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A man in his fifties with recurrent urticaria, fever and joint pain

EDUCATIONAL CASE REPORT

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BACKGROUND

Schnitzler's syndrome is a rare, acquired and probably underdiagnosed disorder. It is a type of autoinflammatory condition with late onset.

CASE PRESENTATION

A man in his fifties had had recurrent urticaria, fever and chronic joint pain during the previous year. After an extensive investigation, no evidence of infection, autoimmune disease or malignancy was found. Blood samples showed moderately elevated SR and CRP, mild thrombocytosis and presence of monoclonal IgM in low concentration (MGUS). The combination of sterile inflammation, joint/muscle pain, urticaria and M-component was consistent with Schnitzler's syndrome. He was placed on a treatment trial with anakinra (interleukin [IL]-1 receptor antagonist) 100 mg x 1 daily, given as a subcutaneous injection. His condition was excellent until one week after the first injection. The initial treatment indicated a good clinical effect of IL-1 blockade, but due to the very unpleasant localised side effects (extensive dermatitis), treatment with anakinra was withdrawn, and canakinumab (monoclonal antibody against IL-1β) was chosen instead. He responded very well to this treatment and experienced no adverse effects. One year after starting treatment, the patient still has an excellent treatment response.

INTERPRETATION

Anakinra is the treatment of first choice for this condition, but this case history illustrates that canakinumab can be tried if anakinra is not tolerated by the patient.

A man had been suffering from recurrent urticaria, fever and joint pain for approximately a year when, prior to elective knee surgery, he was also found to have elevated inflammatory markers. Further investigation led to the diagnosis of a rare disorder for which effective treatments are now available.

A man in his fifties had had persistent pain in his right knee for the past year. He was diagnosed with osteoarthritis of the knee and was admitted to the orthopaedic department of his local hospital for elective arthroplasty. Apart from this long-term musculoskeletal condition, his health had mostly been good. He had no known history of hereditary disease, and nothing in his travel history to suggest exposure to any tropical or other infectious diseases. Upon admission, the patient reported several months of periodic night sweats and fever, but no weight loss and no symptoms of respiratory or urinary tract infection. Examination revealed erythematous lesions over the entire abdomen as well as on his chest and limbs. The lesions were 1–2 cm in diameter but were neither raised nor pruritic. He reported no gastrointestinal, respiratory or urinary tract symptoms, and clinical examination was otherwise normal. Blood tests on admission showed C-reactive protein (CRP) 27 mg/L (reference <5) and leukocytes 13.2 × 10^9/L (3.5–11.0 × 10^9/L). The night before his scheduled knee arthroplasty, he experienced episodes of heavy sweating.

In the morning he was subfebrile and felt as though he had influenza, with aching muscles and nasal congestion. Blood samples taken in the morning showed CRP 22 mg/L (<5), leukocytes 13.1 x 10^9/L (3.5–11.0 × 10^9/L), platelets 424 × 10^9/L (130–400 × 10^9/L) and sedimentation rate (SR) 34 mm/h (<20). The operation was postponed due to a suspected viral infection, and the patient was discharged with an appointment to see his general practitioner (GP) one week later.

The GP could find no obvious explanation for the patient's fever and therefore began workup for fever of unknown origin. As is common practice, samples were taken to allow infectious diseases including syphilis, hepatitis B/C and endocarditis, as well as HIV infection, to be ruled out early on. Serum protein electrophoresis, CT using lymphoma protocol, and gastroscopy were ordered to screen for malignancy. A general autoantibody screen was also requested to rule out autoimmune disease, and the patient was referred to a dermatologist for assessment and biopsy of the rash.

Fever of unknown origin is defined as a temperature above 38.3°C for more than three weeks that is otherwise unexplained. The condition is usually the result of infection, autoimmune disease, or cancer. The relative distribution of

these causes varies with age and geography; roughly speaking, the proportion of cases that are attributable to autoimmunity and cancer increases with age and degrees of latitude (1).

