

CASE REPORT

Improvement of recurrent urticaria in a patient with Schnitzler syndrome associated with B-cell lymphoma with combination rituximab and radiotherapy

Hiroyuki Murota, MD, PhD,^a Yukiko Shoda, MD, PhD,^c Tomohiko Ishibashi, MD,^d
Hiroyuki Sugahara, MD, PhD,^d Itaru Matsumura, MD, PhD,^b and Ichiro Katayama, MD, PhD^a
Osaka, Japan

Schnitzler syndrome is a rare condition defined by chronic urticaria, osteosclerotic bone lesions, and monoclonal IgM gammopathy. Schnitzler syndrome can precede the onset of a true lymphoproliferative disorder including Waldenström macroglobulinemia and rarely systemic marginal zone B-cell lymphoma. We describe a case of intractable chronic urticaria accompanied by a retroperitoneal neoplasm. IgM monoclonal gammopathy, lumbar pain, intermittent fever, and elevation of C-reactive protein were the clues for the diagnosis of Schnitzler syndrome. An evaluation for malignancy using systemic computed tomography scan and fluorodeoxyglucose positron emission tomography revealed the retroperitoneal tumor, and a subsequent bone-marrow aspirate confirmed the diagnosis of B-cell lymphoma. Combined rituximab and radiotherapy ameliorated the skin symptoms. This case indicates that a detailed search for malignant neoplasms might be required for the long-term management of Schnitzler syndrome, and that B-cell lymphomas may contribute to the pathogenesis of this condition. (J Am Acad Dermatol 10.1016/j.jaad.2008.12.040.)

Key words: B-cell lymphoma; combination therapy; radiation; rituximab; Schnitzler syndrome.

In 1972, Schnitzler¹ first described a patient with combined symptoms of chronic urticaria, intermittent fever, osteosclerotic bone lesions, and monoclonal gammopathy. Subsequently, this syndrome was also reported by other groups and now bears her name. The association of Schnitzler syndrome with various lymphoproliferative disorders such as marginal zone B-cell lymphoma, IgM myeloma, and Waldenström macroglobulinemia (WM) has been reported.²⁻⁵ However, the best therapeutic strategy for such complicated cases has not been established. This report presents a case of B-cell lymphoma developing in a patient with Schnitzler syndrome, who was treated by combination therapy of rituximab and radiotherapy.

Abbreviations used:

LPL: lymphoplasmacytic lymphoma
WM: Waldenström macroglobulinemia

CASE REPORT

A 73-year-old woman was referred in December 2007 for chronic urticaria. She had experienced a typical persistent urticarial eruption for 5 years, associated with lumbar pain and periodic fever, which reached 39°C. She had not received any drug therapy. She was initially thought to have autoimmune urticaria based on a positive autologous serum skin test results, but she did not respond to antihistamines and montelukast sodium. Physical examination revealed that the individual lesions, which consisted of urticarial wheals with pruritic macules or papules (Fig 1), appeared on the trunk and extremities, sparing the face, palms, and soles, and resolved within 24 to 48 hours without sequelae. The intermittent fever and lumbar pain occurred regardless of the skin symptoms. In addition, mild tenderness of both knees on passive and active movement was observed with no sign of arthritis.

Histology of a skin biopsy specimen showed a superficial perivascular inflammatory cell infiltrate consisting of small lymphoid cells, neutrophils, and

From the Department of Dermatology, Course of Integrated Medicine,^a and Department of Hematology and Oncology,^b Graduate School of Medicine, Osaka University; and Departments of Dermatology^c and Hematology,^d Sumitomo Hospital. Funding sources: None.

Conflicts of interest: None declared.

Reprint requests: Hiroyuki Murota, MD, PhD, Department of Dermatology, Osaka University, 2-2 Yamadaoka, Suita, Osaka, Japan 5650871. E-mail: h-murota@derma.med.osaka-u.ac.jp.

Published online July 24, 2009.

