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OLGU SUNUMU CASE REPORT

Schnitzler syndrome: a rare cause of difficult to treat chronic urticaria

Schnitzler sendromu: Tedavisi güç nadir bir kronik ürtiker

Aslı GELİNCİK[1], Mustafa DEMİRTÜRK[1], Suna BÜYÜKÖZTÜRK[1], Ayşegül TELCİ[2], Nesimi BÜYÜKBABANİ[3], Bahauddin ÇOLAKOĞLU[1], Murat DAL[1]

[1] **Division of Allergy, Department of Internal Medicine, Faculty of Istanbul Medicine Istanbul University, Istanbul Turkey**
İstanbul Üniversitesi İstanbul Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Allerji Bilim Dalı, İstanbul, Türkiye

[2] **Division of Clinical Biochemistry, Department of Internal Medicine, Faculty of Istanbul Medicine, Istanbul University, Istanbul, Turkey**
İstanbul Üniversitesi İstanbul Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Klinik Biyokimya Bilim Dalı, İstanbul, Türkiye

[3] **Department of Pathology, Faculty of Istanbul Medicine, Istanbul University, Istanbul, Turkey**
İstanbul Üniversitesi İstanbul Tıp Fakültesi, Patoloji Anabilim Dalı, İstanbul, Türkiye

ABSTRACT

Schnitzler syndrome is a rare cause of urticaria and is defined by monoclonal gammopathy and chronic urticaria or urticarial vasculitis combined by at least two of the following features: fever, arthralgia or arthritis, bone pain, hepato-and/or splenomegaly, palpable lymph nodes, elevated erythrocyte sedimentation rate, and leukocytosis. Although the pathophysiology is not completely evaluated, it usually presents with resistance to corticosteroids and many patients respond to anakinra, an IL-1 receptor antagonist. The mean age of onset is 51, but very few cases have been documented in elderly patients. Here we describe a 79-year-old woman diagnosed as Schnitzler syndrome who fulfilled the diagnostic criteria of the syndrome with multiple mediastinal lymph nodes, fever and arthralgia, bone pain, elevated erythrocyte sedimentation rate, urticarial vasculitis and a IgG kappa monoclonal gammopathy of undetermined significance. On capillary serum protein electrophoresis of the patient with the Capillarys System, the morphology of the γ-region was disturbed. Although there wasn't any obvious monoclonal peak on Capillarys (immunotyping), the

ÖZET

Schnitzler sendromu, nadir bir ürtiker nedenidir. Monoklonal gammopati, kronik ürtiker veya ürtikeryal vaskülit birlikteliği ile ateş, artralji veya artrit, kemik ağrısı, hepato- ve/veya splenomegali, palpabl lenf nodları, artmış eritrosit sedimentasyon hızı ve lökositoz kriterlerinden en az ikisinin varlığı olarak tanımlanmaktadır. Sendromun patofizyolojisi tam olarak anlaşılamamıştır. Genellikle olgularda kortikosteroide direnç görülmekle beraber, bir IL-1 reseptör antagonisti olan anakinraya birçok olgu olumlu yanıt vermiştir. Sendromun ortalama başlangıç yaşı 51 olarak bildirilmektedir. Ancak nadiren yaşlı hastalar literatürde bulunmaktadır. Bu bildiride ateş, artralji, kemik ağrısı ve multipl lenfadenopatileri olan, artmış eritrosit sedimentasyon hızı, ürtikeryal vaskülit bulguları ve IgG kappa tipi önemi bilinmeyen monoklonal gammopati saptanması üzerine Schnitzler sendromu tanısı konulan 79 yaşında bir kadın hasta sunulmaktadır. Kapiller sistem ile bakılan serum protein elektroforezinde γ-bölgesi bozulmuş olarak saptanmıştır. Bu bulgu, aşikar bir monoklonal pik görülmemesine rağmen, IgG kappa tipi monoklonal immünglobulin olarak

Yazışma Adresi/Address for Correspondence
Doç. Dr. Aslı GELİNCİK
İstanbul Üniversitesi İstanbul Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Allerji Bilim Dalı, Çapa-İstanbul, Türkiye
e-posta: gelincik@istanbul.edu.tr

result was diagnosed as an IgG kappa type monoclonal immunoglobulin. For the confirmation of our finding we performed immunofixation electrophoresis which is accepted as the gold standard method for the characterization of monoclonal proteins, although it failed to detect an IgG kappa type band. Both kappa and lambda free light chain concentrations were within the reference range, however the kappa/lambda ratio was abnormal. The patient initially responded well to corticosteroids, but later needed to be treated with azathioprine as a corticosteroid sparing drug. After total clinical improvement methylprednisolone was discontinued with tapering and azathioprine was kept on. At the end of 3 months of therapy, she was accepted to be in clinical remission. During her follow up she has remained in remission approximately for a year with the low dose of azothiopurine.