The dermatologist concluded, after histological analysis of the skin biopsy, that the man had chronic urticaria. CT of the spine, thorax, abdomen, and pelvis was normal, as was the gastroscopy. The autoantibody screen was negative, as was serology for Hepatitis B/C, HIV and Treponema. No bacterial growth was observed in blood cultures. Serum protein electrophoresis showed a faint band in the gamma region, which was identified as monoclonal IgM-kappa, consistent with monoclonal gammopathy of undetermined significance (MGUS). It was not possible to fully rule out Waldenström's macroglobulinaemia or some other lymphoproliferative disorder. Immunophenotyping of peripheral blood was normal.

Since testing by the GP and local hospital had not revealed the cause of the patient's symptoms, he was referred on to an outpatient clinic for infectious diseases at a central hospital. Here he reported a six-month history of recurrent fever. The fever lasted for 2–3 days each time and was accompanied by pronounced lethargy, which disappeared when he became afebrile. The episodes were separated by fever-free intervals of up to a week. Over the past year, he had also developed a recurrent pruritic urticarial rash, which showed little response to antihistamines. He described daily pain in his muscles and joints, with the pain in his hips, back and knees bothering him the most. He had also recently begun to experience pronounced morning stiffness and had difficulty getting up quickly from a chair.

None of the tests performed so far had provided any evidence of malignancy, and nor had any chronic bacterial or viral infection been identified. CT scans had revealed no hidden abscesses, and neither the patient's medical history nor clinical findings were consistent with tuberculosis or endocarditis.

Blood tests now showed a moderately elevated SR of 39 mm/h, CRP of 63 mg/L and mild thrombocytosis at 411 × 10^9/L. Monoclonal IgM was still present at a low concentration, but s-ferritin was normal (151 µg/L (15–350)).

Given that the blood tests continued to suggest chronic inflammation, the malignancy workup was extended to include colonoscopy and bone marrow biopsy. There was no sign of vasculitis to explain the chronic urticaria, and S-tryptase levels were inconsistent with systemic mastocytosis.

The findings from the colonoscopy were normal. Bone marrow aspirate showed normal and well-differentiated cell lines with no clear pathology. A bone marrow biopsy showed normocellular bone marrow with normal structures, suggesting that the persistent symptoms were not the result of lympho- or myeloproliferative disease.

A comprehensive workup had thus provided no evidence of infection, autoimmune disease or malignancy. However, the clinical picture with fever, elevated inflammatory markers, urticarial rash, monoclonal gammopathy of undetermined significance, and joint/muscle pain raised suspicion of an autoinflammatory condition. Autoinflammatory diseases typically involve a sustained increase in activation of the innate (non-specific) immune system,

giving rise to systemic inflammation without concomitant antigen-directed autoimmunity. With a combination of sterile inflammation, urticaria and M-component, the patient's medical history and clinical findings could be considered consistent with so-called Schnitzler's syndrome (2, 3) (Box 1).

Box 1 Revised diagnostic criteria for Schnitzler's syndrome from an expert consensus meeting in Strasbourg in 2013 (2)

Obligate criteria

- Chronic urticarial rash and
- monoclonal IgM or IgG

Minor criteria

- Recurrent fever (must be > 38 °C and otherwise unexplained. Occurs usually, but not obligately, with the rash)
- Objective findings of abnormal bone remodelling with or without bone pain (assessed by means of bone scintigraphy, MRI, or elevation of bone-specific alkaline phosphatase)
- Neutrophilic dermal infiltrate on skin biopsy (usually corresponds to the entity described as neutrophilic urticarial dermatosis without fibrinoid necrosis or significant dermal oedema (3))
- Leukocytosis and/or elevated CRP (neutrophilic granulocytes > 10×10^9/L and/or CRP > 30 mg/L).

Two obligate criteria *plus* at least two minor criteria with IgM, or three minor criteria with IgG, gives a *definitive diagnosis*.

Two obligate criteria *plus* at least one minor criterion with IgM, or two minor criteria with IgG, gives a *probable diagnosis*.

Schnitzler's syndrome is a rare, acquired and probably underdiagnosed condition. The main clinical signs are urticarial rash, bone and/or joint pain, enlarged lymph nodes and fever. These are associated with monoclonal gammopathy, typically of the IgM type (mainly IgM-kappa), but sometimes of the IgG type (so-called variant Schnitzler's syndrome). An autoinflammatory condition with late onset (2), Schnitzler's syndrome is in principle an interleukin (IL)-1-driven disease. There is currently no approved treatment for Schnitzler's syndrome, but therapeutic IL-1-blockade is most effective. Anakinra, a soluble IL-1 receptor antagonist that blocks both IL-1α and IL-1β receptors is the most commonly used drug for the treatment of Schnitzler's syndrome (2).

