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Case Report

A Comprehensive Review of Schnitzler Syndrome

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Abstract

Schnitzler syndrome is a rare disorder characterized by a chronic red, hive-like rash and elevated levels of a specific protein in the blood (monoclonal IgM gammopathy). Symptoms associated with Schnitzler syndrome may include recurrent bouts of fever, inflammation of the joints (arthritis), joint pain (arthralgia), bone pain, and other findings such as enlarged lymph nodes (lymphadenopathy). Most cases of Schnitzler syndrome have a chronic, benign course. However, over a 10-year period, approximately 15% of people with the condition develop cancer, often caused by an overproduction of white blood cells (lymphoproliferative disorders) such as Waldenström macroglobulinemia. The exact cause of Schnitzler syndrome is unknown. Researchers believe that certain parts of the immune system may not function properly, ultimately causing Schnitzler syndrome. People with Schnitzler syndrome also have a clinical finding called monoclonal IgM gammopathy, in which abnormalities affecting the production of immunoglobulins lead to increased levels of immunoglobulin M (IgM) in the body. The first-line treatment for mild cases is nonsteroidal anti-inflammatory drugs (NSAIDs). But this is often not enough. In more severe cases, standard treatment is with therapy to inhibit the cytokine IL-1.

Schnitzler syndrome overview

Schnitzler syndrome is a rare disorder characterized by a chronic red, hive-like rash and elevated levels of a specific protein in the blood (monoclonal IgM gammopathy). Symptoms associated with Schnitzler syndrome may include recurrent bouts of fever, inflammation of the joints (arthritis), joint pain (arthralgia), bone pain, and other findings such as enlarged lymph nodes (lymphadenopathy). 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 that these proteins play and the exact cause of Schnitzler syndrome are unknown. Schnitzler syndrome is difficult to classify, and some researchers believe that the syndrome is an acquired autoinflammatory syndrome. Autoinflammatory syndromes are a group of disorders characterized by recurrent episodes of inflammation due to abnormalities 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 [1].

Clinical signs and symptoms of schnitzler syndrome

The symptoms associated with Schnitzler syndrome can vary from person to person. Symptoms can appear all at once, or because they often come and go, they can appear at different times. Chronic symptoms last for years (chronic disease) [1].

A reddish, hive-like rash is the hallmark finding of Schnitzler syndrome. The distinctive rash usually consists of raised, reddish bumps (papules) and larger lesions (plaques). In most cases, the rash is the first symptom to appear in people with Schnitzler syndrome. The rash usually lasts one to two days and then disappears without scarring. However, a new rash often develops every day, so the rash is a constant phenomenon, but the frequency of the rash can vary greatly

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from person to person, with some people only getting a rash a few times a year (Figure 1) [1].

When the rash first appears, it is usually not itchy. However, in about 45 percent of cases, the rash becomes itchy over several years. The trunk, arms, and legs are most often affected. The head, neck, palms, and soles of the feet are usually spared. Some people with the condition have reported that alcohol, spicy foods, and stress have aggravated the rash [1,2].

Fevers that come and go over a period of time (chronic intermittent fever) are the second most common symptom in people with Schnitzler syndrome. The frequency of fevers varies widely, from a daily occurrence to just a few times a year. Fevers are usually not associated with the rash, are well-tolerated, and are rarely accompanied by chills [1,2].

Additional symptoms associated with Schnitzler syndrome include bone pain, which mostly affects the lower legs and buttocks, and joint pain, often affecting the large joints such as the hips, knees, wrists, and ankles. In some cases, inflammation of the joints (arthritis) may occur, accompanied by swelling, redness, and a burning or warm feeling in the joints. Despite joint involvement, joint destruction has not been reported in people with Schnitzler syndrome. Abnormal enlargement of the lymph nodes (lymphadenopathy), liver (hepatomegaly), and spleen (splenomegaly) may also occur in some cases. Other nonspecific symptoms reported in people with Schnitzler syndrome include unintentional weight loss, fatigue, and a general feeling of poor health (malaise). Rapid swelling caused by fluid accumulation under the skin (angioedema) is very rare in this syndrome [1,2] (Figure 2).

