## Schnitzler's syndrome with biclonal gammopathy successfully treated with hydroxychloroquine and low dose steroids

Sirs,

Schnitzler's syndrome is a rare condition with chronic urticarial rash and monoclonal IgM gammopathy, accompanied by at least two of the following: intermittent unexplained fever, arthralgia/arthritis, bone pain, lymphadenopathy, hepato-splenomegaly, acute phase response and abnormal findings on bone investigations (1). Since 1972 (2), about 90 cases have been reported, the majority of which are long-standing; however, about 15% of patients will develop lymphoproliferative disorders (1, 3). The pathophysiology of the disease still remains unclear, although autoantibody-mediated mechanisms have been proposed. Treatment is often disappointing even if there have been promising developments with anakinra, an analogue of interleukin-1 receptor antagonist (4). We report a further case of Schnitzler's syndrome first treated with cyclosporine, then with hydroxychloroquine and steroids, who presented a good outcome still persisting after a 30-month follow-up.

A 63-year-old Italian male came to our division in June 2003. Because of a history of urticaria and arthralgia, he had received steroids, anti-histamines and non-steroidal anti-inflammatory drugs (NSAIDs) with short-term efficacy. Laboratory investigations revealed an erythrocyte sedimentation rate (ESR) of 41 mm/h, C-reactive protein (CRP) level of 27 mg/L and serum IgM of 830 mg/dL; autoantibody screening was negative. Serum protein electrophoresis demonstrated two monoclonal IgM components with lambda (0.17 g/dL) and kappa (0.07 g/dL) light chains on immunofixation. Physical examination showed red non-pruritic diffuse papules without fever detection A cutaneous biopsy revealed neutrophilic hypocomplementemic urticaria. Therefore, on the basis of the combination of neutrophilic urticaria, clonal IgM gammopathy, arthralgia and acute phase response, a Schnitzler's syndrome diagnosis has been formulated. Cyclosporine 3 mg/kg daily plus prednisone 50 mg weekly were then administered with initial improvement, followed by relapse of symptoms.

In July 2004 a lymph-node ultrasonography documented bilateral presence of multiple lymphadenopathies; ESR and CRP levels were elevated, serum IgM reached 1450 mg/dL, monoclonal IgM-λ increased to 1 g/dL and IgM-κ was 0,18 g/dL (Fig. 1). Bone marrow examination and lymphnode biopsy excluded a lymphoproliferative evolution. Hydroxychloroquine 400 mg daily was started in addition to prednisone 50 mg weekly. After two months, a progressive resolution of urticaria and arthralgias with ESR (32 mm/h) and CRP (5 mg/L) reduction, permitted us to taper the prednisone to a 30 mg-dose weekly. In the last 30 months the patient has been experiencing an almost complete symptom control excluding rare episodes of acute arthralgia; serum monoclonal IgM-λ and κ remained stable.

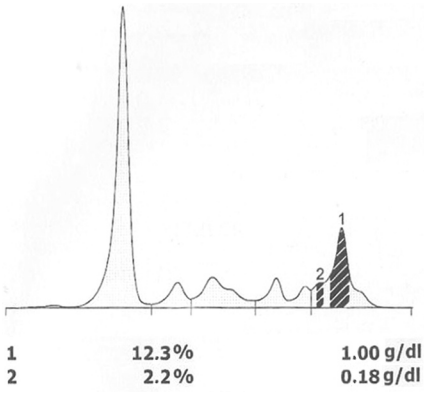


**Fig. 1.** Serum protein electrophoresis showing two monoclonal IgM components, n° 1 and n° 2 correspond to lambda and kappa light chains respectively on the immunofixation.

Whereas most patients with this syndrome reported having monoclonal IgM paraprotein associated with kappa light chain (1), this patient belongs to an extremely rare variant with biclonal IgM gammopathy and prevalence of lambda light chains. To our knowledge, only another patient with biclonal gammopathy has been described (5). Treatment of Schnitzler's syndrome remains a challenge, NSAIDs, anti-histamines, steroids are reported as first-line therapy (6). In this patient initial treatment with these drugs obtained only partial control of skin rash and subsequent administration of cyclosporine was unable to reach satisfactory results. Because of the disabling arthralgia and persisting skin lesions as well as the unknown safety profile about malignancies induction by the use of anakinra, it was decided to start hydroxychloroquine, which was inconstantly described as an effective treatment of this syndrome (1, 7, 8). Hydroxychloroquine with low dose steroids promptly improved urticarial lesions and arthralgias, leading to progressive resolution; moreover it stabilized the biclonal IgM components and serum IgM level. The benefit induced by treatment was immediate and still persists after 30 months. It may be hypothesised that hydroxychloroquine efficacy in this patient, could be the consequence of direct action of antimalarials on macrophages, inhibiting production of inflammation mediators such as interleukin-1 and interleukin-6 (9).

We believe that this case may be of interest not only for the unusual presentation of a biclonal gammopathy, but also for the excellent response to a combination therapy with hydroxychloroquine and low dose steroids.

B. Laganà[1]
E. Podestà[1]
A. Picchianti Diamanti[1]
G. Salerno[2]
R. Di Rosa[1]*
R. D'Amelio[1]*

*[1]Chair and Division of Allergy, Clinical Immunology and Rheumatology; [2]Department of Cellular Biotechnology and Hematology, "La Sapienza" University, 2nd School of Medicine, Rome, Italy.*

**These authors contributed equally to this work*

*Address correspondence to:*
*Dr. Bruno Laganà, Allergy, Clinical Immunology and Rheumatology, La Sapienza" University, 2nd School of Medicine, Via di Grottarossa 1039, 00189 Roma, Italy.*
*E-mail: blagana@infinito.it*

*Competing interests : none declared.*

### References

1. LIPSKER D, VERAN Y, GRUNENBERGER F *et al.*: Schnitzler's syndrome. Four new cases and review of the literature. *Medicine (Baltimore)* 2001; 80: 37-44.
2. SCHNITZLER L: Lésions urticarienne chroniques permanentes (érythème pétaloide?). Cas clinique n. 46B. *Journée dermatologique d'Angers*. 28 Octobre 1972.
3. DALLE S, BALME B, SEBBAN C *et al.*: Schnitzler's syndrome associated with systemic marginal zone B-cell lymphoma. *Br J Dermatol* 2006; 45: 1032-8.
4. De KONING HD, BODAR EJ, Van Der MEER JWM, SIMON A: Schnitzler's syndrome: beyond the case reports: review and follow-up of 94 patients with emphasis on prognosis and treatment. *Semin Arthritis Rheum* 2007; 37: 137-48.
5. FAMULARO G, BARRACCHINI A, MINISOLA G: Sever thrombophilia with antiphospholipid syndrome and hyperhomocysteinemia in a patient with Schnitzler's syndrome. *Clin Exp Rheumatol* 2003; 21: 366-8.
6. LIPSKER D, IMRIE K, SIMON A *et al.*: Hot and hobbling with hives: Schnitzler syndrome. *Clin Immunol* 2006; 119 :131-4.
7. PERONATO G, DE SANDRE P, BONOLDI E: Urticaria, osteocondensation and monoclonal gammopathy (Schnitzler Syndrome): a new case report. On-line *Arch Rheumatol* 1999; 3: 4.
8. LIN RY, JAGANNATH S: Treatment of Schnitzler's syndrome with colchicine: a case report. *Internet J Asthma* 2005; 4.
9. LAFYATIS R, YORK M, MARSHAK-ROTHSTEIN: Antimalarian agents: closing the gate on Toll-like receptors? *Arthritis Rheum* 2006; 54: 3068-70.