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Schnitzler Syndrome: A Rare and Recurrent Autoimmune Disease.

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ABSTRACT

The Schnitzler syndrome is uncommon and recurrent autoimmune disorder that involves many systems of the body. No specific test has been established yet and the diagnosis is often delayed, so its diagnosis requires a high index of accuracy. Its main signs includes: chronic non pruritic urticarial and monoclonal immunoglobulin M gammopathy. Moreover, it has at least two of the following criteria: recurrent fever, joint and/or bone pain, arthralgia or arthritis, enlarged lymph nodes, splenomegaly and/or hepatomegaly, raised ESR, neutrophilia, abnormal bone imaging findings. For quite a while, no particular medication had tried sufficiently. The principle objectives of this review are to systematically explore the disease characteristics and to provide inclusive overview of the symptoms of this syndrome, underline its specific rash, and its pathophysiology, diagnosis, complications and new medications used in its treatment.

Keywords: autoimmune, chronic urticaria, immunoglobulin IgM, recurrent fever.

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Historical Background

Between 1972 and 1974, a French dermatologist; Liliane Schnitzler described a clinical syndrome in which an association between chronic urticaria and an IgM monoclonal protein [1, 2].

The diagnostic criteria were established later by Lipsker et al [3]. Afterwards, it was agreed by the Schnitzler Syndrome Study Group [4]. Thereafter, about hundred patients were reported from all over the world including North America and Japan, but most of them were from Europe [5, 6, 7].

Definition

Schnitzler syndrome is an autoimmune disorder where a combination of an urticarial skin rash associated with monoclonal IgM component. At least two of the following signs appear: recurrent fever, arthralgia or arthritis, bone pain, lymphadenopathy, organomegaly (enlarged liver or spleen), increased white blood corpuscles count, an elevated ESR, and abnormal findings on bone morphologic investigations [3].

Etiology of The Syndrome

The reason for Schnitzler disorder is still obscure. A change in the cytokine system has been recorded. Interleukin 1 alpha binding activity has been noticed in some cases. One report noted that a presence of polyclonal immunoglobulin G (IgG) type autoantibodies directed against IL-1 alpha in the serum from patients with this syndrome [8]. This polyclonal immunoglobulin G has been shown to increase the half-life of IL-1alpha, thus a change of IL-1 alpha tissue distribution and increase its effects. The increase in IL-1alpha activity could be the cause of urticaria and fever [9].

Raised serum interleukin 6 (IL-6), granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been noted in the some cases [10]. Interleukin 1 alpha is a cytokine or inflammatory mediator that can elucidate some of the pathogenesis of the syndrome. There is no familial cases and no clear risk factors have been specified [4].

Epidemiology

The diagnosed cases with this syndrome have varied from 13 years to 71 years. The average age of onset of the symptoms is in their 50s [7, 4]. There is a little male prevalence. yet this syndrome is generally a disorder of the adult, since only four cases started the disease before age of 35 [4].

Pathophysiology

Pathogenesis for Schnitzler's syndrome have not been reported yet. Yet, Schnitzler's syndrome is characterized by unusual increase of monoclonal gammopathy of M-proteins (IgM) in the patients' blood [11]. Reported cases have shown precipitation of IgM in the involved tissue. Using anti-idiotype of antibodies, IgM monoclonal antibodies were evidenced to interact with epidermal antigens [12]. In one case, monoclonal IgM was found to target 50-, 31-, and 17-kd proteins within epidermal extracts [8]. These results suggest that the IgM may be implicated in the pathogenesis, by means of formation of immune complexes and activation of the complement system.

On the other hand, there is another suggested mechanism for Schnitzler's syndrom. It involves the uncontrolled activation of interleukin 1-alpha (IL-1alpha). Morita et al. reported that the serum taken from 6 of 9 patients with Schnitzler's syndrome contained polyclonal immunoglobulin G (IgG)–type autoantibodies directed against IL-1alpha [13]. These auto-antibodies significantly increase IL-1alpha half-life and change its profile of tissue distribution. Therefore, this enhancement of the IL-1alpha activity may be the possible cause of the accompanied urticaria and fever symptoms [10].