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Key words: Schnitzler syndrome, chronic urticaria, monoclonal gammopathy, capillary electrophoresis, urticarial vasculitis

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değerlendirilmiştir. Monoklonal proteinlerin belirlenmesinde altın standart metot kabul edilen immünfiksasyon yönteminde ise IgG kappa tipi bant saptanamamıştır. Bakılan kappa ve lambda serbest hafif zincir konsantrasyonları referans değerler içinde ölçülmüştür. Ancak kappa/lambda oranı artmış olarak bulunmuştur. Hastanın tedavisinde başlangıçta kortikosteroide olumlu yanıt alınmış, ancak steroid dozu azaltılırken alevlenme görülmesi üzerine tedaviye immünsüpresif ajan olan azatiopirin eklenmiştir. Klinik düzelme görüldükten sonra metilprednizolon azaltılarak kesilmiş, azatiopirin tedavisine devam edilmiştir. Üç aylık tedavi sonunda hasta klinik remisyonda kabul edilmiştir. Hastanın yaklaşık bir yıllık takibinde düşük doz azatiopirin ile iyilik halinin devam ettiği gözlenmiştir.

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Anahtar kelimeler: Schnitzler sendromu, kronik ürtiker, monoklonal gammopati, kapiller elektroforez, ürtikeryal vaskülit

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INTRODUCTION

Urticaria is defined as rapidly appearing wheals and/or angioedema, where wheals consist of central swelling with surrounding reflex erythema, associated with itching or sometimes with burning sensations and a fleeting nature, with the skin turning to its normal appearance usually within 24 hours. Chronic urticaria is considered when the disease lasts longer than six weeks[1].

The subtypes of urticaria are classified for clinical use in a recent guideline[1]. Accordingly, some diseases related to urticaria for historical reasons and syndromes that include urticaria are presented separately in another group[1]. This classification may provide clinicians a better understanding of heterogeneous conditions related to urticaria and lead individualized approach for each patient.

Each patient must be evaluated for different presentations and diagnosed separately. For example patients with periodic fever with urticaria, and other systemic symptoms like arthralgia, myalgia may be diagnosed as adult onset Still's disease. Very rare conditions like Schnitzler syndrome or genetical diseases such as certain types of the cryopyrin-associated periodic syndromes may be considered[1]. Each accompanying symptom, sign or laboratory finding including biopsy specimens must be carefully analyzed individually.

Schnitzler syndrome is defined by monoclonal gammopathy and chronic urticaria or urticarial vasculitis combined by at least two of the following features: fever, arthralgia or arthritis, bone pain, hepato-and/or splenomegaly, palpable lymph nodes, elevated erythrocyte bedimentation rate, and leukocytosis[2]. Although the physiopathology is not completely understood, it usually presents with resistance to corticosteroids and many patients respond to anakinra, an IL-1 receptor antagonist[3,4]. The mean age of onset is 51, but very few cases have been documented in elderly patients[2,5]. In a

recently published letter, the symptoms in an elderly patient resolved with corticosteroids in moderate doses[5].

Here we describe an old patient diagnosed as Schnitzler syndrome after detailed assays, including immunotyping, a new alternative assay of immunofixation. This patient initially responded well to corticosteroids, but later needed to be treated with azathioprine as a corticosteroid sparing drug.

