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THE SCHNITZLER SYNDROME: AN ACQUIRED AUTOINFLAMMATORY SYNDROME BY MONOCLONAL IMMUNOGLOBULIN

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ABSTRACT

Schnitzler syndrome is a rare disorder characterized by a chronic reddish rash that resembles hives (urticaria) and elevated levels of a specific protein in the blood (monoclonal IgM gammopathy). Symptoms associated with Schnitzler syndrome may include repeated bouts of fever, joint inflammation (arthritis), joint pain (arthralgia), bone pain, and other findings such as enlarged lymph nodes (lymphadenopathy). A monoclonal IgM gammopathy refers to the uncontrolled growth of a single clone (monoclonal) of plasma cells, which results in the abnormal accumulation of M-proteins (also known as immunoglobulin M or IgM) in the blood. However, the specific role these proteins play and the exact cause of Schnitzler syndrome is unknown. Schnitzler syndrome is difficult to classify and some researchers have suggested that it is an acquired autoinflammatory syndrome. Autoinflammatory syndromes are a group of disorders characterized by recurrent episodes of inflammation due to an abnormality of the innate immune system. They are not the same as autoimmune disorders, in which the adaptive immune system malfunctions and mistakenly attacks healthy tissue. This review will provide a comprehensive overview of the clinical and biological features of this syndrome, emphasizing its particular rash, its complications and its treatment.

KEYWORDS: Fever, Joint Pain, Schnitzler Syndrome, Organomegaly.

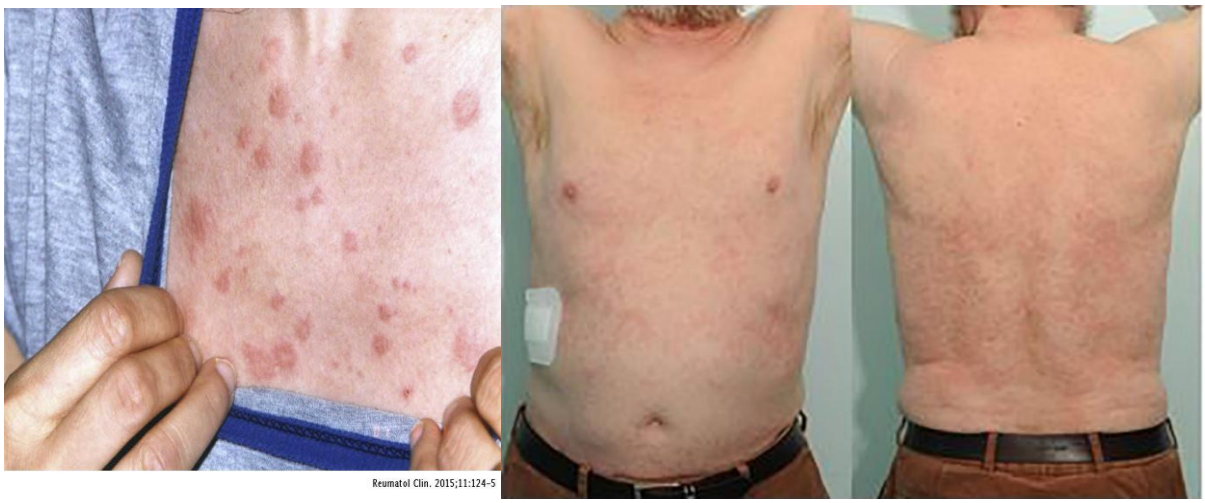

Figure 1: Schnitzler syndrome.

