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Case Report

Refractory Schnitzler syndrome presenting with subcutaneous lesions and response to rituximab therapy

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Abstract

Background: Schnitzler syndrome (SchS) is a rare auto-inflammatory disease characterized by urticarial exanthema, fever, bone and muscle pain and monoclonal gammopathy. Currently there is a lack of data regarding diagnostic imaging (e.g., PET-CT) and treatments of this rare disease, particularly in refractory cases. Herein, we describe unique findings on PET-CT and successful therapeutic interventions with immunoglobulins and B cell depletion for refractory SchS.
Case presentation: A 57 years old female was referred to our center for evaluation of monthly episodes of atypical urticarial rash accompanied by fever, malaise and joint pain. Laboratory findings revealed elevated inflammatory markers, liver function tests and leukocytes during the episodes as well as a monoclonal peak of IgG kappa. Skin biopsy was consistent with neutrophilic dermatosis and no evidence of malignancy. On PET-CT subtle ill-defined infiltration of subcutaneous fat were observed in several sites, compatible with skin lesions presented on physical examination. The disease was steroid responsive in the beginning but upon progression it became high dose steroid dependent. Biological targeted therapies IL-1 and IL-6 inhibitors failed to relieve the symptoms. Hence plasmapheresis and anti-CD20 monoclonal antibody were used, leading to clinical resolution.
Conclusions: In this case study of Schnitzler syndrome PET-CT detected subcutaneous fat inflammatory lesions. Additionally, treatment with B-cell depletion therapies enabled controlling of very aggressive disease that was resistant to all other line of therapies. The role of imaging as well as B-cell depletion therapy for s subset of patients with resistant SchS require further studies.

Keywords

Schnitzler syndrome (SchS), anti-interleukin-6, neutrophilic dermatosis, Anti-CD20 (Mabthera; Rituximab), plasmapheresis.

Declaration Of Conflicting Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Introduction

Schnitzler syndrome was first described in 1972 by the French dermatologist Liliane Schnitzler (1). It is a rare auto-inflammatory disease with few hundreds of cases reported so far. To date, there is no evidence of familial clustering of Schnitzler syndrome, suggesting that this is an acquired condition. Two sets of diagnostic criteria were put forward, the Lipsker criteria published in 2001 (2) and the Strasbourg criteria published in 2012 (3). The former, regarded as classical SchS, require the presence of urticarial skin rash and a monoclonal IgM component and at least 2 of 8 minor criteria: fever, arthralgia or arthritis, bone pain, palpable lymph nodes, liver or spleen enlargement, elevated erythrocyte sedimentation rate, leukocytosis and abnormal findings on bone morphology (2). In 2007 an IgG variant was proposed (4) leading to the development of the more extensible Strasbourg criteria, that require chronic urticarial rash with monoclonal IgM or IgG and 2 (in the case of IgM) or 3 (in the case of IgG) out of 4 minor criteria: recurrent fever, objective findings of abnormal bone remodeling with or without bone pain, a neutrophilic dermal infiltrate on skin biopsy, and leukocytosis /or elevated CRP (3).

The differential diagnosis of Schnitzler syndrome (SchS) includes a number of disorders. Some of them share inflammatory or idiopathic features such as chronic spontaneous urticaria, adult-onset Still's disease, cryopyrin-associated periodic syndrome (CAPS) and vasculitis (hypocomplementemic, urticarial, or cryoglobulinemic), while others like monoclonal gammopathy of undetermined significance (MGUS), mastocytosis, lymphoma and Waldenstrom macroglobulinemia are clonal in nature (2-5).

The pathogenesis of SchS is yet to be revealed and probably lies in acquisition of an innate immune defects as well as some adaptive ones. On the one hand, inflammasome activation and production of cytokines is evident turning the syndrome into an auto-inflammatory disease (3-6). This is further supported by spontaneous production of TNF-α, IL-6, IL-1β by Peripheral Blood Mononuclear Cells and response to specific cytokine blockers as Anakinra (IL-1 receptor antagonist) (6). On the other hand, the presence of monoclonal gammopathy hints to the importance of the clonality. In other clonal diseases, e.g., Multiple Myeloma (MM), the treatment goal is to destroy the abnormal clone, even though it is well known that abnormal B cell clone cannot survive without proper inflammatory signals from its microenvironment (7). The current recommended treatments for SchS focus on its auto-inflammatory components and target the involved cytokines. This approach may sometime be insufficient to control disease alluding to the notion that B cell/immunoglobulin targeted therapies and potentially other immunomodulation therapies used for clonal diseases may be beneficial (8). Here we present a unique case of refractory SchS with findings of inflammatory subcutaneous lesions and an excellent response to B cell depletion therapy.