CASE REPORT

A 79-year-old woman referred to our clinic for a 10 month history of urticarial lesions with a preference for the upper extremities and the neck (Figure 1,2). Severe pruritus was present. Detailed history revealed that one month ago fatigue, intermittent subfebrile fever, bone pain and arthralgia including monoarthritis of the right wrist were added to the clinical picture. Therapy with several antihistamines was unsuccessful. Only partial effect in arthralgia and fever was seen with short-term therapy of 16 mg/day methylprednisolone and non-steroid anti inflammatory drugs. She had been taking diltiazem 60 mg per day for hypertension for 20 years. Physical examination revealed urticarial lesions on the left lower arm and the neck and monoarthritis of the right wrist. When marked, each urticarial lesion lasted longer than 24 hours and a mild residual hyperpigmentation was seen on resolved areas.

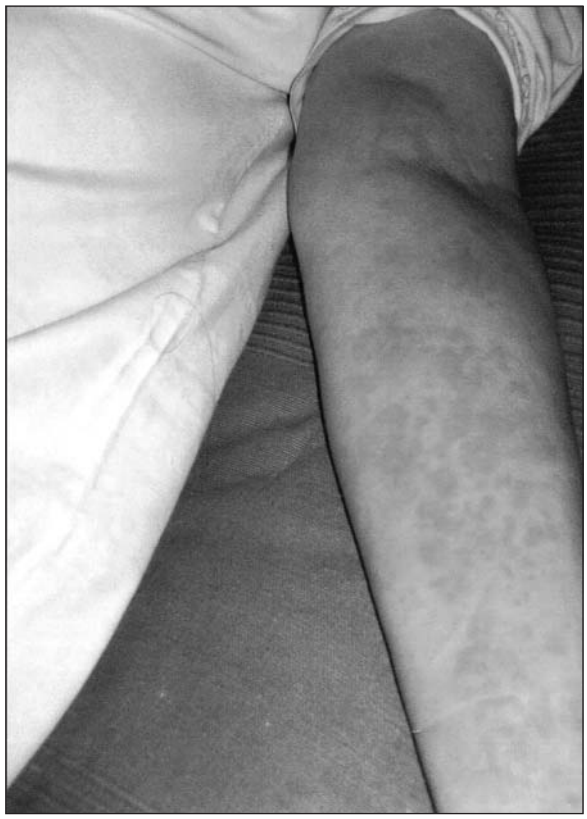

Figure 1. Clinical lesions at admission.

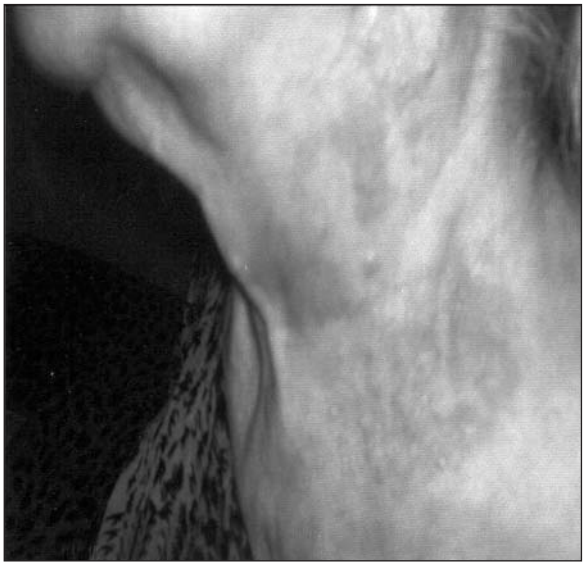

Figure 2. Clinical lesions at admission.

Laboratory findings revealed normochromic normocytic anemia, an erythrocyte sedimentation rate of 71 mm/hour, increased high sensitive CRP (50 mg/L), hypoalbuminemia (3 g/dL), and hypogammoglobulinemia (0.49 mg/dL). Radiographic examinations of the bones revealed no punched-out lesions.

On capillary serum protein electrophoresis of the patient with the Capillarys System (Sebia, Paris, France), we observed that the morphology of the γ-region was disturbed but there wasn't any obvious monoclonal peak (Figure 3). The serum monoclonal protein was detected and characterized (immunotyping) as an IgG kappa type monoclonal immunoglobulin on Capillarys. For the confirmation of our finding