Most cases of Schnitzler syndrome have a chronic, benign course. However, over a 10-year period, approximately 15% of people with the condition develop cancer, often caused by an overproduction of white blood cells (lymphoproliferative disorders) such as Waldenström macroglobulinemia. Some people with Schnitzler syndrome have different levels of the protein than people with classic Schnitzler syndrome. These

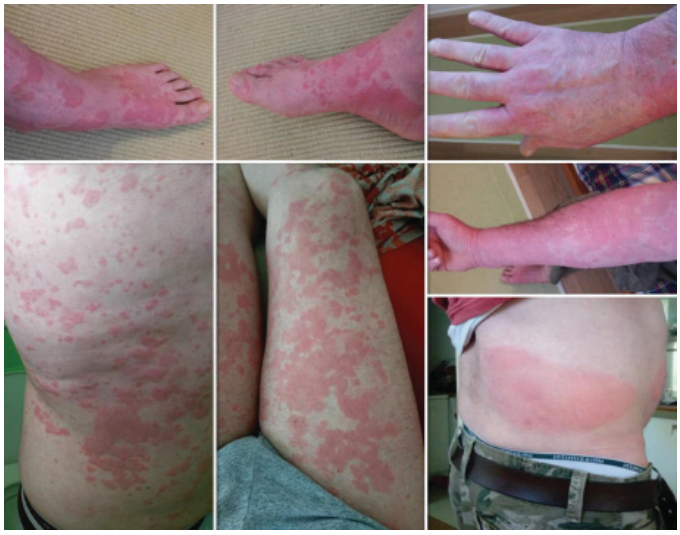

Figure 1: Images of skin disorders in Schnitzler syndrome [1].

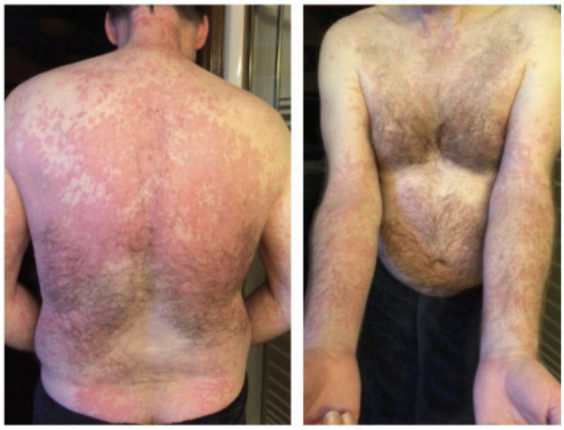

Figure 2: Other images of skin disorders in a man with Schnitzler Syndrome [1].

people have a variant Schnitzler syndrome and have symptoms that are very similar to those of classic Schnitzler syndrome [1,2].

Etiology of schnitzler syndrome

The exact cause of Schnitzler syndrome is unknown. Researchers believe that certain parts of the immune system may not function properly, ultimately causing Schnitzler syndrome. People with Schnitzler syndrome also have a clinical finding called monoclonal IgM gammopathy, in which abnormalities affecting the production of immunoglobulins lead to increased levels of immunoglobulin M (IgM) in the body. Immunoglobulins are proteins produced by a specific type of white blood cell. There are five classes of immunoglobulins known as IgA, IgD, IgE, IgG, and IgM. Immunoglobulins protect the body by destroying or coating foreign substances or microorganisms so that they can be easily destroyed by white blood cells. At the time of diagnosis, IgM levels may be only slightly elevated and may remain stable for years. A different type of Schnitzler syndrome has been reported in which people have IgG monoclonal gammopathy instead of IgM. Certain cytokines (specialized proteins secreted by specific immune cells that stimulate or inhibit other immune cells) have been implicated in the development of Schnitzler syndrome. The cytokine interleukin-1 (IL-1) is an important mediator of inflammation in Schnitzler syndrome. Abnormal clinical findings involving interleukin-1 have been found in some people with Schnitzler syndrome, and treatment with drugs that block interleukin-1 activity has resulted in complete recovery [1,3].

Frequency of schnitzler syndrome

Schnitzler syndrome affects men more than women. However, approximately 160 cases of this rare disorder have been reported in the medical literature, so no definitive conclusions can be drawn about ethnic or gender predispositions. Because of the varied symptoms and rarity of Schnitzler syndrome, diagnosis is often delayed for several years, and researchers believe that the disorder is underdiagnosed, making it difficult to determine its true frequency in the general population. Most

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people with Schnitzler syndrome are in their 50s when they develop characteristic symptoms [1,3].

Rarely, symptoms have been observed in people in their 30s. In one reported case, symptoms were identified in a 12-year-old. It must be asked whether these cases were classic Schnitzler syndrome. Schnitzler syndrome was first described in the medical literature in 1972 by French dermatologist Liliane Schnitzler. Most reported cases of Schnitzler syndrome have been from Europe, particularly France, but cases have also been reported from Australia, Japan, and the United States [1,3] (Figure 3).