At the begining of the pathological signs, there is an activation/regulation of the IL-1β-producing inflammasome. The IL-1β-producing inflammasome is a cytoplasmic protein complex , that activate the IL-1β cleaving enzyme caspase-1 that in turn cleaves the inactive IL-1β precursor protein (pro-IL-1β) and releases the mature active form of the cytokine [14]. Recent data have shown that the IL-1β-producing inflammasome also

produces another cytokine of the IL-1 family; IL-18, by cleaving its precursor protein with a mechanism identical to IL-1β maturation [3]. Excess production of IL-18 is an expected feature of inflammasome over-activation in auto inflammatory diseases. Thus, Schnitzler's syndrome may be an auto inflammatory disease.
Serum derived from some cases showed increased levels of interleukin 6 (IL-6), granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF) [14]. The role of these cytokines in pathogenesis of Schnitzler syndrome is still unclear.

Another hypothesis for Schnitzler's syndrome assumed that there is genetic predisposition involving an activating NLRP3 mutation. *Nlrp3* gene involved in the cryopyrinopathies was reported in one case. Nuc1eotide-binding domain and Leucine-rich repeat containing gene family pyrin-containing domain are involved [15, 1].

Clinical Presentation

Schnitzler's syndrome is a recurrent disorder, with periods of spontaneous remission of variable duration. The main clinical picture includes:

Chronic Urticaria

In Schnitzler disease rashes are the most stationary and first clinical sign in all patients. Skin rash was classically referred as "urticaria". Pathophysiology of the rash may be related to the deposition of IgM in the skin. In this disorder, urticaria is chronic, recurrent and continues from 4 to 36 hours and repeat after duration of at least one and half a month [16, 17]. Elevated serum total IgE levels may be accompanied with the flare of chronic urticarial and incomplete response to antihistamines treatment [18].

Skin rash is not present in Schnitzler-like syndrome where all other signs of the Schnitzler syndrome are exist [19]. These peculiar rashes were optimistic in point of interest and nosologically separated from regular urticaria [20]. Those rashes are rose pale or red eruptic macules (flat lesions) that are 0.5 to 3 cm in diameter or slightly elevated papules and plaques. They are generally not or only moderately itchy (Fig 1). Rashes can occur all over the body, where face and extremities are rarely affected. Face affection including angioedema and characteristic mucosal swelling with dyspnea and/or dysphonia are rare symptoms [4, 21].
At the beginning of the disease pruritus is usually not present, but after several years in approximately 45% of the patients lesions became pruritic. With the use of antihistaminic drugs severe an antihistamine- resistant pruritus occurred in only a few cases [22, 23]. Alcohol, spicy food, and even stress were reported as aggravating factors in many patients [24, 25].

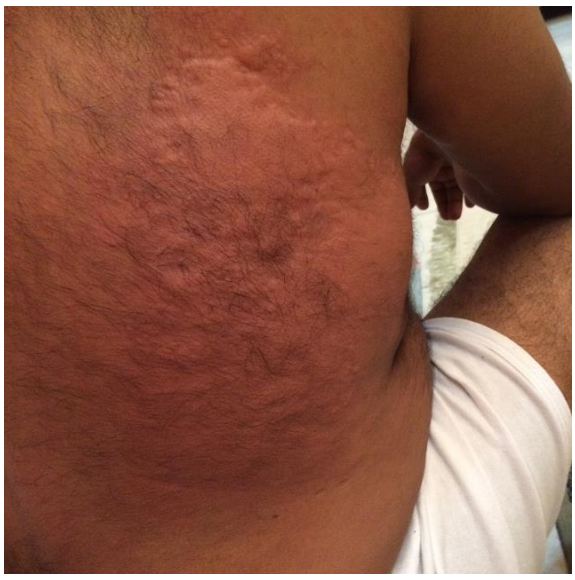

Figure 1: Schnitzler syndrome rashes, which are: rose pale or red eruptic macules or slightly elevated papules and plaques.