In consultation with a specialist in infectious diseases/immunology at Rikshospitalet, it was decided to attempt treatment with anakinra 100 mg × 1 daily given as a subcutaneous injection. The choice of both drug and dosage are supported by the literature (2).
The patient was admitted to hospital to receive the first dose, plus training in injection technique, and to allow the effects of the drug and any adverse effects to be monitored. In the morning prior to the first injection, he experienced pronounced stiffness throughout his body and had difficulty

getting up from a sitting position on account of the stiffness and pain. Upon arrival at the hospital, his CRP level was 16 mg/L and SR 33 mm/h. He had no fever, and only faint lesions reminiscent of urticaria on his abdomen. Following the injection, he experienced a dramatic response to the treatment. He felt loose and supple and had significantly more energy, and his pain and stiffness disappeared after only a few hours. The day after his first injection, he managed to perform a squat and to get up again unaided. The morning stiffness had also gone. He experienced no adverse effects while in hospital, and no fever. On days 2 and 3, he administered the injections himself under supervision, and was then discharged home with an appointment scheduled for one month's time. Unfortunately, no blood samples were taken prior to discharge.

The patient remained in very good health up until a week after the first injection. When he then injected anakinra into one side of his abdomen, an erythematous rash appeared with a ring around the injection site.

Erythema around the injection site is a common adverse effect of anakinra that is tolerated by many patients. It is therefore usually acceptable to continue treatment if the changes are minimal.

About three hours after the injection, the mosquito bite-like lesion on his abdomen became much worse. A pruritic urticarial rash appeared over his entire abdomen, and several hard lumps gradually formed subcutaneously. The event was interpreted as an allergic reaction to anakinra, a rare but known adverse effect. In consultation with a specialist in infectious diseases, the man was advised to discontinue treatment, and was started on antihistamines with follow-up by his GP. After 2–3 days, the itching subsided. However, 5 days after the last anakinra injection, he again developed an urticarial rash over large parts of his torso and limbs. His muscle and joint pains had returned to pre-treatment level. He could no longer do squats. The morning stiffness, urticaria and periodic fever were also back.

The initial response to anakinra suggested a beneficial effect of IL-1 blockade, but because of the strong adverse reaction, it was decided in consultation with a specialist in infectious diseases/immunologist at Rikshospitalet not to attempt treatment with anakinra again. Instead, treatment would be attempted with canakinumab (Ilaris), a monoclonal antibody against IL-1β.

Whereas anakinra acts as an antagonist of both IL-1α and IL-1β by blocking IL-1 receptor type 1 (IL-1R1), canakinumab acts as a specific antagonist of IL-1β by binding to the signalling molecule itself. Canakinumab has shown efficacy in several published case reports, with results suggesting that IL-1β is most likely the cytokine responsible for the inflammation in Schnitzler's syndrome (4, 5). The first randomised placebo-controlled trial also concluded that canakinumab is efficacious for the treatment of Schnitzler's syndrome (6).

The patient was readmitted to hospital for observation during treatment. Upon admission, he had an urticarial rash on his hip and thigh. Blood tests showed SR 27 mm/h and CRP 33 mg/L. Canakinumab 300 mg was administered subcutaneously under preparedness for anaphylaxis. The injection was uncomplicated, and no adverse effects occurred during a 24-hour observation period. His response was not as immediate as it had been with anakinra, but

the rash on his hip/thigh disappeared. He was therefore discharged home with instructions to continue administering subcutaneous canakinumab 300 mg every 4 weeks.