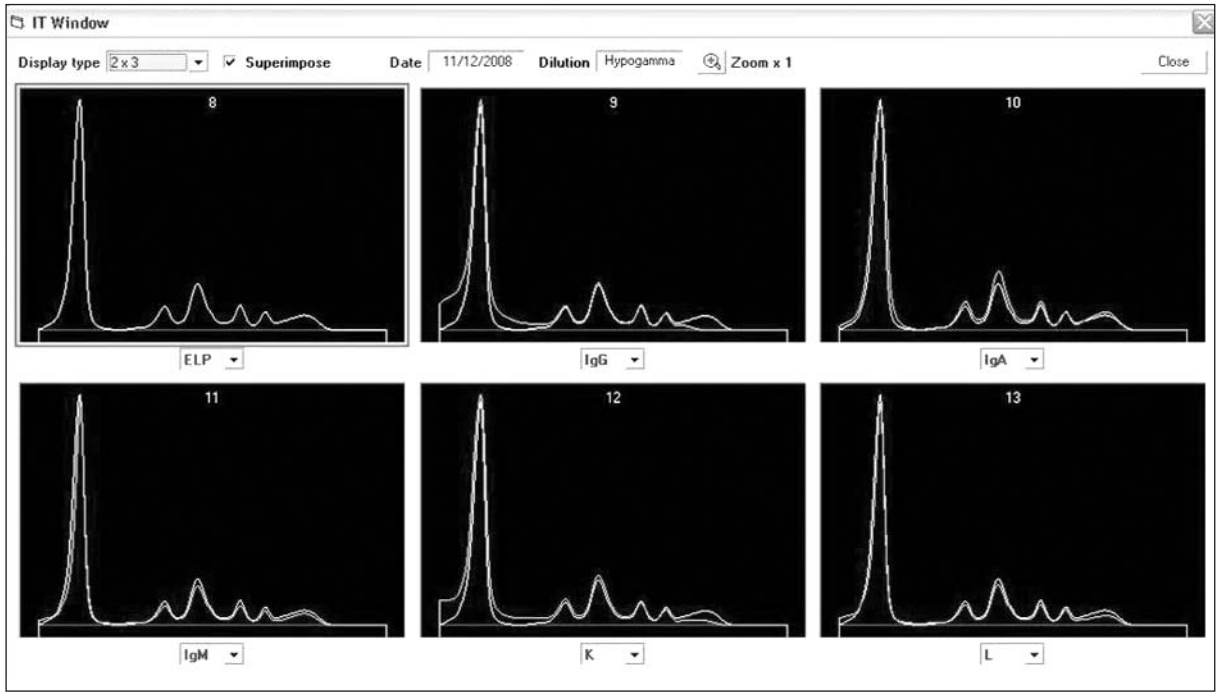

Figure 3. IgG kappa type monoclonal gammopathy with immunotyping.

we performed immunofixation electrophoresis which is accepted as the gold standard method for the characterization of monoclonal proteins, although it failed to detect an IgG kappa type band.

We also performed kappa and lambda free light chain (FLC) quantitation (Freelite, The Binding Site, Birmingham, UK) nephelometrically (Dade Behring BN ProSpec, Marburg, Germany). Both kappa and lambda free light chain concentrations were within the reference range, however the kappa/lambda ratio was abnormal [(kappa free: 19.17 mg/L (N: 3.30-19.40 mg/L); lambda free: 9.90 mg/L (N: 5.71-26.30 mg/L); kappa/lambda: 1.94 (N: 0.26-1.65)]. Also serum IgA, IgG and IgM were detected in normal ranges (101 mg/dL, 623 mg/dL, 62.3 mg/dL respectively).

Although serum free light chain assays do not measure intact monoclonal immunoglobulins, abnormal kappa/lambda ratios supported the diagnosis of a monoclonal gammopathy[6]. Bone marrow biopsy showed a normocellular bone marrow. Accordingly, an IgG/kappa monoclonal gammopathy of undetermined significance (MGUS) was diagnosed.

A skin biopsy of an active lesion was performed. Histopathology revealed upper dermal edema, ectasic and engorged small vessels, perivascular neutrophilic infiltrate and rare leucocytoclasia (Figure 4). Although the clinical course suggested the diagnosis of urticarial vasculitis, due to the absence of vessel wall alterations, the microscopic findings did not formally support this diagnosis. Serum C3 was 141 mg/dL, and ANA, anti-DNA ANCA were all negative, which may be interpreted as a normocomplementemic urticarial vasculitis and exclude other connective tissue diseases.

