sciendo
10.2478/AMB-2018-0021

A NEW CASE OF SCHNITZLER SYNDROME IN BULGARIA

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Abstract. *We describe the case of a 74-year-old Bulgarian woman with a long history of chronic urticaria with severe burning sensation, arthralgia and fever. Additional symptoms of Schnitzler such as monoclonal immunoglobulin – kappa component, elevated erythrocyte sedimentation rate and enlarged lymph nodes were detected six years after the onset of the symptoms. The first diagnoses hypersensitive vasculitis and dermatitis were established in 2009. Schnitzler syndrome was recognized and the diagnosis was established 2 years later after some examination tests. The time course of the values of IgM, C-reactive protein, erythrocyte sedimentation rate and neutrophils were presented. The mean value of IgM is 13.8 ± 2.19 g/l, the mean value of erythrocyte sedimentation rate is 48.6 ± 14.46 mm/h and the mean value of C-reactive protein – 29.8 ± 7.34 mg/l. The use of nonsteroid anti-inflammatory drugs throughout the period and corticosteroids prescribed parenterally and orally resulted in the relief of arthralgia and fever.*

Key words: *Schnitzler syndrome, Bulgaria, rare disease*

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INTRODUCTION

Schnitzler syndrome is an extremely rare disease which affects many organs and systems in the human body. It was described for the first time in 1972 by the French dermatologist Liliane Schnitzler [1]. Now it is considered as a late-in-life acquired autoimmune and auto-inflammatory syndrome [1-3]. To date, 281 cases have been reported, with a male–female ratio of 1.5:1 [1-2].

Soon after description of the syndrome the cases were presented usually in French medical journals, but nowadays the cases from 25 countries of all continents have been included in literature reviews. According to Koning et al. the average follow–up is 9.5 years after onset of symptoms but there are patients with a follow-up of 20 years as well as with a follow-up of less than 1 year [2, 6].

Schnitzler syndrome is defined with urticaria and monoclonal gammopathy as well as with at least 2 minor criteria: fever, bone pain, arthralgia or arthritis, lymphadenopathy, organomegaly, an increased erythrocyte sedimentation rate (ESR), leukocytosis or increased neutrophil counts and evidence of osteosclerosis [1, 4, 6-7].

The major diagnostic criterion, a chronic rash, precedes the other symptoms. The frequency of urticaria is more than once per year. Half of the patients with Schnitzler syndrome suffer from red skin lesions which cover the trunk, extremities, head and neck. Individual lesions persist less than 24 to 48 h. Skin lesions are often associated with a burning rather

than pruritic sensation. Pruritus is minimal or absent initially and develops over time in approximately 20-45% of all cases [1, 6].

The second most common symptom is intermittent fever which is described in 72-85% of the patients. Chills and fever spikes are usually reported with high temperature and occur in 90% of the patients [6]. Urticaria usually preceded the fever (median of 3 years; range 1-14 years) but rarely fever preceded the urticaria or they occurred concurrently [2]. Weight loss is reported in 16% of the cases. Between 66% and 70% of the patients complain about pain in the knees, hips, back, hands, feet and bones. There are also additional symptoms which are developed months to years after the disease onset. Approximately 26-50% of the patients develop lymphadenopathy, 5% – organomegaly, 12.5% – hematologic malignancy and approximately 20% develop a lymphoproliferative disorder [2]. The results of laboratory tests show that 79-80% of the patients have IgM-k monoclonal gammopathy, 70-75% have leukocytosis and between 70-97% of the patients develop an increased erythrocyte sedimentation rate [2,5].

Histopathologic examination shows a predominantly neutrophilic perivascular and interstitial inflammation (57%) or a mononuclear cell perivascular inflammation (29%), with eosinophils in 50% of the cases [2, 5-6]. Neutrophilic urticaria is the most common histological pattern, although a few cases of leukocytoclastic vasculitis have been reported [8].

Diagnosis is often delayed and requires performance of many laboratory tests. The delay of diagnosis is 5 years on average ranging from several months to 20 years [9]. There are two cases of patients with Schnitzler syndrome in Bulgaria described in the literature and in the current study we present the third case.

The aim of the study is to describe a new case of Schnitzler syndrome in Bulgaria. Most of the reported cases are written at the time of diagnosis and information about the progression of the disease is not available. Our main focus is on the history of the disease using the follow-up data of laboratory investigations. The treatment patterns of the disease during the years are also presented.