0190-9622/\$36.00

© 2009 by the American Academy of Dermatology, Inc.

doi:10.1016/j.jaad.2008.12.040



Fig 1. Urticarial rash on abdomen.

eosinophils (Fig 2, A and B). Direct immunofluorescence assay of a skin specimen revealed that IgM and fibrinogen were deposited in the dermis in a granular pattern and homogenous pattern, respectively (Fig 2, C). However, no findings of vasculitis were found (Fig 2, B).

Laboratory results showed eosinophilia of $714/\text{mm}^3$ and elevated levels of fibrin degradation products and lactate dehydrogenase at $1.52 \mu\text{g/dL}$ (normal $<0.04 \mu\text{g/dL}$) and 490 U/L (normal $115\text{--}245 \text{ U/L}$), respectively. Serology for Epstein-Barr virus (viral capsid antigen-IgM, Epstein-Barr virus nuclear antigen), anticytomegalovirus IgM, viral hepatitis, and antinuclear antibody revealed negative findings. Rheumatoid factor and anti-SS-A/Ro, SS-B/Lo antibody also produced negative findings. C-reactive protein level was 2.51 mg/dL (normal $<0.04 \text{ mg/dL}$), whereas serum ferritin concentration was normal. CH50, C3, C4, and C1 inactivator were in the normal range. The IgM level was increased at 694 mg/dL with a monoclonal κ component, whereas the serum IgA, IgG, and IgE levels were within normal limits. The Bence-Jones protein urine test and serum cryoglobulins revealed negative findings. Elevated serum concentrations of soluble interleukin-2 receptor at 1923 U/mL (normal $<530 \text{ U/mL}$) and β_2 -microglobulin at 2.2 mg/L (normal $<2.0 \text{ mg/L}$) suggested an associated lymphoproliferative disorder. Systemic computed tomography scan revealed a retroperitoneal mass. Abdominal magnetic resonance imaging and systemic fluorodeoxyglucose positron emission tomography scan examined the suspicious lesion for B-cell lymphoma (Fig 3). These imaging studies did not reveal any bone metastasis. Bone-marrow aspirates were analyzed for B-cell differentiation using a fluorescence-activated cell sorter, which revealed a deviation to sIg- κ (78%) and a slight increase in the sIg- κ^+ , CD20 $^+$, CD19 $^+$, CD10 $^-$ cell population (2%). This finding indicated that clonal matured lymphoma cells existed in the bone marrow. Based on these results, a diagnosis of possible Schnitzler syndrome associated with B-cell lymphoma was made. Although a tissue biopsy from the retroperitoneal

tumor was required for a definitive diagnosis, it was not performed for the following two reasons: (1) the location of the tumor mass made it technically difficult; and (2) early therapeutic intervention was needed for her refractory lumbar pain and urticaria, which markedly impaired her quality of life. Regarding the choice of methods for therapeutic intervention, the finding of the deposition of IgM in lesional skin made us hypothesize that the monoclonal IgM might be a therapeutic target for the urticarial rash.

Subsequently, to decrease the serum IgM level, weekly rituximab infusions (375 mg/m^2) were initiated, and the size of retroperitoneal tumor and serum markers, such as the IgM level, were evaluated. Five days after the initiation of rituximab treatment, the size of the retroperitoneal tumor and serum concentration of C-reactive protein and lactate dehydrogenase markedly decreased (Fig 4). However, no improvement of the skin symptoms, such as the urticarial eruption and the intense pruritus, was observed. The excoriations, prurigo-like eruption, and erythema gradually increased (Fig 5, A). Oral prednisolone and dapsone were initiated to improve the skin symptoms (Fig 4). Unfortunately, these treatments had no impact. One month after the start of rituximab treatment, the retroperitoneal tumor had almost disappeared. Furthermore, the blood test results, such as the serum IgM level, were within normal limits (Fig 4). Despite the improvement in these parameters, the severity of the symptoms of urticaria was unchanged. To improve her quality of life, we therefore planned further therapy, with the goal of completely removing the remaining tumor mass. Subsequent radiation therapy ($2 \text{ Gy} \times 15$ in total) successfully achieved complete remission of the retroperitoneal tumor. Thereafter, the skin symptoms had begun to improve gradually and completely disappeared within 1 month after completion of rituximab administration (Figs 4 and 5). The prednisolone dosage was tapered to 2.5 mg and relapses of the general symptoms including the skin were completely eliminated.