Background: The Schnitzler syndrome is a rare and acquired systemic disease which bears in common many features with a group of inherited diseases referred to as auto-inflammatory syndromes. Its main clinical features include fever, an urticarial rash, muscle, bone and/or joint pain and enlarged lymph nodes. A monoclonal IgM component is the biological hallmark of the disease. Conventional therapies including anti-histamines for the skin rash, as well as anti-inflammatory drugs, steroids and immunosuppressive drugs for the systemic signs, are usually ineffective. However, the IL-1 receptor antagonist anakinra was found to rapidly control all the symptoms of this syndrome. However, signs recur as soon as the treatment is stopped. About 15% to 20% of patients with a Schnitzler's will develop a lymphoproliferative disorder, a prevalence shared with other patients with monoclonal IgM gammopathies of undetermined significance (MGUS). AA-amyloidosis is a concern in untreated patients.[1]

History: The different signs of this syndrome were first reported in 1972 and then published in 1974 as an autonomous entity by Liliane Schnitzler, a French dermatologist. In the following years, cases were reported from all over the world including North America and Japan, but mostly from Europe. The European preeminence is probably related to a better knowledge of this entity in the old World. In 1999, Lipsker et al reported 4 cases and performed an extensive literature review which allowed them to establish diagnostic criteria, which are currently accepted. In their paper, they included the CINCA (Chronic infantile Neurological Cutaneous and Articular syndrome)/NOMID (Neonatal Onset Multi-

Inflammatory Disease) and the Muckle-Wells syndrome in the differential diagnosis and thus pointed for the first time to similarities between the Schnitzler syndrome and the auto-inflammatory syndromes, of which the latter are a paradigm. Indeed, the CINCA syndrome, the Muckle-Wells syndrome and familial cold auto-inflammatory syndrome are different phenotypes of the cryopyrinopathies, monogenic diseases involving the innate immune system. Their pathophysiology implies exaggerate activation of the inflammasome, an IL-1 synthesizing cellular machinery. And indeed, IL-1 inhibition is a very effective treatment modality in patients with CINCA. Since the Schnitzler syndrome shares many features with the CINCA syndrome, anakinra, an IL-1 inhibitor was also tried in the former syndrome. It proved to be the first really efficient treatment of the Schnitzler syndrome.[2]

Sign and Symptoms: The symptoms associated with Schnitzler syndrome can vary from one person to another. The symptoms can occur all at once or, because they often come and go, the symptoms can occur at different times. The symptoms tend to persist for many years (chronic disease).

A reddish, rash that resembles hives (urticaria) is the hallmark finding associated with Schnitzler syndrome. The distinctive rash usually consists of raised, reddish bumps (papules) and flatter, wider lesions (plaques). In most cases, a rash is the first symptom to appear in individuals with Schnitzler syndrome. The rash usually lasts for a day to two and then disappears without scarring. However, a new rash often develops each day so that a rash is a constant occurrence but the frequency of the rash can vary greatly from one person to another and some people only develop a rash a few times during the year. When the rash first develops, it usually is not itchy (not pruritic). However, in approximately 45 percent of cases, the rash will become itchy within a few years. The trunk, arms and legs are most often affected. The head, neck, palms and soles are usually spared. Some affected individuals have reported that alcohol, spicy foods and stress have aggravated the rash. Fevers that come and go over a period of time (chronic, intermittent fevers) are the second most common symptom in individuals with Schnitzler syndrome. The frequency of fevers varies greatly, ranging from being a daily occurrence to only a couple times per year. Fevers are usually unrelated to the skin rash, are well-tolerated and are rarely accompanied by chills.[3]

Figure 2: Symptoms of schnitzler syndrome (Fever, body rash, joint pain).

Additional symptoms associated with Schnitzler syndrome include bone pain, most often affecting the lower legs and hips, and joint pain, most often affecting the large joints such as the hips, knees, wrists and ankles. In some cases, inflammation of the joints (arthritis) may develop with accompanying swelling, redness and a feeling of heat or warmth in the joint. Despite joint involvement, joint degeneration or destruction has not been reported in individuals with Schnitzler syndrome. Abnormal enlargement of the lymph nodes (lymphadenopathy), the liver (hepatomegaly) and the spleen (splenomegaly) may also occur in some cases. Additional nonspecific symptoms that have been reported in individuals with Schnitzler syndrome include unintended weight loss, fatigue and a general feeling of poor health (malaise). Rapid swelling due to fluid accumulation just beneath the surface skin (angioedema) is very rare.

