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CHRONIC URTICARIA IN ELDERLY PEOPLE: A CASE OF SCHNITZLER SYNDROME

To the Editor: Schnitzler syndrome is a rare and only recently described syndrome¹ characterized by a chronic urticarial rash and the presence of a monoclonal immunoglobulin (Ig) gammopathy. Other symptoms include arthralgia and lymphadenopathy.

An 81-year-old man was first hospitalized in 2002 for chronic fever associated with urticaria. His medical history included ischemic cardiac insufficiency, arrhythmia, and hypertension. There had been no recent modifications of medications. Clinical examination did not reveal other abnormalities. Biological findings showed isolated inflammation with a C-reactive protein level of 95 mg/L. Renal and hepatic function and lactate dehydrogenase rate were normal. The infectious assessments were inconclusive, including serology (hepatitis C, Cytomegalovirus, *Chlamydiae pneumoniae*, *Coxiella burnetti*, and *Mycoplasma pneumoniae*) and repeated blood cultures. The laboratory tests were negative for serum antinuclear antibodies. A bone marrow biopsy was performed to exclude a lymphoproliferative disorder, and the results were normal. A thoraco-abdomino-pelvic computed tomographic scan did not show tumors. Corticosteroids were prescribed (15 mg/d), and the

symptoms resolved. Treatment was slowly tapered over a 3-month period with no recurrence.

Four years later, the patient was readmitted for fever of unknown origin and recurrence of a urticarial rash of 4 weeks' duration. Virological and bacteriological infections were excluded. A thoraco-abdomino-pelvic scan showed pleural effusion. Needle evacuation was performed, but no malignant process or amyloid deposit was identified. Biological investigation showed a monoclonal gammopathy of the IgM type evaluated at 21.9 g/L. According to records from a previous admission 4 years before, the patient's IgM gammopathy had been low then (14.4 g/L). A diagnosis of Schnitzler syndrome was suspected. A bone technetium scan was performed but did not show fixation. Treatment with prednisone was prescribed (15 mg/d), and the patient improved within 2 days. After 10 months of follow-up, the patient remains in good health without recurrence despite tapering of the corticosteroids to 1 mg/month.

A French dermatologist first described Schnitzler syndrome in 1972. It is also referred to as chronic urticaria associated with macroglobulinemia. The incidence of the disease is unknown. Approximately 90 cases have been reported in the literature.¹⁻³ The mean age of onset is 51, and few cases have been documented in elderly patients. The differential diagnosis includes Still's disease and hematological or autoimmune disorders.

Cutaneous histopathological examination usually reveals neutrophilic urticaria. IgM deposits in the superficial dermal vessels are detected in 30% of cases. The most commonly affected areas are the limbs and trunk. In some patients, alcohol ingestion can induce rashes. It is unclear whether the IgM gammopathy results from a continuous antigenic stimulation or whether it is the primary process. The fever is constant and intermittent, is often well tolerated, and resolves spontaneously. The other clinical characteristics are intermittent: bone pain and arthralgia or arthritis, all of which occur in 59% of cases. The ankles and the knees are the most commonly affected joints. Enlargement of the liver or spleen and lymph nodes occurs in 33% to 50% of cases. Radiological examinations can reveal bone heterogeneous and focalized densifications. Bone technetium scanning showing hyperfixation can help establish the diagnosis of Schnitzler syndrome. Histological examination of a bone specimen might show nonspecific inflammatory lesions or osteosclerosis with many lymphoid proliferative islets.

The monoclonal gammopathy is constant, usually of the IgM type, with a kappa light chain in 89% of cases. It is important to perform medullar examinations to exclude hematological proliferation, because a lymphoproliferative disorder might occur in 15% of cases.

Treatment of Schnitzler syndrome is difficult. Non-steroidal antiinflammatory drugs, colchicine, or dapsone can improve the skin symptoms. In some patients, photochemotherapy with psoralen and ultraviolet A therapy can reduce the intensity of the skin lesions.⁴ Corticosteroids and immunosuppressive drugs are required when systemic signs such as fever or arthralgia are refractory to the first-line treatment. Successful treatment with interferon, thalidomide, or cyclosporin has also been reported.