Disorders associated with schnitzler syndrome

The following disorders may have symptoms similar to those of Schnitzler syndrome. Comparison may be useful for differential diagnosis:

Autoinflammatory syndromes are a group of disorders characterized by recurrent episodes of inflammation due to abnormalities of the innate immune system. Symptoms of these syndromes often include periodic fevers, rashes, abdominal pain, joint pain, bone pain, and other characteristic findings associated with chronic inflammation. These disorders include cryopyrin-associated periodic syndromes (familial cold autoinflammatory syndrome, CINCA, and Muckle-Wells syndrome), mevalonate kinase deficiency (also known as hyperimmunoglobulin D syndrome (HIDS)), familial Mediterranean fever (FMF), and TRAPS [1,4].

Autoimmune disorders are a group of disorders in which abnormalities affect the adaptive immune system, including cells and proteins (antibodies) that protect the body from infection. These antibodies mistakenly attack healthy tissue and may be referred to as autoantibodies. Common symptoms of many autoimmune disorders include recurrent episodes of fever, rash, abdominal pain, joint pain, and other symptoms associated with chronic inflammation. Autoimmune disorders

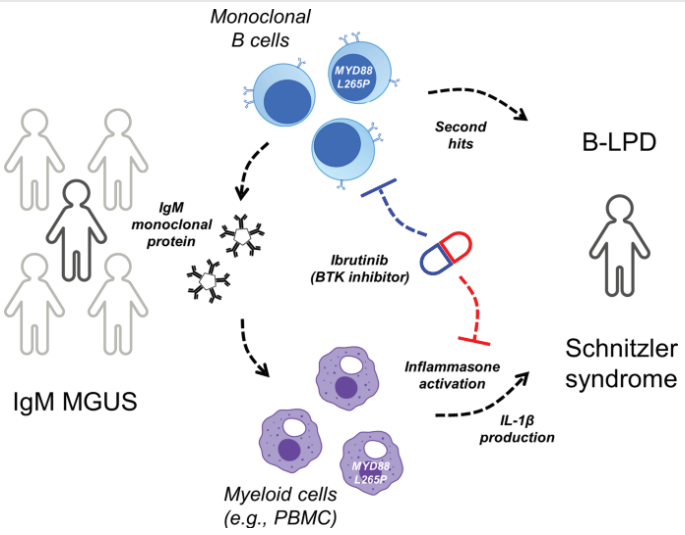

Figure 3: Schematic of the immunopathogenesis mechanism in Schnitzler syndrome [1].

that may resemble Schnitzler syndrome include Still's disease in adults, systemic lupus erythematosus, urticarial vasculitis, chronic idiopathic (or spontaneous) urticaria. POEMS syndrome is an extremely rare multisystem disorder. POEMS is an acronym for (P) polyneuropathy, a disease that affects many nerves, (O) oganomegaly, an abnormal enlargement of an organ; (E) Endocrinoapthy, a disease that affects the hormone-producing glands that help regulate growth rate, sexual development, and some metabolic functions (endocrine system); (M) Monoclonal gammopathy or M protein; and (S) Kinship deficiency. Common symptoms include progressive nerve weakness in the arms and legs, abnormal enlargement of the liver or spleen (hepatosplenomegaly), abnormal darkening of the skin (hyperpigmentation), and excessive hair growth (hypertrichosis). Endocrine abnormalities such as failure of the ovaries and testicles (gonads), primary gonadal failure, and type 1 diabetes may be present. The specific endocrine disorders associated with POEMS syndrome vary from case to case. Other important features of the disease include swelling around the optic nerve, abnormal fluid retention, which may occur in the ankles (edema), the abdominal cavity (ascites), or around the lungs (pleural effusion), painless bone lesions that are visible on X-rays (osteosclerosis), and an increase in the number of platelets (a blood cell responsible for clotting). POEMS syndrome is associated with a group of disorders known as monoclonal gammopathy or plasma cell dyscrasias. These disorders are characterized by the uncontrolled growth of a single clone (monoclonal) of plasma cells, leading to an abnormal accumulation of M proteins (IgM) in the blood [1,5].

Waldenström macroglobulinemia (WMG) is a malignant (cancerous) blood disorder closely related to lymphoma and characterized by an abnormally high number of a certain type of white blood cell called B lymphocytes. As these cells accumulate in the body, they produce excessive amounts of an antibody called monoclonal immunoglobulin M (IgM). This causes the blood to become thick (hyperviscosity) and affects the flow of blood through smaller blood vessels, leading to some of the symptoms of the disorder. The accumulation of B lymphocytes in the bone marrow can prevent the bone marrow from producing new blood cells (pancytopenia). Affected people may have low levels of red blood cells (anemia), white blood cells (leukopenia), and platelets (thrombocytopenia). As a result, affected individuals may experience fatigue, paleness, nosebleeds, and susceptibility to infection. Some individuals with Schnitzler syndrome develop Waldenström macroglobulinemia later in life. The exact relationship between the two disorders is not fully understood. The exact cause of Waldenström macroglobulinemia is unknown [1,5].