DISCUSSION

Based on the distinctive clinical manifestations, this patient was given the diagnosis of Schnitzler syndrome. This case also fulfills the diagnostic criteria advocated by Lipsker et al.⁶ The hallmark symptom of this case was the intense itching of the skin eruption. The frequency of pruritus in Schnitzler syndrome is 45%.⁷ Another review article mentioned that pruritus in Schnitzler syndrome develops gradually, about 3 to 4 years after the onset of skin lesions.⁶ The current case showed a similar clinical course of events.

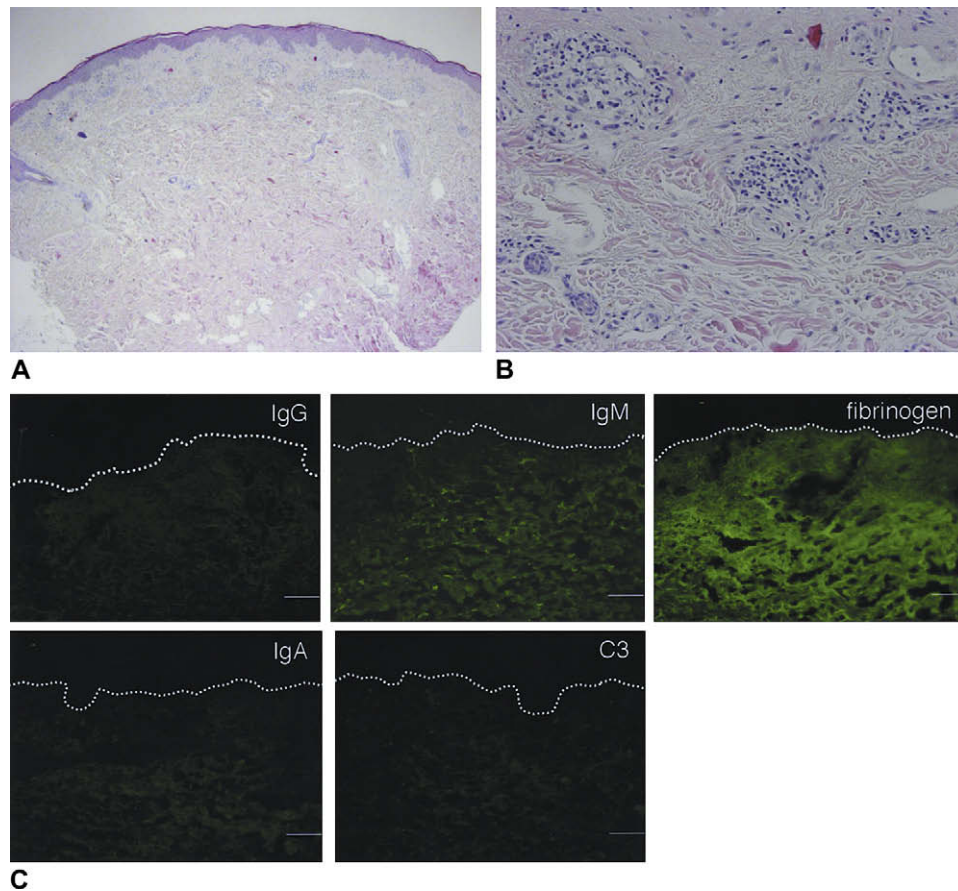


Fig 2. **A** and **B**, Histologic features of skin specimen. **C**, Direct immunofluorescence. Dotted line = basal layer; scale bar = 100 μ m. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, $\times 40$; **B**, $\times 200$.)