FEVE

The second most common symptom is a fever which is recurrent spiking, intermittent and well tolerated. Fever occurs in more than 80% of patients. Body temperature can reach 40°C or more. The recurrence of fever varies incredibly among patients, which may range from daily to twice a year.

The febrile episodes generally disappear within a few hours but may last for up to 1 to 2 days. During the fever chills are rare while fatigue flares. In many cases, there is no relationship between the fever and the skin rash. In few cases high temperature responds to NSAI D and/or to steroids and is usually totally controlled with anakinra [26, 3].

Muscloskeletal Symptoms

Relapsing arthralgia occurs in 80% of patients. All joints may be affected, especially large joints including the hips, knees, wrists, tibia, ilium, femur, forearm, spine, and clavicle ankles. Joints Examination reveals no joint destruction or deformities. [27, 28]. Bone pain has been recorded, especially in the. Myalgia was reported in some patients, which was difficult to be differentiated from bone pain.

Organomegaly

Hepatomegaly, splenomegaly and palpable lymph nodes was noticed in about 30% ,12% and 45% of the patients respectively [3, 4]. Lymphadenopathy is mainly present in the axilla and inguinal region, less commonly in cervical region. Those lymph nodes size can reach 2 or 3 cm and may be persistent, multiple and permanent hence suggests lymphoma, but biopsy shows non-specific inflammation.

Neuronal Affection

Peripheral neuropathy in Schnitzler syndrome is due to the presence of IgM monoclonal [29, 30].

Other Symptoms

Malaise, fatigue, weight loss and chronic inflammatory demyelinating polyneuropathy is common among those patients [31]. Pseudoxanthoma elasticum [32, 33], headache, depression, and vertigo were also recorded [32]. Peripheral neuropathy accompaned with anti-MAG (Myelin Associated Glycoprotein) serum activity was noted in 2 patients [34, 35]. Monoclonal IgM antibodies against MAG can result in a chronic demyelinating polyneuropathy in which IgM deposition in skin-myelinated nerve fibers [36], however the association with the paraprotein in Schnitzler syndrome is vague. Serious thrombophilia with antiphospholipid syndrome and hyperhomocysteinemia also reported in one case [37]. Another case reported hearing loss; intriguingly, this case was cured completely by using an IL-1 inhibitor [24].

Complications

The most seen complications are disabling skin rash, fever, and musculoskeletal involvement. Severe anemia of chronic disease is the most serious complication. lymphoplasmacytic malignancy was seen in 15% of cases. This hematologic transformation can occur after 20 years from the onset of the disease, thus long-term follow-up this disorder is advisable [3]. Lymphoproliferative disorder, either lymphoma, including lymphoplasmacytic lymphoma, lymphoma of the Richter type, marginal zone lymphoma, IgM myeloma or Waldenström's disease also noticed [38, 35, 9].

About 85% of cases usually has a benign course, but lymphoproliferative disorder occurs in the other percent of patient where it is considered as Long-term complications [39]. Prediction of the development of a lymphoproliferative disorder has not been reported yet. Type A amyloidosis is Long-term complications [40, 41, 4].

Morbidity and Mortality

These patients experience impressive morbidity due to their symptoms. Morbidity of the disease includes a profound influence on patients' lives .Mortality doesn't appear to be of significantly issue in comparison to final population [4].

Laboratory Finding

No specific test for this syndrome has been established yet. A 5 years latency between the onset of symptoms and diagnosis of this syndrome is present[25]. Monoclonal immunoglobulin M is an exclusive diagnostic parameter. Ig M only detected later in the course of disease. A monoclonal IgG was detected in some cases of variant Schnitzler syndrome. IgM concentrations do not exceed 10 g/L in more than two-thirds of cases. Annual detection of immunoglobulin M show either stable concentration or a progressive increase of about 0.5 to 1.0 g/L per year. The monoclonal IgA also recorded in conjunction with a monoclonal IgM [33]. IgA and IgG levels are diminished in about 25% of cases [42].