Thorax computerized tomography demonstrated multiple mediastinal lymph nodes with the greatest size of 10 x 7 mm. The whole body PET scan suggested these lymph nodes were reactive, without any other lesions. All these findings indicated that there was no evidence for any malignancy related with the monoclonal gammopathy and vasculitis.

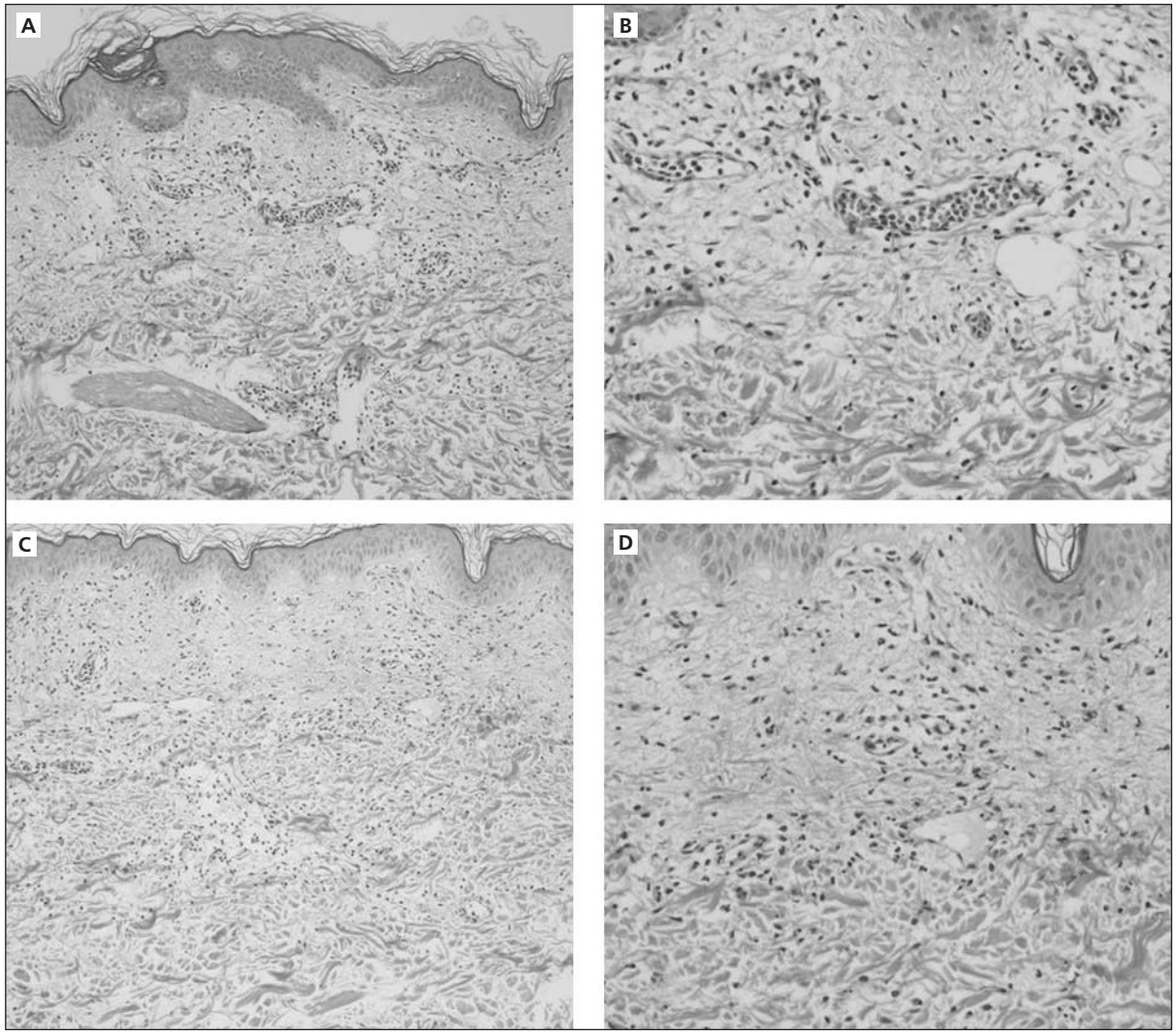

Figure 4. a. Panoramic view of an area where upper dermal edema, small vessel ectasia and engorgement are noticed. b. Close-up of the same area. Numerous neutrophils are noticed. c. On a different area of the same biopsy, edema, small vessel ectasia and more perivascular distribution of the infiltrate. d. Close-up shows neutrophils, a few nuclear fragments. But clear cut vessel wall alteration is absent.