Understandably, there are many differential diseases similar to Schnitzler syndrome. Primarily, adult-onset Still disease should be excluded. In this case, the serum concentration of ferritin was within the normal limits and the chronically recurrent urticarial lesions and monoclonal gammopathy were characteristic of Schnitzler syndrome.⁸ Autoinflammatory syndromes also present similar manifestations to Schnitzler syndrome, and should be differentiated.⁹ Unfortunately, because no determination of the serum IgD level was performed, hyper-IgD syndrome was not excluded from the differential diagnosis. However, the lack of a family history of similar problems reduced the possibility of hyper-IgD syndrome. Because there was no induction of urticarial wheals by cold stimuli and no sensorineural deafness, the possibility of cryopyrin-associated periodic syndrome and Muckle-Wells syndrome were eliminated.

This case was complicated by likely B-cell lymphoma, which was not definitively diagnosed because biopsy was not performed. As mentioned above, the diagnosis of B-cell lymphoma was made

based on the following 4 findings: the existence of a small population of clonal lymphoma cells in the bone marrow, the apparent fluorodeoxyglucose avidity of the retroperitoneal tumor, the elevation of the serum IgM κ paraprotein level, and the effect of rituximab. Although the intensity of fluorodeoxyglucose uptake in retroperitoneal tumor somewhat conflicted with the diagnosis, the absence of lymphoma cells in both the histopathological findings and smear sample of bone marrow led us to think that this B-cell lymphoma might preferably be classified as either lymphoplasmacytic lymphoma (LPL) or marginal B-cell lymphoma rather than as an aggressive lymphoma.

The finding of granular deposits of IgM in the dermis of the affected areas, which is frequently observed in case of WM with urticaria,^{5,10} was also confirmed by direct immunofluorescence in this case. WM is a malignant lymphoplasmoproliferative disorder characterized by monoclonal pentameric IgM production. The most distinctive feature of the bone marrow of patients with WM is the presence of pleomorphic B-lineage cells at different stages

