) Skin lesions after 2 months of treatment. Almost complete remission of skin lesions can be observed.

were observed together in a patient (1). Only 17.4% of patients met all three histopathological criteria, and the diagnosis of the disease was frequently delayed despite of its overt clinical picture (2). In 1984, Lanham *et al.* proposed new diagnostic criteria which included the presence of bronchial asthma, eosinophilia in a peripheral blood smear >1.5 thousand per mm3, and signs of vasculitis involving at least two organs other than the lungs (3). Lanham's criteria could also delay the recognition of the syndrome before involvement of internal organs, and the American College of Rheumatology therefore established classification criteria in 1990. These included the presence of bronchial asthma, migratory infiltrates in the lungs as assessed by radiographs, the presence of abnormalities in the paranasal sinuses (polyps, allergic rhinitis, chronic inflammation), mono- or polyneuropathy, peripheral blood eosinophilia (>10% of leukocytes must be eosinophils), and extravascular eosinophilic infiltrates in a histopathological examination. Patients who met 4 out of 6 criteria were classified as having Churg-Strauss syndrome (4). The term EGPA was recommended to define patients with Churg-Strauss syndrome in 2012 (5).

EGPA is a condition with low incidence (0.11-2.66 cases per million) and morbidity. It usually occurs in the fifth decade of life (6,7), although 65 cases reports of EGPA in people under 18 years of age could be found in the PubMed and Ovid Medline Database at the end of 2020 (8). The etiopathogenesis of the disease has not been fully explained so far. Approximately 40-60% of patients are positive to pANCA (9), but the role of these antibodies in the pathogenesis of EGPA remains unclear. They are suspected to mediate binding of the Fc receptor to MPO exposed on the surface of neutrophils. Subsequently, this may active neutrophils and contribute to a damage of the vascular endothelium (9,10). Glomerulonephritis, neuropathy, and vasculitis are more common in patients with EGPA who have detectable pANCA when compared with seronegative patients.

There are at least several drugs which potentially may EGPA. The strongest association with the occurrence of EGPA was found with the use of leukotriene receptor antagonists (montelukast, zafirlukast, pranlukast), although they are commonly used in the treatment of asthma, which is paradoxically one of the complications of the syndrome (13).

Although no relationship has been demonstrated so far between the occurrence of EGPA and the intake of drugs from the groups used by the presented patient, a clear time relationship can be observed between the commencement of torasemide and the onset of symptoms in our patient. To date, only three cases of leukocytoclastic vasculitis have been reported after the administration of torasemide. Both of them developed cutaneous symptoms of the disease within 24 hours of the administration of torasemide in patients with no previous history of drug hypersensitivity, but they disappeared quickly within 8-15 days after drug discontinuation (14,15).

The chemical structure of torasemide is similar to the molecule of sulfonamides which were previously found to be a triggering factors for EGPA (12). This drug belongs to the group of loop diuretics classified as sulfonamide derivatives. A comparison of the

chemical structure of torasemide and sulphanilamide molecules is presented in Figure 1. The clear time relationship between starting the administration of torasemide and the occurrence of purpura-like lesions suggests that it was an aggravating factor for EGPA in our patient. A coexistence of several disorders (asthma, nasal polyps, symptoms of peripheral neuropathy) in our patient suggest EGPA could have developed in her years before oral intake of torasemide. The sudden onset of skin symptoms shows torasemide to be possible inducing factor for the development of vascular purpura in patients suffering from EGPA but without previous cutaneous involvement.

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