Eventually, the patient was diagnosed as Schnitzler syndrome. The patient fulfilled the diagnostic criteria of the syndrome with elevated erythrocyte sedimentation rate, multiple mediastinal lymph nodes, fever and arthralgia, bone pain and urticarial vasculitis and a IgG kappa MGUS. Methylprednisolone 24 mg/day was initiated and after three weeks the dose was tapered to 4 mg per week and hydroxy chloroquine 200 mg per day was started. At the end of five weeks her lesions ceased and she was discharged stopping her methlyprednisolone. Seven weeks later, she came back with aggravation of her symptoms including urticaria and hydoxy chloroquine was discontinued, instead methylprednisolone 24 mg/day and azathioprine 50 mg/day were started. The clinical picture improved gradually within a week. After total clinical improvement methylprednisolone was discontinued with tapering and azathioprine was kept on. At the end of three months of therapy, she was accepted to be in clinical remissi-

on. During her follow up she has remained in remission approximately for a year with the low dose of azothiopurine.

DISCUSSION

Schnitzler syndrome is a rare, recently described syndrome with chronic urticaria, accompanying with various systemic symptoms and therefore different specialists such as immunologists, dermatologists, hematologists and rheumatologists need to be aware of this potential diagnosis. The accompanying paraprotein and the inefficiency of antihistamines are some of the important features of this syndrome.

The urticarial lesions seen in Schnitzler syndrome usually present as a course of chronic urticaria, but urticarial vasculitis is found in 25% of the cases[2]. Although in our patient the clinical appearance of the lesions resembled urticarial vasculitis, the biopsy results failed to confirm this. The lesions in this syndrome usually are not accompanied by pruritus at the beginning, but in approximately 45% of patients after several years become pruritic[2]. Interestingly our patient complained of intractable itching from the very beginning of the disease especially increasing at nights. Similarly with the previous cases, the symptoms including itching did not cease with classical urticarial treatment. Although in some cases, anakinra was shown to be effective during the continuity of the treatment, we decided to start the treatment with a moderate dose of methylprednisolone considering the patient's age. Similarly in a recently published letter the effectiveness of corticosteroid was shown in an elderly diagnosed patient[5]. Our patient responded to the treatment in moderate doses, but a flare-up of symptoms was observed when the dose was tapered to 4 mg per day and hydroxychloroquine was initiated as a dose sparing agent. Unfortunately, the symptoms did not cease with this regimen and hydroxychloroquine was discontinued. Then another relatively safe cytotoxic agent, azothoprine was found to be successful and she remained in remission for 12 months.

In immunotyping procedure, serum sample is mixed with individual antisera specific against gamma (IgG), alpha (IgA), and mu (IgM) heavy chains; and kappa and lambda (free and bound) light chains. Serum protein fractions are separated in silica capillaries and detected by their absorbance at 200 nm. The electrophoregrams are evaluated visually and the type of the monoclonal protein is diagnosed by the disappearance or the reduction of the heavy and the light chain of the immunoglobulin (capillary zone electrophoresis/immunosubtraction).

We have found IgG kappa type monoclonal gammopathy with immunotyping. In a recent review by Koning et al. it is stated that eigth cases with the IgG variant were reported to date and seven of them were of IgG kappa type[2]. In all of these cases immunofixation was used. Although immunofixation is the gold standard method for detecting monoclonal proteins according to recent evidence, immunotyping is a new promising method especially in cases where immunofixation fails to detect the paraproteins. Similarly, capillary electrophoresis has been reported to display higher sensitivity than agarose gel electrophoresis (Hydrasys, Sebia), (97.2% and 93.5%, respectively) for the detection of monoclonal proteins[7].

In conclusion, Schnitzler syndrome is a rare, difficult to treat form of chronic urticaria with accompanying paraproteinemia. In case of intractable chronic urticaria with or without vasculitis, Schnitzler syndrome must be one of the diagnoses to be considered.

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