DESCRIPTION OF THE CASE STUDY

The long-term disease progression of a 74-year-old woman with Schnitzler syndrome was presented. Follow-up data regarding laboratory investigations and the results of skin histology were obtained from the medical records of the patient for the period 2005-2016.

The first symptoms of the disease were rash, fever and artralgia and began in 2005, which had preceeded the other symptoms for a period of two years. Recurrent red skin lesions covered the trunk and extremities during the years and were associated with a burning sensation. The skin lesions lasted longer than ordinary urticaria and usually persisted for 10 days. Lesions up to 10 cm in diameter were measured and their dimensions increased over time and merged. Lesions-free periods were more often at the beginig of the disease but the periods in which lesions cleared completely shortened with time.

In 2006 new common symptoms – an intermittent fever with chills, fever spikes and pain in the joints developed. The patient developed high temperature. The skin lesions lasted longer than usual and persisted for several weeks. The diagnosis dermatitis and hypersensitive vasculitis was established in 2009 after performing skin biopsy during a short hospital admission. The diagnoses neutrophilic perivascular and interstitial inflammation (neutrophilic urticarial dermatosis) without true vasculitis were established.

In 2011 the patient had been experiencing signs of a chronic inflammation and the health practitioner suspected an excess of abnormal immunoglobulin production. An electrophoresis test was done which showed albumin electrophoresis levels of 53.05 g/l (reference values 35.8-52 g/l) and gamma electrophoresis – 25.47% (reference values 11.5-18.6%). After these abnormal results a test for immunoglobulins was ordered and the levels of immunoglobulins IgG, IgA, and IgM were measured. In our case only monoclonal elevation of IgM was detected, while the levels of immunoglobulins IgG, IgA were in the range 9.87-10.74 g/l and 4.8 g/l, accordingly.

At the end of 2011 the patient was diagnosed with the Schnitzler syndrome. Documented urticaria and monoclonal gammopathy were major criteria while intermittent fevers and elevated erythrocyte sedimentation rates were the additional symptoms for establishing the diagnosis.

The additional symptom lymphadenopathy was developed in 2012. Nodes, located in the inguinal sites and neck, were found. Up to 2017 there were no symptoms of lymphoproliferative disease.

Osteoporosis of the distal extremities and backbone was an underlying disease. Osteoporosis was diagnosed with a specific marker for the increased bone resorption – elevated serum concentrations of beta-CTx (Beta-GrossLaps). Osteoporosis was proved with a value of beta-CT x 1.16 ng/ml (referent values – up to 0.704 ng/ml). The level of osteocalcin was 34.41 [ng/ml] (normal range between 15-46 [ng/ml]).

During this period the patient was hospitalized four times – twice before the real diagnosis was established, when the patient was treated for hypersensitive vasculitis and twice after that.

Results from erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), levels of immunoglobulins and neutrophils (NEU) were monitored twice a year in the period 2011-2015. The time course of erythrocyte sedimentation rate, C-reactive protein, neutrophils, the level of immunoglobulins in the blood; skin histology, bone imaging and response to the applied treatment were analysed throughout disease establishment and progression.

The values of ESR were invariably elevated in the period under investigation. The reference values of ESR were up to 15 mm/h at 2005 and up to 30 mm/h from 2006. Medical reports showed that in April 2005, ESR was 29 mm/h but all other blood parameters were normal. During the next period the values of ESR were again double the normal values – from 29 to 68 mm/h, mean value 48.6 ± 14.46 mm/h (Fig. 1).

The levels of C-reactive protein were also increased. The mean value of the parameter CPR was 29.8 ± 7.34 mg/l, while the reference values of CRP should be less than 8 mg/l (Fig. 2).

The neutrophil levels were also monitored. The value of neutrophils was doubled in the four-year period but was still less than the maximum referee of 70% (Fig. 3).