Case presentation

A 57 years old female patient was referred to our center for evaluation. She suffered from recurrent episodes of fever and painful erythemal rash that appeared three times per year in the previous 10 years. In the year prior to her referral her symptoms worsened with monthly episodes, each episode lasted 1-3 weeks, and was associated with pronounced malaise and joint pain, the lesions left blueish discoloration after subsiding and her disease became high-dose steroid dependent. Laboratory workup was remarkable for elevation of white blood cell counts, inflammatory markers and liver enzymes during flares. A diagnosis of Cryopyrin Associated Periodic Syndrome (CAPS) was contemplated but the appropriate genetic workup including mutations for CAPS, TRAPS (Tumor Necrosis Receptor-Associated Periodic Syndrome) and Familial Mediterranean Fever (FMF) was unrevealing. Skin biopsy was compatible with neutrophilic dermatosis with no evidence of malignancy. A monoclonal peak of IgG kappa was documented, with normal cellular bone marrow aspiration, supporting the definition of variant SchS according to the Strasbourg criteria.

In order to exclude other plausible diagnoses and particularly a lymphoproliferative disease a F-18 FDG-PET-CT was performed. The study revealed uptake in soft tissues and subcutaneous fat in various body parts including the upper and lower limbs bilaterally, with hint of focal fat infiltration on CT. These findings were not seen by a conventional CT scan [figure 1, Panel A, arrows]. Additionally, diffused pronounced uptake in bone marrow of long bones of the humerus and the proximal femur was demonstrated. Notably these lesions on PET-CT were compatible to the lesions observed on her skin and were not present on follow-up PET-CT performed during remission.

At that point high dose of glucocorticoids (1-2mg/kg/day) were required to control symptoms and relapses were frequent while tapering down of steroid dose below 30 mg/day of prednisone. Disease Modifying Anti Rheumatic Drugs (DMARDs) such as azathioprine and methotrexate as well as anti-IL-1 (both anakinra and canakinumab) and anti-IL-6 blocker (actemra) failed. Thus, considering the monoclonal gammopathy and as all previous lines of therapy were unsuccessful, plasmapheresis was performed leading to clinical improvement, followed by B-cell depletion therapy given every 6 months with anti-CD20 antibody (Mabthera) leading to clinical resolution during three years of follow up.