Diagnosis of schnitzler syndrome

The diagnosis of Schnitzler syndrome is based on a thorough clinical evaluation, a careful patient history, exclusion of other disorders, and identification of characteristic findings, especially urticaria, M protein, and at least two of the following: fever, joint pain or inflammation, bone pain, palpable lymph nodes, liver or spleen enlargement, increased white blood cell count (leukocytosis), increased red blood

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cell (erythrocyte) sedimentation rate, or abnormalities on bone morphology studies, which may indicate increased bone density (osteoporosis) [1,6].

The sedimentation rate is the time it takes for red blood cells to settle in a test tube for a given period of time, which is measured in this syndrome. Many people with Schnitzler syndrome have an elevated sedimentation rate, which indicates inflammation. In younger patients, careful attention should be paid because alternative diagnoses are very likely and often overlooked, such as urticarial vasculitis, hematologic diseases, or chronic idiopathic urticaria, which require a different approach to treatment. Therefore, the diagnosis of Schnitzler syndrome in young patients should be made only after extensive workup to exclude other diagnoses [1,6].

Treatment options for schnitzler syndrome

The first-line treatment for mild cases is nonsteroidal anti-inflammatory drugs (NSAIDs). But this is often not enough. In more severe cases, 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 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 two studies that show the efficacy of the interleukin-1 antibody canlakinumab [1,7].

High-dose corticosteroid regimens have temporarily improved symptoms in some cases, but usually have to be discontinued due to side effects. In a small percentage of cases, colchicine (a drug used to suppress inflammation in acute gout) and dapsone have been effective in treating some people with Schnitzler syndrome. Interleukin-6 is a cytokine that can be induced by interleukin-1. Anti-interleukin-6 therapy has also recently been tested in three patients with Schnitzler syndrome, where it has been effective [1,8] (Figure 4).

At least three people with Schnitzler syndrome have been successfully treated with thalidomide, a drug that affects the function of the immune system (immunomodulatory drugs). Thalidomide caused complete resolution of the rash and significant improvement in other symptoms in three people who received the drug as a treatment for Schnitzler syndrome. However, thalidomide is often associated with significant side effects, including pain, numbness, and tingling in the hands and feet (peripheral neuropathy). Two of the three patients had to stop taking thalidomide because of side effects. In addition, two other people with Schnitzler syndrome did not improve after treatment with thalidomide. More research is needed to determine the safety, effectiveness, and long-term role of thalidomide in treating people with Schnitzler syndrome [1,8].

A small study examined the effect of the antibiotic pefloxacin in treating Schnitzler syndrome. Eleven patients received pefloxacin, which resulted in rapid and significant improvement in the rash and systemic symptoms associated with the disorder. Further research is needed to determine the safety and long-term effectiveness of pefloxacin in treating people with Schnitzler syndrome. Schnitzler syndrome does not affect life expectancy in most cases, but it does require periodic follow-up because of the increased risk of cancer [1,9] (Figure 5).

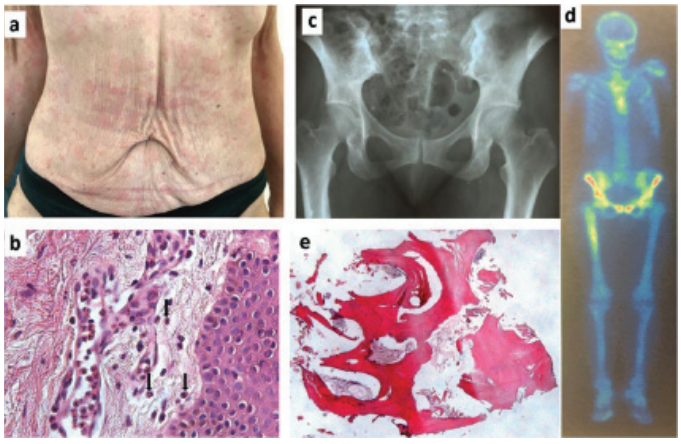

Figure 4: Images of disorders associated with schnitzler syndrome [1].