It has been shown that an association between raised serum IL-6 concentrations and fever followed by raised serum Hepcidin levels, while serum iron was low[43].

Investigations of inflammation in those patients shows: raised ESR, raised acute phase proteins concentrations, leukocytosis, and occasionally anemia of chronic disease. ESR and C-reactive protein (CRP) concentrations are constantly increased all through the course of the disease, while during exacerbations the peaking occurs. Leukocytosis and lymphopenia were detected in 69% of cases [44, 45].

Complements are normal or increased. Diminished complement concentration was reported in 2 patients that may be due to a genetic deficiency of complement 4a (C4a) [35]. Increase in transaminases usually not detected in Schnitzler's syndrome. Low-glycosylated ferritin levels seldom, if ever, go beyond 1200 ng/ml in Schnitzler's syndrome [25].Investigation of bone marrow, serum and urinary proteins immunoelectrophoresis must be done in those patients' also enlarged lymph nodes should be biopsied.

Histopathological Finding of the Plaque

Early biopsy of a plaque identify, dermis is infiltrated with neutrophilic. Epidermis is generally normal; neutrophils infiltrate hypodermis and enclose sweat ducts inquiring a histopathologic aspect of eccrine hidradenitis as an epiphenomenon. Interstitial dispersion with neutrophils along the collagen bundles is typical identical with leukocytoclasia. There are no vasculitis and no dermal edema, which allows its differentiation from urticarial vasculitis and the Sweet syndrome respectively. Vasculitis only recorded in less than 20% of patients. [4, 20].

Biopsy from skin in acute lesion stage detected perivascular lymphocytic infiltrates consisting of $CD4^+$ and $CD8^+$ T lymphocytes. A lower $CD4^+/CD8^+$ ratio of circulating T lymphocytes was detected [39].

Radiological Findings

Bone imaging findings in Schnitzler syndrome shows: osteocondensation of distal femora and proximal tibiae. No radiological finding of malignancy was present. Detected Lytic lesions [46, 47] and periosteal apposition [48, 49].

Bone technetium scanning shows hyperfixation in the areas of involvement [49]. Magnetic resonance imaging shows bone cortical thickening and medullar involvement .Bone marrow infiltration without space occupying features in the areas of involvement [48,49].

Differential Diagnosis

Differential diagnosis of Schnitzler syndrome involves many autoimmune, infectious, neoplastic and idiopathic conditions [4, 25]. Differential diagnosis includes: cryoglobulinemia, hypocomplementic urticarial vasculitis, acquired C1 inhibitor deficiency, hyper IgD syndrome and adult onset Still's disease [8]. Muckle–

Wells syndrome (MWS), including urticarial rash, fever episodes, arthralgia, arthralgia and myalgia, and risk of amyloidosis. In MWS there is NLRP3 gene mutations that leads to overproduction of interleukin-1 (IL-1) [50, 51]. In comparison with MWS and other CAPS, Schnitzler occurs late in life (mean age at onset is 51 years). Recently, an NLRP3 mutation consistent with CAPS has been detected in a case of Schnitzler [15].Adult-onset Still's disease (AOSD) must be differentiated from Schnitzler's syndrome. Both disorders are manifested by an urticarial rash, fever, joint pain, leukocytosis, and no specific diagnostic marker. In AOSD pharyngitis and very high Low-glycosylated ferritin level are found. In Schnitzler's syndrome pharyngitis is absent, while ferritin rarely, if ever, exceeds 1200 ng/ml in patients with Schnitzler's syndrome [25].