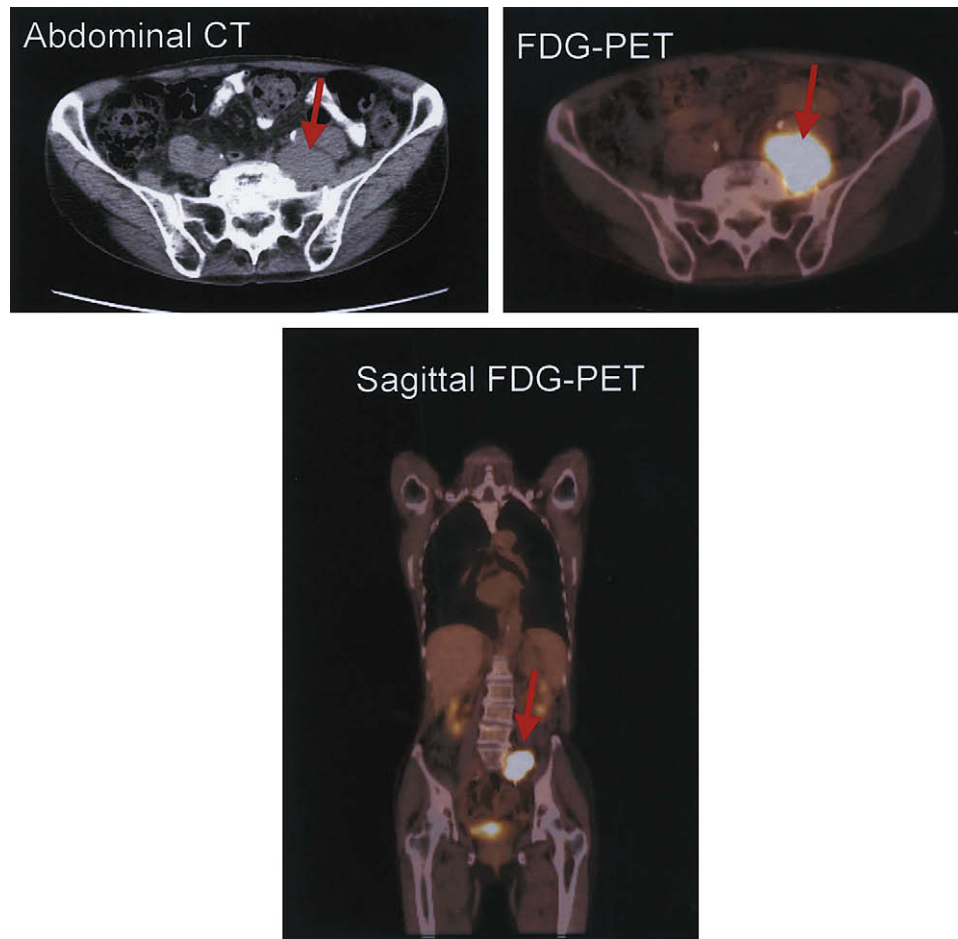


Fig 3. Diagnostic imaging with computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET) revealed retroperitoneal tumor (arrows).

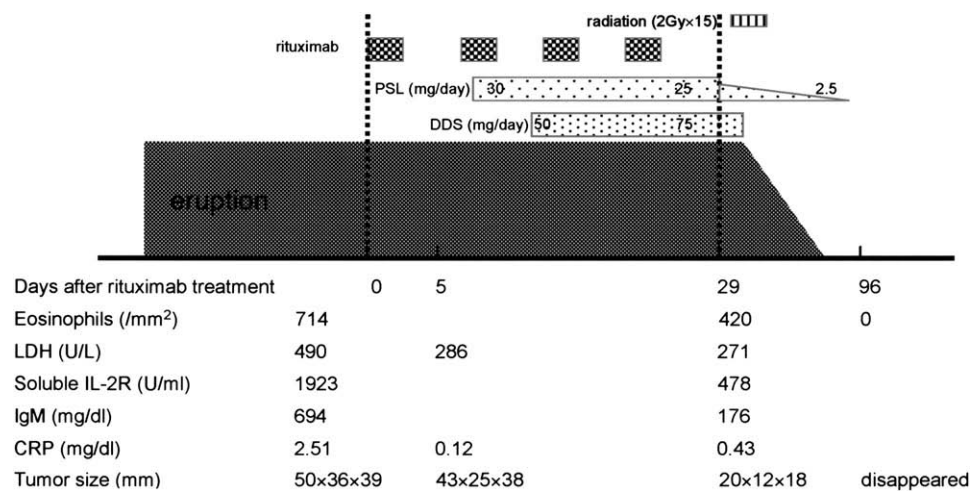


Fig 4. Summary of clinical course. CRP, C-reactive protein; DDS, dapsone; IL, interleukin; LDH, lactate dehydrogenase; PSL, prednisolone.

of maturation, such as lymphoplasmacytoid cells.¹¹ Currently, although WM is combined with LPL and designated LPL/WM in the World Health Organization

classification, WM is recognized to be a clinical syndrome and it is, therefore, not synonymous with LPL.^{12,13} Schnitzler syndrome is thought to be