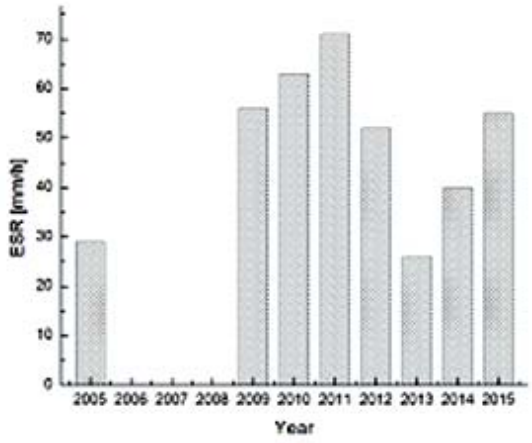

Fig. 1. The time course of ESR for the period 2005-2015 (left)

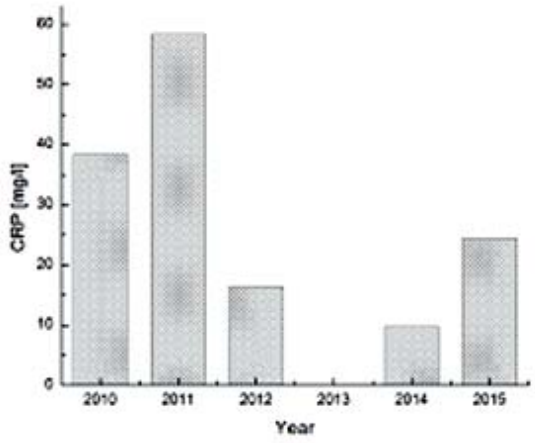

Fig. 2. The time course of CRP values (right)

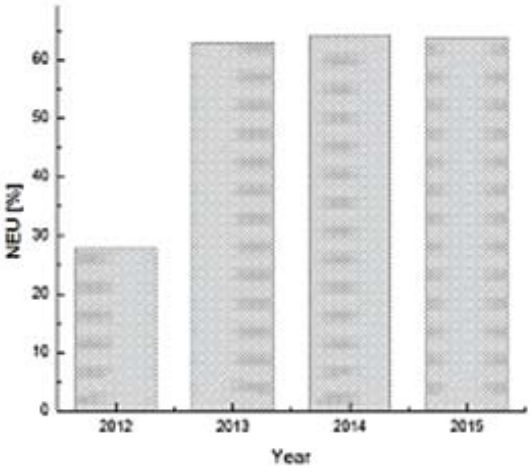

Fig. 3. The levels of neutrophils (NEU) (left)

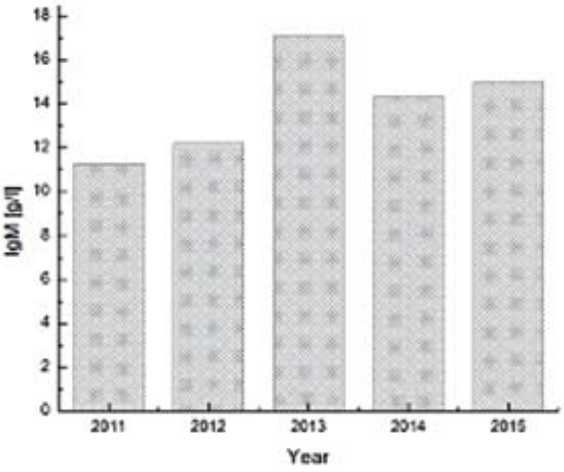

Fig. 4. The time course of IgM values (right)

The normal values of IgM were in the interval of 0.4-2.3 g/l but our patient had values more than six folds greater – between 10.8-17.1 g/l with mean value of 13.8 ± 2.19 [g/l]. (Fig. 4).

The treatment of the disease began after the establishment of Schnitzler syndrome in 2011 and included corticosteroids (methylprednisolone), antihistamins (loratadine, cetirizine dihydrochloride, chloropyramine hydrochloride), potassium gluconate and antibiotics (ciprofloxacin). Nonsteroidal anti-inflammatory drugs (aceclofenac) were also added in order to decrease the level of pain in the joints [10]. There was a relief of the symptoms as a sign of response to the treatment but the increased risk of osteoporosis imposed the need of a lower dose of corticosteroids. A recurrence of the symptoms was experienced after the reduction of corticosteroids. The last laboratory results of the patient revealed her current condition (Table 1).