Most cases of Schnitzler syndrome have a chronic, benign course. However, over a period of 10 years, approximately 15 percent of affected individuals developed cancer, most often cancer caused by the overproduction of white blood cells (lymphoproliferative disorders) such as Waldenström macroglobulinemia. Some individuals with Schnitzler syndrome have elevated levels of a different protein (see Causes section below) than individuals with classic Schnitzler syndrome. These individuals are classified as having variant Schnitzler syndrome and have very similar symptoms to classic Schnitzler syndrome.

Causes: The exact cause of Schnitzler syndrome is unknown. Researchers believe that specific parts of the immune system may not function properly, eventually causing Schnitzler syndrome.

Individuals with Schnitzler syndrome also have a clinical finding called monoclonal IgM gammopathy, in which abnormalities affecting the production of immunoglobulins result in elevated levels of a specific immunoglobulin M (IgM) in the body. Immunoglobulins are proteins produced by certain white blood cells. There are five classes of immunoglobulins known as IgA, IgD, IgE, IgG, and IgM. Immunoglobulins play a role in defending the body against foreign substances or microorganisms by destroying them or coating them so they are more easily destroyed by white blood cells. At the time of diagnosis, IgM levels may only be slightly elevated and may remain stable for years. A variant form of Schnitzler syndrome has been reported in which individuals have a monoclonal gammopathy of IgG instead of IgM. Certain cytokines (specialized proteins secreted from certain immune system cells that either stimulate or inhibit the function of other immune system cells) play a role in the development of Schnitzler syndrome. The cytokine interleukin-1 (IL-1), is an important mediator of the inflammation in Schnitzler syndrome. Abnormal clinical findings involving interleukin-1 have been found in some individuals with Schnitzler syndrome and therapy with drugs that block the activity of interleukin-1 have brought about complete remission.

Affected population: Schnitzler syndrome affects males slightly more often than females. However, only approximately 160 cases of this rare disorder have been reported in the medical literature so no definitive conclusions can be made about ethnic or gender predispositions. Because of the varied symptoms and rarity of Schnitzler syndrome, a diagnosis is usually delayed by several years and researchers believe that the disorder is underdiagnosed, making it difficult to determine its true frequency in the general population. Most individuals with Schnitzler syndrome are in their 50s when the characteristic symptoms develop.

Less often, symptoms have been noted in individuals in their 30s. In one reported case, symptoms were identified in an individual 12 years old. It is to be questioned whether these cases were classical Schnitzler syndrome (see Related Disorders below).Schnitzler syndrome was first described in the medical literature in 1972, by a French dermatologist named Liliane Schnitzler. Most of the reported cases of Schnitzler syndrome have been from Europe,

particularly France, but cases from Australia, Japan and the United States have been reported too.[4]

Epidemiology: There is a slight male predominance and mean age of disease onset is 51 years. The youngest patient reported started urticaria at age of 13, but the Schnitzler syndrome is basically a disease of the adult, since only four patients started disease before age of 35. The delay to diagnosis exceeds 5 years in many cases.

The skin rash: As the skin rash - with the monoclonal component - is a defining criterion of the syndrome, it is present *by definition* in all patients. Patients with all signs of the Schnitzler syndrome except the skin rash should be referred to as Schnitzler-like syndrome. The skin rash is usually the first clinical sign and most patients started their disease with the eruption. The skin rash was classically referred to as "urticaria". However, recently this peculiar rash was described in detail and nosologically delineated from common urticaria. Patients with the Schnitzler syndrome have a rose pale or red eruption consisting of macules (flat lesions) or slightly raised papules and plaques. They last less than 24 hours, and are usually not or only moderately itchy. Lesions can occur on every body part, though involvement of face and extremities is rare.