At a follow-up appointment one month later, he continued to have an excellent response to canakinumab. His rash had disappeared, and he had very little muscular pain, although he still had some pain in his right knee, consistent with known osteoarthritis. He had not experienced any side effects, and inflammatory markers in the blood had normalised to SR 6 mm/h and CRP <5 mg/L.
Six months after starting canakinumab, he was still responding very well and had no adverse effects. The muscle pain had not returned, and he did not report any rash. In consultation with Rikshospitalet, the dose of canakinumab was halved to 150 mg every 4 weeks.
One year after starting treatment, the patient continues to respond well. The muscle pain has not returned, and he describes seeing only a mild rash a few days prior to each injection. He feels he can live with the pain in his right knee and does not wish to have surgery at present. Inflammatory markers in the blood remain normal, with SR 2 mm/h and CRP <5 mg/L.

Discussion

Schnitzler's syndrome was first described in 1972 by the French dermatologist, Liliane Schnitzler (7, 8). The condition is rare, with just over 300 cases described in the literature (2). These include one case report published in Norway in 2011 (9), while the first case report from Sweden was published in 2008 (10).

The pathophysiology underlying the syndrome has yet to be fully characterised. In particular, it is unclear whether the clinical signs are linked to monoclonal gammopathy. Recent studies have shown that systemic overproduction of IL-1β potentiates the pro-inflammatory effects of Th17 cells (11). Blockade of IL-1β function appears to restore IL-10 expression and the regulatory properties of Th17 cells. This may have important implications for the development of new strategies for treating the syndrome (2). However, it is worth noting that IL-1 itself is a central mediator of fever and joint pain (12).

Schnitzler's syndrome shares many clinical and biological characteristics with hereditary autoinflammatory syndromes, including cryopyrin-associated periodic syndrome (CAPS), which is caused by activating mutations in the *NLRP3* gene. In both conditions, patients have recurrent fever, urticarial rash with neutrophil infiltration evident on biopsy, neutrophilia and elevated CRP levels. Elevated ferritin levels, indicative of macrophage activation, are also seen frequently, although they were not observed in our patient. *NLRP3* mutations have not been detected in gametes in Schnitzler's syndrome (2), and monoclonal gammopathy is not present in CAPS.

There is no gold standard for the diagnosis of Schnitzler's syndrome, and many other conditions must be ruled out before this diagnosis can be considered. Important differential diagnoses include adult-onset Still's disease, hereditary

periodic fever syndromes, Muckle-Wells syndrome, lymphoma and Waldenström's disease, as well as more specific autoimmune conditions and, not least, malignancy.

Lipsker et al. developed the first diagnostic criteria for Schnitzler's syndrome in 2001, and these were subsequently revised and improved upon at an expert consensus meeting in Strasbourg in 2013 and later validated (2) (Box 1). The main complication is the development of lymphoproliferative disease, which occurs in 15–20 % of cases; in addition, amyloidosis occasionally occurs in untreated patients as a complication of prolonged systemic inflammation (2).

The efficacy of anakinra was first reported in 2005 (13), with long-term efficacy subsequently confirmed in a multicentre retrospective cohort study (14). The treatment is symptomatic, and if the patient misses an injection, symptoms will usually return after 36–48 hours (2). Prior to beginning treatment, the patient should be examined for latent tuberculosis (TB-IGRA) and be given booster doses of vaccines against pneumococci and influenza. The patient should not receive any live attenuated vaccines during treatment. Haematological status, blood tests, CRP, serum electrophoresis, quantification of immunoglobulins, and liver function tests should be repeated every three months (15).

A few patients will not respond to IL-1 inhibition, and in these individuals the diagnosis should be reconsidered. If the diagnosis of Schnitzler's syndrome is considered certain, an anti-IL-6 treatment such as tocilizumab may be effective. This may be particularly relevant for cases in which the biochemical profile is dominated by high CRP levels, driven by IL-6 (2).

Schnitzler's syndrome is a rare, acquired and probably underdiagnosed condition. It is an autoinflammatory disorder with late onset. Autoinflammatory disease should be suspected in patients with otherwise unexplained chronic recurrent inflammation with high levels of CRP and possibly ferritin. Schnitzler's syndrome is one of several autoinflammatory conditions that should be considered if, in addition to recurrent fever and systemic inflammation, the patient also has an urticarial rash and IgM-monoclonal gammopathy of uncertain significance. In Norway, the Department of Infectious Diseases at Rikshospitalet has specialist expertise in the diagnosis and treatment of such conditions and can be consulted if required.

The patient has consented to the publication of this article.

The article has been peer-reviewed.

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