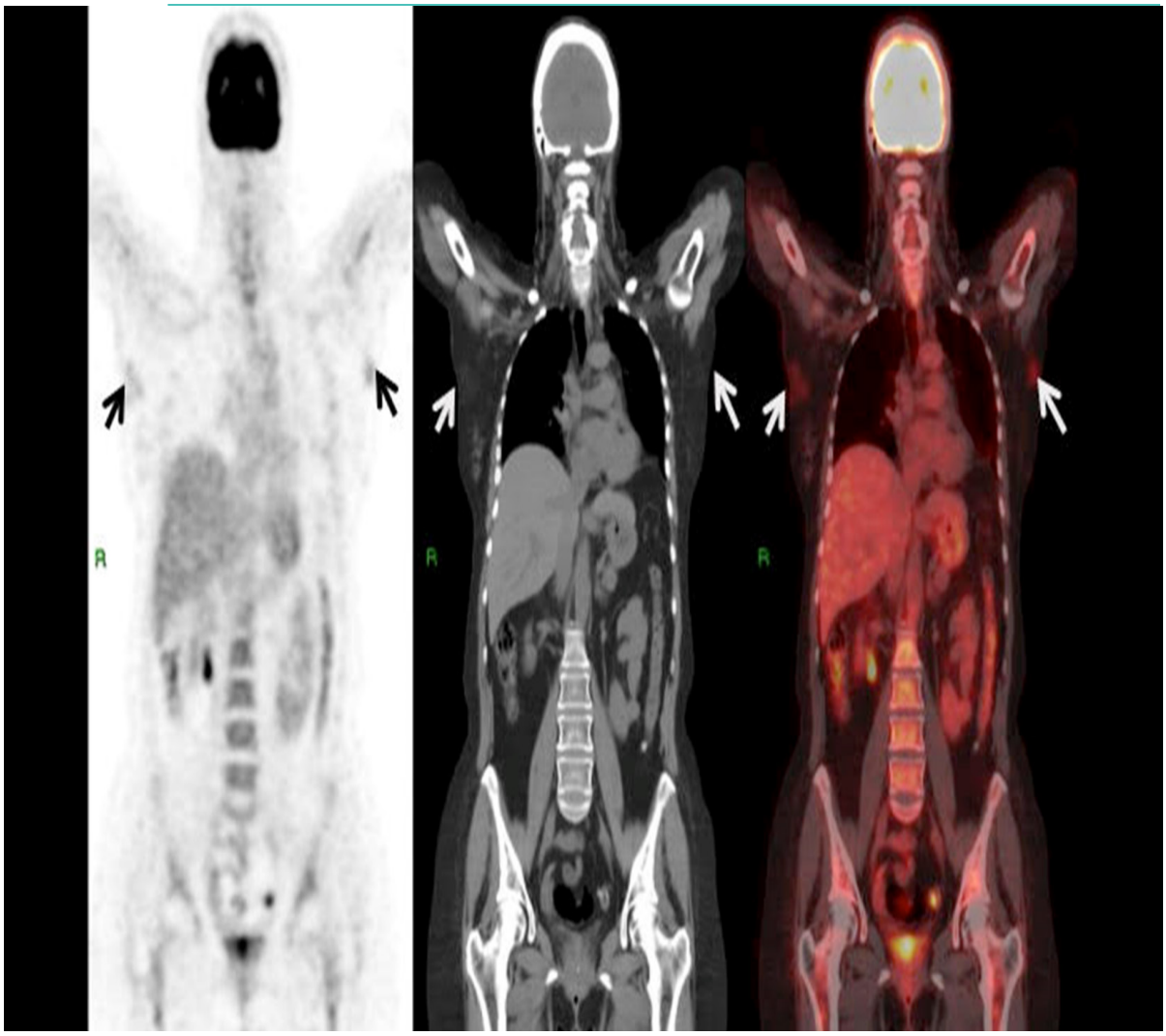

FIgure 1 Subtle ill-defined infiltration of the subcutaneous fat in the bilateral axillae are demonstrated (arrows) by different techniques, F-18 FDG PET (on the left), CT (middle panel), the most prominent effect seen by combining these two together (on the right). This is a pathological inflammatory enhancement corresponding to palpable masses on our patient's physical examination.

Discussion

In this report we present for the first time to the best of our knowledge evidence for inflammatory skin and soft tissue lesions on F-18 FDG-PET-CT imaging that correlated with SchS activity at these locations. PET scans have been used for evaluation of SchS (9), mostly revealing diffuse bone-marrow and bone uptake (10), as noted on our patients' PET. These finding were reported in 40% to 64% of tests performed (9,11), femur and the tibia are usually involved, bone sclerosis around the knee being the most common finding, lytic lesions were also described (9). Herein, F-18 FDG uptake was observed also in soft tissue which was previously described in other monoclonal conditions. In MM, F-18 FDG-PET-CT detects extra-medullary disease, with great precision (12,13) *. The presence of uptake on F-18 FDG-PET differentiates active myeloma from smoldering when conventional radiological studies fail to show disease. This advanced imaging is used as a tool to monitor response to treatment as well (13). Upon extrapolating these data to SchS, one may speculate that such uptake of F-18 FDG PET-CT by soft tissue may relate to a unique subtype of SchS, a monoclonal gammopathy with cutaneous significance (14), which may require specific therapeutic interventions.

There are no guidelines for treatment of Schnitzler syndrome. Corticosteroids, cyclooxygenase inhibitors and steroid sparing drugs, have all been used with limited clinical effect and mainly for mild disease (2-5). In alignment with SchS auto-inflammatory nature, other immune modulators and particularly drugs that inhibit Interleukin-1 (IL-1) activity have been preferred. In 2012 a consensus group has recommended Anakinra as the first line treatment in patients with debilitating symptoms or significantly elevated inflammatory markers (3). Yet, IL-1 inhibitor has no effect on the paraproteinemic

monoclonal component. Apart from IL-1 blocking therapies, anti-IL-6 therapies were used for Schnitzler syndrome with some success (15), but none were efficacious for our patient.

Treatment of SchS with Rituximab was reported previously in two case reports of classical SchS. In the first, four weekly doses of the drug led to complete resolution that lasted for twelve months (16), while in the second rituximab induced short term remission of SchS present concomitantly with marginal zone lymphoma (17). In here, B-cell depletion with Rituximab was beneficial in controlling the disease of our patient with repeated doses given 6-8 months apart during 3 years of follow-up. Thus, our patient diagnosed with variant SchS is the third to be successfully treated with Rituximab. In this line of thought it seems that B-cell depletion therapy can serve as a practical and efficient solution in refractory cases of SchS when the disease persists despite standard anti-inflammatory therapy. Rituximab targets the pathological clone. Apart from assessing the patient by standard measures, it seems prudent to perform advanced imaging, like PET-CT (or even MRI) in order to assess better the extent of the disease that can present in soft tissues, similarly to MM.

** Extra-medullary disease means in soft tissue or solid organs.*

Conclusions

Schnitzler syndrome is a rare auto inflammatory disease with scarce data on imaging and treatment options. In this case report, F-18 FDG-PET-CT demonstrated a unique skin and soft tissue uptake that correlated with clinical findings. This may support the role of this mode of imaging in assessment of severe and refractory SchS. Moreover, following failure of several lines of therapies, we induced immunoglobulin reduction by plasmapheresis followed by repeated B-cell depletion with rituximab that resulted in remission of 3 years, alluding to the significance of the pathological clone in sub-population of patients with SchS.

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