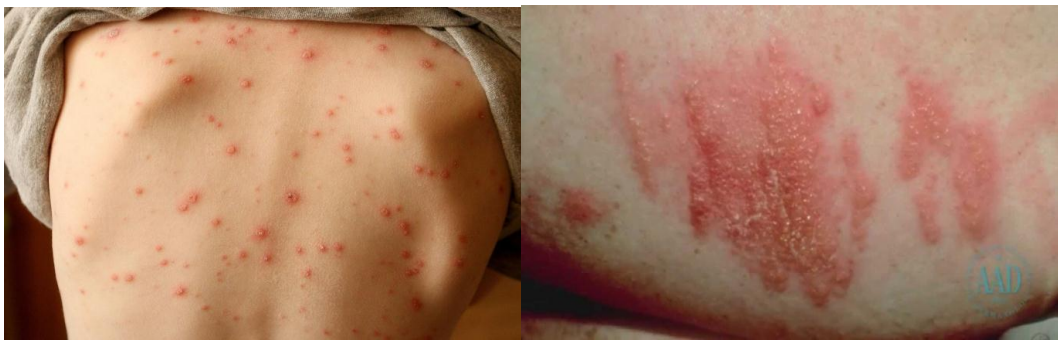

Figure 3: Skin rash.

Edematous swelling of the face (angioedema) is very rare and significant mucosal swelling with dyspnea and/or dysphonia is exceptional. Many patients report exacerbating factors including heat exposure, cold-exposure, alcohol consumption, some aliments, physical work, and stress. There is no specific chronology of the rash, as would be typical for example in patients with adult onset Still disease (AOSD) who report flares in the late afternoon. Confluence of lesions is possible, as is dermographism, i.e. friction of skin induces slightly raised plaques, though they are usually not itchy as they would be in authentic dermographism. The frequency of flares is variable from patient to patient, and in the same

patient from factors we yet ignore. Patients can have daily flares for months or years or remission for days to weeks. It is however exceedingly rare to be free of rash for a period longer than a month in untreated patients. Skin lesions resolve within hours without any sequel.

The fever: Almost all patients will develop fever. The fever is intermittent. Body temperature can rise above 40°C. Most patients manage the fever and due its recurrent nature, get used to it. The fever is usually well tolerated and chills are rare. Fatigue is however frequent during the fever flares. In most patients, there is no relation between the fever and the skin rash. Fever responds in some patients to NSAI drugs and/or to steroids and is usually completely controlled with anakinra.[5]

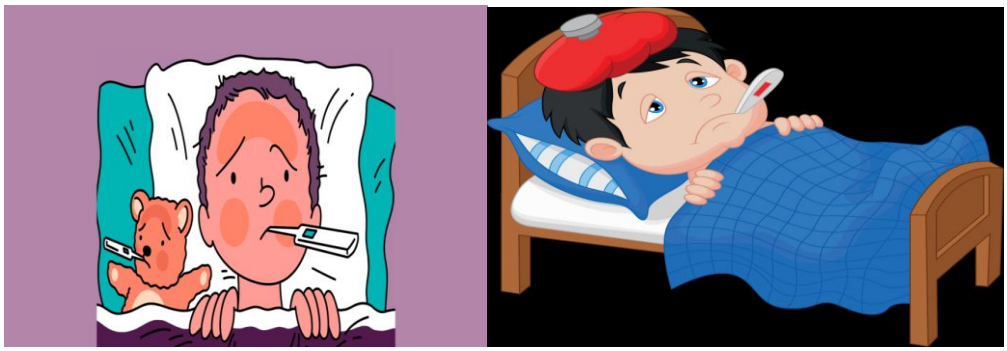

Figure 4: Fever.