Treatment

No successful medication had tried sufficiently. None of anti-inflammatory or immunosuppressive drugs, caused a complete cure for all symptoms [3]. Treatment of rashes with antihistamines was not viable. The inadequacy of antihistamines proposes a histamine-independent etiology of the rash. A high dose of corticosteroids causes a considerable cure of symptoms in about 40% of patients. Colchicine is highly effective in few patients [34, 48, 52, 53], but inadequate in most cases. Peflacine, causes complete regression in a few patients, however its mechanism of action not yet known [17, 54].

Interferon (IFN) seemed to be a hopeful treatment [55, 45]. Using IFN for one year and half causes relapse in urticarial and bone pain. IFN tolerance was afforded [45], hence it induces many side effects.

Thalidomide causes polyneuropathy [24, 56], so it is a less preferable [38].

Oral pefloxacin mesylate, it treats urticarial and systemic symptoms of the disease [57].

Daily use of anakinra, as a sole medication, causes remission of all symptoms of the disease within 24 hours after subcutaneous injection of 100 mg anakinra. Anakinra was first described by Martinez-Taboada et al in 2005 [14] and thereafter it was confirmed by numerous reports [58, 59, 60, 2]. Gilson described the response to anakinra that it is dramatic and immediate [8]. Patients recover a health-state that they did not apprehend for years. Anakinra has a short half-life of 6 hours. The only noticed side effect of the drug is a painful erythematous lesion at site of injection [1]. Neutrophillic count must be monitored. In vitro and in vivo anakinra showed decrease or even normalization of lipopolysaccharide (LPS) induced production of inflammatory cytokines by peripheral blood mononuclear cells (PBMCs) [61].Stoppage of anakinra in 3 patients causes reappearance of Schnitzler symptoms within 24 hours, but those symptoms vanished as soon as anakinra was restarted [24]. Rigors, fever, and recurrence of the rash was noticed within 2 days in a patient who missed 2 doses of anakinra. Those symptoms disappeared with recontinouty of the drug. Schuster stated that anakinra seems to be the treatment of choice [2].

Rilonacept used in a loading dose of subcutaneous 320 mg followed by weekly subcutaneous doses of 160 mg for up to 12 months led to a significant clinical response and reduce serum C-reactive protein and serum amyloid A. Tolerance with rilonacept was well established. There were no serious side effects [62].

Canakinumab selectively binds to interleukin-1β and inactivates its signaling. [63] It has no cross-reactivity with other interleukin-1 family members, including interleukin-1α and its receptor interleukin-1 Ra. Subcutaneous injection of 150 mg of canakinumab once every 8 weeks produces a rapid disappearance fever and arthralgia, fatigue and rash and normalization of serum C-reactive protein level [50]. Stoppage of canakinumab led to a flare of symptoms, those symptoms disappeared with recontinouty of canakinumab. The patient remained in complete remission. Canakinumab was well tolerated. This drug is prominent over other interleukin-1 inhibitors (anakinra and Rilonacept), not require daily administration and has low injection-site reactions [23].

Follow Up

Following-up should include routine analysis of: complete blood count, C - reactive protein every 3 months, serum electrophoresis, creatinine, calcium, LDH, urinary proteins .Analysis of monoclonal of undetermined significance (MGUS) (once yearly if monoclonal immunoglobulin under 10 g/L, twice a year if < 30 g/l and every 3 months if > 30 g/L), [2].

CONCLUSION

In conclusion, there is no exact clue of the pathogenesis of Schnitzler syndrome but it may involves a genetic predisposition involving an activating NLRP3 mutation that is similar to the hereditary determined auto-inflammatory disease. No particular test for this syndrome has been established yet. Diagnostic tests are frequently used to exclude other disorders similar to our syndrome.

Canakinumab is a well-tolerated medication with long half-life, low incidence of injection-site reactions and not require more frequent administration that gives the drug benefits over other interleukin-1 inhibitors and may be a promising treatment.

A high index of suspicion and careful prognosis are needed to avoid diagnostic delays in this syndrome which may lead to a serious hematological complication.

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