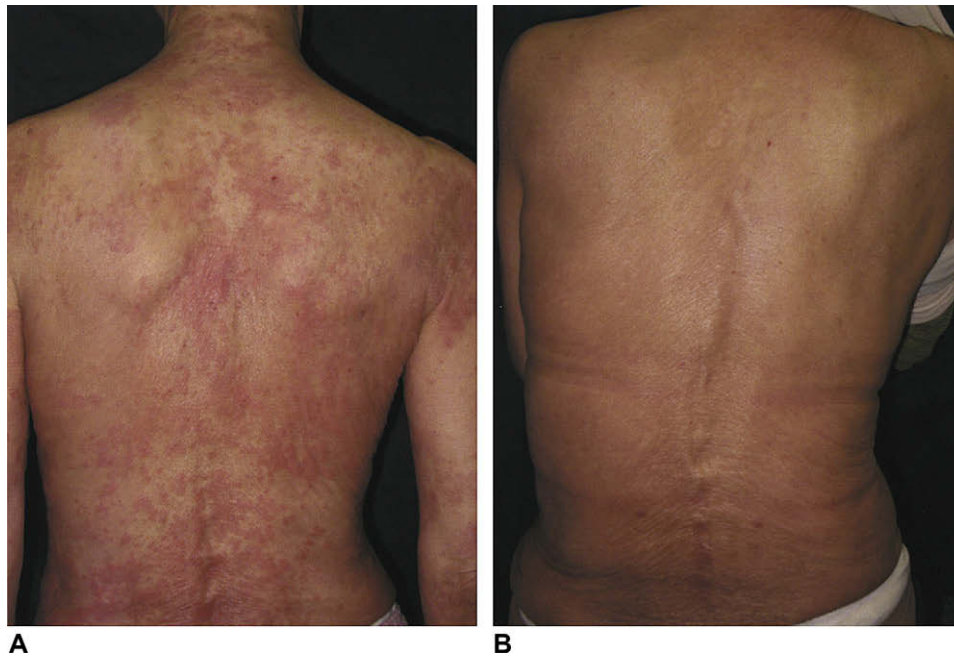


Fig 5. Response of skin manifestations to treatment. Clinical features after rituximab administration (**A**) and 1 month after addition of radiation therapy (**B**).

Table I. Clinical efficacy of rituximab in Schnitzler syndrome

Sex	Age, y	Affected period, y	Fever	Bone pain	Localization of eruption	Itch	Palpable lymph nodes	BMA findings	Effect of rituximab	Study
1 Female	64	3	+	—	Systemic	Mild	+	Small monoclonal population of B lymphocytes, κ type	Complete resolution of symptoms	16
2 Male	54	6	—	+	Predominantly on trunk	Moderate	—	No evidence of lymphoproliferative disease	No	17
3 Male	63	10	—	+	No description	Unknown degree	—	No evidence of lymphoproliferative disease	Improved renal failure; partially improved urticaria; only slight relief from bone pain	18
4 Female	73	5	+	+	Systemic	Severe	+	Small monoclonal population of B lymphocytes, κ type	Effect on tumor regression; no effect on skin symptoms	This case

BMA, Bone-marrow aspirate.

associated with the potential development of lymphoproliferative disorders, in particular, WM/LPL. It has been reported that the incidence of WM in patients with Schnitzler syndrome gradually increases

with time, with WM occurring in 15% of cases 10 years after the onset of skin symptoms.⁷ Therefore, it is possible that B-cell lymphoma occurred as part of the natural evolution of Schnitzler syndrome in this case.

Rituximab has been used successfully in patients with CD20⁺ indolent and aggressive B-cell non-Hodgkin lymphomas.^{14,15} A search of MEDLINE (1966-December 2008) yielded 3 reports that mentioned the effect of rituximab against Schnitzler syndrome (Table I). The effect of rituximab against Schnitzler syndrome differed from case to case, and was difficult to predict. Complete resolution of the skin symptoms was only observed in one case,¹⁶ with the remaining two cases showing either a low response or no response at all to rituximab treatment.^{17,18} Administration of rituximab dramatically and rapidly improved the B-cell lymphoma-related symptoms in our patient. In contrast, skin symptoms showed delayed improvement after the disappearance of B-cell lymphoma-related symptoms. The relatively long serum half-life (about 3-4 weeks) of IgM suggested that this delayed response to rituximab treatment might be achieved by the clearance of slow clearance of the IgM paraprotein. Furthermore, it was noteworthy that marked improvement of skin symptoms was observed after the complete remission of retroperitoneal tumor after radiotherapy. Despite its predicted adverse effects, it can be said that addition of 30 Gy of radiotherapy apparently improved the quality of life in this patient as a result of the relief of the severe itching associated with the urticaria. This favorable effect of combination rituximab and radiotherapy on the skin symptoms might suggest that the B cell was indeed a factor in causing the urticarial rash with pruritus.