Table 1. The laboratory results

WBC	7.74*10^9/L	Sodium	142 mmol/l
Hemoglobin	127 g/L	Chlorine	100.3 mmol/l
Hematocrit	0.404 L/L	Glucose	4.47 mmol/l
Platelets	345*10^9/L	Phosphorus	1.01 mmol/L
Allkaline Phosphatase	78 U/l	Potassium	4.37 mmol/l
ASAT/ALAT	14.6U/l / 10.6U/l	Creatinine	63 μmol/l
ESR	55 mm/h	Calcium	2.32 mmol/l

DISCUSSION

The study presents a new case of Schnitzler syndrome in Bulgaria. The symptoms of rash and fever began in 2005. It took six years before the correct diagnosis was established.

A long-term course of elevations of ESR, CRP, NEU together with IgM for the period of 16 years is presented (Figs. 1-4). Our patient is among 80-85% of patients with reported IgM kappa (IgM k) monoclonal gammopathy [2, 5-6]. The abnormal values of monoclonal protein in the blood usually causes problems. Monoclonal elevations of IgM is connected to the development of chronic lymphocytic leukemia (CLL), MGUS (monoclonal gammopathy of undetermined significance), lymphoma, Waldenstrom's macroglobulinemia and IgM primary systemic amyloidosis. According to Lipsker about 15% of the patients with elevated IgM or IgG progress to a lymphoproliferative disorder such as Waldenström macroglobulinemia or B-cell lymphoma [1].

According to Simon et al. patients with monoclonal gammopathy should be monitored once per year if IgM is under 10 g/l and twice a year if IgM is about 30 g/l [4]. The mean value of IgM 13.8 g/l in our case means that monitoring has to be done at least once per year. The patient has no symptoms of leukocytosis although leukocytosis, usually neutrophilia, is found in three-quarters of the patients [2]. The levels of osteocalcin were tested in 2011 and the value was 34.41 ng/ml which is higher than those reported in the study of Terpos et al. [7]. The level of osteocalcin in the patients from the control group was 10 ng/mL and for patients with Scnitzler syndrome – 20 ng/ml [7].

The medicines used for treatment of Schnitzler syndrome are corticosteroids and immunosuppressants as well as antihistamins, antibiotics; nonsteroidal anti-imflamatory drugs (NSAIDs), phototherapy and biological agents [4]. The first choice of treatment consists of non-steroidal anti-inflammatory drugs such as ibuprofen and systemic corticosteroids [11]. Such a therapy is successful in less than half of the cases [12]. De Koning analyzed data of 185 cases of Schnitzler syndrome and reported that corticosteroids were highly effective in only 18% and partially effective in 46% of the 185 reported cases [2]. This treatment leads to the improvement of skin lesions, fever and pain but the prescribed high doses usually cause significant long-term adverse effects [4].

The traditional immunosuppressive therapies include anakinra, canakinumab, tocilizumab and rilonacept [2, 13]. De Koning reports that the therapies with IL-1 antagonists are highly effective but only anakinra has been used for the treatment of 86 cases [2]. Other medicines have been applied to a group of 4-11 patients and are under investigation [14]. A dose of 100 mg daily Anakinra completely controls all symptoms of Schnitzler syndrome but a recurrence of the signs and symptoms is experienced after interruption of the treatment.

Another treatment for Schnitzler syndrome is immunosuppressive agents (cyclophosphamide, cyclosporine, and methotrexate) [15-16]. Only cyclophosphamide (CPX) has resulted in a complete remission of the disease lasting after a 2-year follow-up [4]. Antihistamines have only 10% partial efficacy in controlling the rash and pruritus, probably due to a histamine-independent etiology of the rash [2].

There is no medicine with an affordable price which can control all symptoms of the disease effectively. This means that the relief of the symptoms depends on a combination of medicines from all the thera-

peutic groups described above. The treatment of the 74-year-old woman did not include anakinra and rilonacept because these drugs are not included in the Positive Drug List in Bulgaria. The main conclusion from the patient's treatment is that the dose of corticosteroids should be reduced in a way that bone pain and fever be prevented but the risk of osteoporosis not increased.

CONCLUSIONS

Schnitzler syndrome is a chronic condition which prognosis is relatively optimistic. It is crucial monoclonal gammopathy to be regularly monitored. Corticosteroids in low doses should be prescribed in order to control some main symptoms. The patients should be closely monitored because of a higher risk of corticosteroid-induced osteoporosis and a significant risk of other side effects.

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