Schnitzler syndrome is a rare disease that might occur late in life. Many infectious and hematological

diseases must be excluded. Low-dose corticosteroid treatment can be effective, as in the case under discussion. Long-term follow-up is required because of the risks of recurrence and possible evolution to a malignant lymphoproliferative disease. The pathophysiological pathways are unknown.

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ACKNOWLEDGMENTS

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the author and has determined that none of the authors have any financial or any other kind of personal conflicts with this letter.

Author Contributions: Antoine Elsendoorn: acquisition of data, analysis and interpretation of data, and preparation of manuscript. Julien Voultoiry: analysis and interpretation of data and preparation of manuscript. Anne-Sophie Gaubert: preparation of manuscript. Pascal Roblot: interpretation of data and preparation of manuscript. Marc Paccalin: study concept and design, analysis and interpretation of data, and preparation of manuscript.

Sponsors' Role: None.

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ANTIPLATELET CILOSTAZOL, AN INHIBITOR OF TYPE III PHOSPHODIESTERASE, IMPROVES SWALLOWING FUNCTION IN PATIENTS WITH A HISTORY OF STROKE

To the Editor: Stroke patients with dysphagia have a high incidence of aspiration, which may lead to pneumonia.¹ Several investigators have reported that cilostazol, a potent inhibitor of type III phosphodiesterase, reduces the incidence of aspiration pneumonia in patients with a history of

stroke,^{2,3} but the mechanism by which it does so has not been completely elucidated.

It has been proposed that swallowing disorders play a significant role in the development of pneumonia in patients with a history of stroke;^{4,5} therefore, it was hypothesized that cilostazol may improve swallowing function in such patients by exerting pleiotropic effects through inhibiting type III phosphodiesterase. The effects of cilostazol administration on the serum and induced sputum levels of substance P, a transmitter in the nucleus of the solitary tract in the brainstem, were examined, because a significant association between systemic or airway depletion of substance P and silent aspiration and swallowing disorders has been reported in poststroke patients.^{6,7}

The study subjects included patients with a 1- to 6-month history of noncardioembolic cerebral infarction confirmed using computed tomography or magnetic resonance imaging. In 48 male patients (mean age $\pm$ standard deviation 68 ± 5), swallowing function was examined before and after the administration of cilostazol and compared with swallowing function after the administration of aspirin. This study was a double-blinded, placebo-controlled, three-period crossover study wherein cilostazol administered at a dose of 200 mg twice daily and aspirin administered at a dose of 200 mg/d were compared with placebo. Patients were evaluated at baseline and after 4 weeks of treatment with each drug; a 4-week washout period was allowed after the completion of treatment with each drug. Swallowing function was examined using a repetitive saliva swallowing test and a swallowing provocation test.^{4,5} In brief, the ability to swallow voluntarily was quantitatively measured for 30 seconds. The swallowing reflex was induced by injecting a bolus of 1 mL of distilled water into the suprapharynx through a 5-Fr small nasal catheter with the patient in the supine position. The swallowing reflex was evaluated as the latency of the response.

The serum and induced sputum levels of substance P were measured using a radioimmunoassay.⁸ After administering 5% saline solution via an ultrasonic nebulizer for 15 minutes, blood and induced sputum samples were collected between 7:30 and 8:00 a.m. before and after the completion of the cilostazol and aspirin treatments.

The significance of differences between the groups was assessed using analysis of variance, followed by *t*-tests with Bonferroni correction. The results are expressed as means $\pm$ standard deviations, and values of $P < .05$ were considered to indicate statistical significance.

Forty-eight patients completed the study. The latent time of swallowing reflex significantly improved after the administration of cilostazol but not after the administration of aspirin (Figure 1). Cilostazol increased the frequency of voluntary swallowing in 30 seconds (from 4.9 ± 0.2 to 5.6 ± 0.2), but aspirin did not (from 4.9 ± 0.2 to 5.1 ± 0.2). The induced sputum and serum substance P levels also improved after cilostazol administration sputum: from 16.6 ± 3.4 to 30.1 ± 6.2 pg/mL; serum: from 28.2 ± 4.4 to 44 ± 5.2 pg/mL) but not after aspirin administration (sputum: from 16.6 ± 3.8 to 18.1 ± 4.4 pg/mL; serum: from 28.2 ± 4.4 to 30.6 ± 4.6 pg/mL). No obvious untoward effects were observed.

The present study indicated that cilostazol but not aspirin improved swallowing reflex in patients with a history