Musculoskeletal involvement: Musculoskeletal involvement is another cardinal feature of the disease affecting about 80% of patients. Bone pain is the most characteristic finding, but arthralgias and sometimes fully developed arthritis, can occur. Joint destruction and/or deformities have not been reported so far. Bone pain affects mostly the iliac bone and the tibia. Femur, spine, forearm and clavicle were less often involved. Bone involvement is common, and 30 to 40% of the patients showed bone lesions on imaging studies. Osteocondensation is the most frequent radiological finding and the most common radiological pattern is a sclerotic bone marrow involvement with cortical hyperostosis of distal femora and proximal tibiae, and a lack of suggestive signs of malignancy. Lytic lesions were reported as well as periosteal apposition. Radiological differential diagnosis is broad and includes mastocytosis, POEMS syndrome, Erdheim-Chester disease, Camurati-Englemann or Van Buchem disease, Buschke-Ollendorf syndrome, osteopetrosis, melorheostosis, ribbing disease and hypertrophic osteoarthropathy. Bone technetium scanning reveals hyperfixation in the areas of radiological involvement.

Figure 5: Joint pain.

Magnetic resonance imaging confirms thickening of cortices and can show medullar bone involvement and marrow infiltration without space occupying features in the affected areas. A solitary sclerotic lesion has been reported and thus radiological differential diagnosis should be expanded to include entities as lymphoma, multiple myeloma, SAPHO syndrome, osteoblastic metastases, osteosarcoma, chronic osteomyelitis, osteoid osteoma, and healing stress fractures. Bone biopsy of involved areas can be normal or show an unspecific inflammation in 5 patients, sometimes associated with hyperactive osteoblasts. One patient had histological evidence of osteosclerosis. Heterotopic ossification after total hip arthroplasty has been reported.

Organomegaly: *Palpable lymph nodes* are found in about 45% of the patients and *hepatic or splenic enlargement* occurs in about a third of the patient. Palpable lymph nodes are found in the axilla and inguinal sites and sometimes in the cervical region. Those lymph nodes can be multiple, permanent and up to 2 or 3 cm large and therefore suggest the diagnosis of lymphoma, but biopsy shows non-specific inflammation.

Diagnosis: A diagnosis of Schnitzler syndrome is based upon a thorough clinical evaluation, a detailed patient history, exclusion of other disorders, and identification of characteristic findings, specifically a urticarial rash, an M protein and at least two of the following findings – fever, joint pain or inflammation, bone pain, palpable lymph nodes, enlargement of the liver or spleen, elevated numbers of white blood cells (leukocytosis), elevated red blood cell (erythrocyte) sedimentation rate or abnormalities on bone morphological study, which can reveal increased bone density (osteosclerosis). Sedimentation rate measures how long it takes red blood cells to settle in a test tube over a given period. Many individuals with Schnitzler syndrome have an elevated sedimentation rate, which is an indication of inflammation.

In younger patients, careful attention should be paid because alternative diagnosis is much more likely and often overlooked – such as urticarial vasculitis, hematological disease or chronic idiopathic urticaria – which needs a different approach to treatment – so a diagnosis of Schnitzler's syndrome in younger patients should only be made after extensive work on exclusion of other diagnoses.[6]

Treatment (Standard therapies): First-line treatment in mild cases is with nonsteroidal anti-inflammatory drugs (NSAIDs). But this is often not sufficient. In more severe cases, the standard treatment is with therapy to inhibit the cytokine IL-1. Patients with Schnitzler syndrome are successfully treated with anakinra, an interleukin-1 receptor antagonist. Anakinra (brand name Kineret) is a biopharmaceutical drug used to treat rheumatoid arthritis. It is a recombinant and slightly modified version of the human interleukin 1 receptor antagonist protein. Anakinra is a drug that blocks the activity of interleukin-1, which some researchers believe plays a key role in the development of Schnitzler syndrome. There have also been at least 2 studies showing the efficacy of the interleukin-1 beta antibody canakinumab. High-dose regimens of corticosteroids have temporarily improved symptoms in some cases, but usually must be stopped due to side effects. In a small percentage of cases, colchicine (a medication used to suppress inflammation in acute gout) and dapsone were effective in treating some individuals with Schnitzler syndrome. Interleukin-6 is a cytokine that can be induced by interleukin-1;, anti-interleukin-6 therapy was also recently tried in three patients with Schnitzler syndrome, in which it was effective. At least three individuals with Schnitzler syndrome have been successfully treated with thalidomide, a drug that affects how the immune system works (immunomodulatory drugs). Thalidomide induced a complete resolution of the rash and dramatic improvement of other symptoms in three individuals who received the drug as a therapy for Schnitzler syndrome. However, thalidomide is often associated with significant side effects including pain, numbness and a tingling sensation in the hands and feet (peripheral neuropathy). Two of the three patients had to stop thalidomide therapy because of side effects. In addition, two additional individuals with Schnitzler syndrome did not improve after treatment with thalidomide. More research is necessary to determine the long-term safety, effectiveness and role, if any, of thalidomide in treating individuals with Schnitzler syndrome. A small study investigated the effectiveness of the antibiotic drug, pefloxacine, for the treatment of Schnitzler syndrome. Eleven affected individuals received pefloxacine, which caused rapid and dramatic improvement of both the rash and systemic symptoms associated with the disorder. More research is necessary to