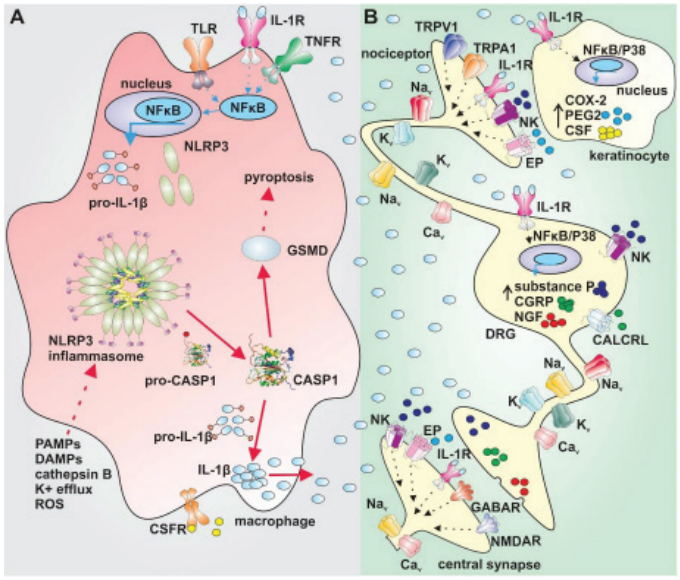

Figure 5: Schematic of the molecular and biochemical pathways of cytokines and interleukins in the immune system [1].

Discussion

A reddish, hive-like rash is the hallmark finding of Schnitzler syndrome. The distinctive rash usually consists of raised, reddish bumps (papules) and larger lesions (plaques). In most cases, the rash is the first symptom to appear in people with Schnitzler syndrome. The rash usually lasts one to two days and then disappears without scarring. However, a new rash often develops every day, so the rash is a constant phenomenon, but the frequency of the rash can vary greatly from person to person, with some people only getting a rash a few times a year. Most cases of Schnitzler syndrome have a chronic, benign course. However, over a 10-year period,

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approximately 15% of people with the condition develop cancer, often caused by an overproduction of white blood cells (lymphoproliferative disorders) such as Waldenström macroglobulinemia. Some people with Schnitzler syndrome have different levels of the protein than people with classic Schnitzler syndrome. These people have a variant Schnitzler syndrome and have symptoms that are very similar to those of classic Schnitzler syndrome. The exact cause of Schnitzler syndrome is unknown. Researchers believe that certain parts of the immune system may not function properly, ultimately causing Schnitzler syndrome. People with Schnitzler syndrome also have a clinical finding called monoclonal IgM gammopathy, in which abnormalities affecting the production of immunoglobulins lead to increased levels of immunoglobulin M (IgM) in the body. Immunoglobulins are proteins produced by a specific type of white blood cell. There are five classes of immunoglobulins known as IgA, IgD, IgE, IgG, and IgM. Immunoglobulins protect the body by destroying or coating foreign substances or microorganisms so that they can be easily destroyed by white blood cells. Rarely, symptoms have been observed in people in their 30s. In one reported case, symptoms were identified in a 12-year-old. It must be asked whether these cases were classic Schnitzler syndrome. The sedimentation rate is the time it takes for red blood cells to settle in a test tube for a given period of time, which is measured in this syndrome. Many people with Schnitzler syndrome have an elevated sedimentation rate, which indicates inflammation. In younger patients, careful attention should be paid because alternative diagnoses are very likely and often overlooked, such as urticarial vasculitis, hematologic diseases, or chronic idiopathic urticaria, which require a different approach to treatment. Therefore, the diagnosis of Schnitzler syndrome in young patients should be made only after extensive workup to exclude other diagnoses. Patients with Schnitzler syndrome are successfully treated with anakinra, an interleukin-1 receptor antagonist. 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 two studies that show the efficacy of the interleukin-1 antibody canlakinumab. Interleukin-1 ligand & Interleukin-1 receptor family plays critical roles in initiating and promoting the host response to injury or infection, including fever, sleep, acute phase protein synthesis, chemokine production, adhesion molecule up-regulation and production and release of matrix metalloproteinases and growth factors. IL-1 affects virtually all cells and organs and is a major pathogenic mediator of autoinflammatory, autoimmune, infectious, and degenerative diseases.

Based on the length of the N-term pro-pieces, the members of IL-1 family can be classified into 3 subfamilies: IL-1 subfamily (IL-1α, IL-1β and IL-33, IL-1Ra), IL-18 subfamily (IL-18 and IL-37), and IL-36 subfamily (IL-36α, IL-36β, IL-36γ, and IL-38, IL-36Ra). Sino Biological provides quality reagents for research on interleu and their receptors, including: recombinant proteins, antibodies, ELISA kits, ORF cDNA clones, and more [1,9].

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