REFERENCES

1. Schnitzler L. Lésion urticariennes chroniques permanents (érythème pétaioide?). Case cliniques n. 46 B. *J Dermatol Angers* 1972;28 (Abstr. 46).
2. Dalle S, Balme B, Sebban C, Pariset C, Berger F, Thomas L. Schnitzler syndrome associated with systemic marginal zone B-cell lymphoma. *Br J Dermatol* 2006;155:827-9.
3. Verret JL, Leclech C, Rousselet MC, Hurez D, Schnitzler L. Schnitzler syndrome and Waldenström disease: fatal outcome of the original case. *Ann Dermatol Venerol* 1993;120:459-60.
4. Govindaraju S, Brochot P, Ringot AC, Paternotte L, Morrone A, Eschard JP, et al. Chronic urticaria-macroglobulinemia (Schnitzler syndrome): developing to IgM myeloma; apropos of a case. *Rev Med Interne* 1993;14:780-3.
5. Pujol RM, Barrnadas MA, Brunet S, de Moragas JM. Urticarial dermatosis associated with Waldenström's macroglobulinemia. *J Am Acad Dermatol* 1989;20:855-7.
6. Lipsker D, Veran Y, Grunenberger F, Cribier B, Heid E, Grosshans E. The Schnitzler syndrome: four new cases and review of the literature. *Medicine (Baltimore)* 2001;80:37-44.
7. de Koning HD, Bodar EJ, Van der Meer JW, Simon A. Schnitzler Syndrome Study Group. Schnitzler syndrome: beyond the case reports; review and follow-up of 94 patients with an emphasis on prognosis and treatment. *Semin Arthritis Rheum* 2007;37: 137-48.
8. Almerigogna F, Giudizi MG, Cappelli F, Romagnani S. Schnitzler's syndrome: what's new? *J Eur Acad Dermatol Venerol* 2002;16:214-9.
9. Kanazawa N, Furukawa F. Autoinflammatory syndromes with a dermatological perspective. *J Dermatol* 2007;34:601-18.
10. Olsen E, Forre O, Lea T, Langerland T. Unique antigenic determinants (idiotypes) used as markers in a patient with macroglobulinemia and urticaria. *Acta Med Scand* 1980;207:379-84.
11. Vijay A, Gertz MA. Waldenström macroglobulinemia. *Blood* 2007;109:5096-103.
12. Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization classification of tumors: pathology and genetics of tumors of hematopoietic and lymphoid tissues. Lyon, France: IARC Press; 2001.
13. Canellos GP, Lister TA, Young B. The lymphomas. Saunders Elsevier Publishing; 2006.
14. Petryk M, Grossbard ML. Rituximab therapy of B-cell neoplasms. *Clin Lymphoma* 2000;1:186-94.
15. Boye J, Elter T, Engert A. An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab. *Ann Oncol* 2003;14:520-35.
16. Ramadan KM, Eswedi HA, El-agnaf MR. Schnitzler syndrome: a case report of successful treatment using the anti-CD20 monoclonal antibody rituximab. *Br J Dermatol* 2007;156: 1072-3.
17. Eiling E, Möller M, Kreiselmaier I, Brasch J, Schwarz T. Schnitzler syndrome: treatment failure to rituximab but response to anakinra. *J Am Acad Dermatol* 2007;57:361-4.
18. Westhoff TH, Zidek W, Uharek L, Steinhoff-Georgieva J, van der Giet M. Impairment of renal function in Schnitzler's syndrome. *J Nephrol* 2006;19:660-3.