determine the long-term safety and effectiveness of pefloxacine in the treatment of individuals with Schnitzler syndrome.

Schnitzler syndrome does not affect lifespan in most cases, but requires periodic follow up because of the increased risk of developing cancer.

Disease course and complications: The course of the disease is longstanding. Spontaneous or treatment-induced remissions have not been published. At least 3 patients developed inflammatory AA amyloidosis, a serious complication. However, though patients have a longstanding course with a monoclonal IgM component, no patient with systemic AL amyloidosis has yet been reported. Nevertheless, AL-amyloidosis should be considered as a possible complication of the syndrome. The overall prognosis of the Schnitzler syndrome depends on the possible evolution into a lymphoproliferative disorder, either lymphoma, including lymphoplasmacytic lymphoma, lymphoma of the Richter type, marginal zone lymphoma, IgM myeloma or Waldenström's disease. About nineteen percent of the reported patients with this syndrome developed lymphoproliferative disorders, a percentage close to the 18% prevalence at 10 years of lymphoproliferative disorders in patients with IgM MGUS in general. However, the number of patients with the syndrome who will eventually develop lymphoproliferative disorder could be higher, since most patients were published shortly after diagnosis and therefore follow-up was too short to draw any conclusion about long-term outcome. Lymphoma or Waldenström's disease appears more than 10 to 20 years after the beginning of the first signs of the syndrome in most cases. Schnitzler's original patient died from diffuse lymphoplasmacytic infiltration of the liver and bone marrow 23 years after the beginning of the disease.[7] In rare cases, Waldenström's disease was revealed by a Schnitzler syndrome. There is no specific predictive factor of the development of a lymphoproliferative disorder. Thus, initial work-up of a patient with this syndrome should include an examination of bone marrow, immunoelectrophoresis of seric and urinary proteins, and dosage of immunoglobulin subtypes. The two latter examinations can then be used to follow-up those patients on a biannual basis. Lymph nodes should be biopsied when they enlarge. This author is aware of one patient with a typical Schnitzler syndrome which evolved for more than 8 years and then went into remission, without medical treatment at this time [patient 2 in reference. The remission now lasts for more than 5 years. The patient has only exceptional cold- or stress- triggered crisis once or twice a year. The monoclonal component is still present at more than 30 g/L. To the best of this author's knowledge, this is the only patient who went into spontaneous remission.

CONCLUSION

This author considers that the Schnitzler syndrome is the paradigm of a late-onset acquired auto-inflammatory syndrome. Though the term "auto-inflammatory disease" is as yet restricted to diseases with Mendelian inheritance, the Schnitzler syndrome obviously shares many clinical, biological and therapeutical aspects with this group of diseases. Though there is no definite proof of its precise pathogenesis, it should therefore be considered as an acquired disease involving abnormal stimulation of the innate immune system, which can be completely reversed by the IL-1 receptor antagonist anakinra. It clearly expands our view of this group of rare genetic diseases and makes the concept of auto-inflammation relevant to polygenic acquired diseases.

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