# Disappearance Of Monoclonal Protein In Schnitzler's Syndrome Treated With Anakinra

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**Citation**

R Lin. *Disappearance Of Monoclonal Protein In Schnitzler's Syndrome Treated With Anakinra*. The Internet Journal of Asthma, Allergy and Immunology. 2012 Volume 8 Number 1.

**Abstract**

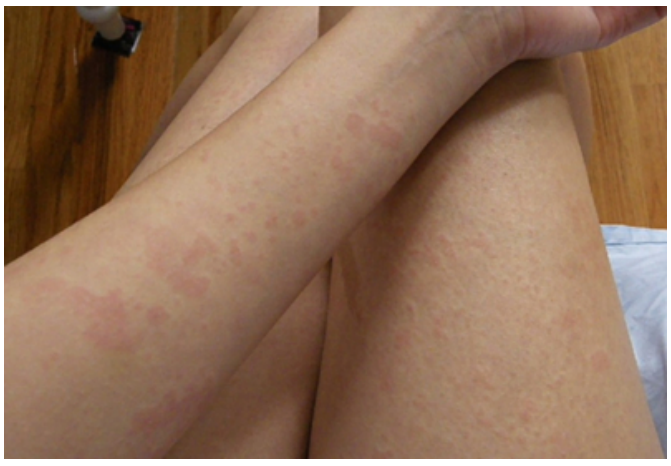
The treatment of cryopyrin-associated diseases has been revolutionized by the availability of monoclonal IL-1 antibody and IL-1 receptor antagonists (1). Other diseases associated with systemic inflammation and fever, which have been treated successfully with these agents, include familial Mediterranean fever (2) and Schnitzler syndrome (3). A patient with Schnitzler syndrome is described, in whom the initial monoclonal protein disappeared following anakinra therapy. Implications for diagnosis and monitoring of patients with Schnitzler syndrome are discussed.

## CASE REPORT

A 31-year-old Asian female developed recurrent rash, and adenopathy in February 2010. She was treated with azithromycin and the symptoms abated. However by July 2010 she began to get daily rash, recurrent arthralgias, 2.3 kg weight loss and chills. She described the rash as slightly raised, occurring in crops, with lesions lasting 1-2 days and having a slight burning sensation. She had tried ibuprofen and antihistamines without any relief. Her physical examination at that time revealed cervical and submental lymphadenopathy and mottled slightly faded macules on both lateral thighs with scatted macules on arms.

**Figure 1**

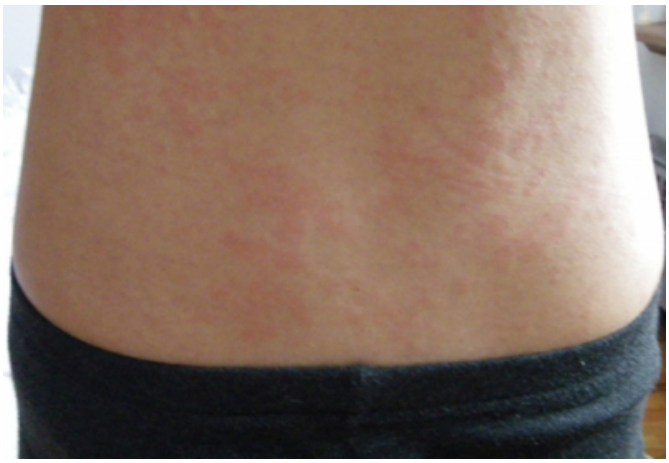
Figure 1: Rash on arm



The temperature was 37.8C. Recent photographs taken of the rash included areas on her extremities and on her trunk (back)

**Figure 2**

Figure 2: Rash on trunk



A skin 2 mm punch biopsy of an arm macule did not show neutrophilic dermatosis or vasculitis. Laboratory testing at that time showed a normal complete blood count and erythrocyte sedimentation rate (Westergren) of 9 mm/hr. The C-reactive protein was elevated at 3.9 mg/dL. The antinuclear antibody, rheumatoid factor, C3, and C4 were normal. Serum iron was 19 mcg/dL(normal 40-175) and the ferritin was 553 ng/mL (normal 10-154). Blood and throat cultures were negative. Serologic studies for acute infection with Borrelia burgdorferi, Epstein Barr virus and cytomegalovirus were negative. She was seen again 1 week

later with complaints of headache, body aches and fever (40ºC) despite treatment with naprosyn and amoxicillin/clavulinate. At this time the C-reactive protein was 5.9 mg/dL, the LDH (lactate dehydrogenase) was 333 U/L (normal 100-200). The CK (creatine kinase), TSH (thyroid stimulating hormone) and histamine release tests were normal. The blood counts showed mild thrombocytopenia 129,000/uL and anemia hemoglobin 11 gm/dL.

Despite administration of 40-60 mg of prednisone per day, the patient continued to be symptomatic during the following month. The C-reactive protein rose to 7.2 mg/dL. Immunofixation revealed a faint IgM lambda monoclonal band. The anti-cyclic citrullinated peptides antibody was normal. The erythrocyte sedimentation rate was 11 mm/hour. The total IgG, IgA, IgM and IgE levels were normal. There were no cyroglobulins detected. Sulfasalazine and colchicine were initiated while continuing prednisone, without benefit. Wrist tendonitis developed and was treated with a corticosteroid injection. Anakinra 100 mg per day subcutaneously was initiated. Two weeks later the patient still had mild, limited rash, but there was resolution of all musculoskeletal symptoms. The C-reactive protein decreased to 0.3 mg/dL, and the anemia and thrombocytopenia had resolved. A skeletal survey and bone marrow examination/bone biopsy were normal. One month after starting anakinra, the patient still complained of mild fever and rash but was able to decrease prednisone to 10-20 mg/day without any other anti-rheumatic medication. The C-reactive protein was 1.2 mg/dL. The following month the patient was able to stop systemic corticosteroid therapy and complained only of intermittent mild rash.

In November 2010, the patient increased the dosing interval for anakinra to every 3 $^{rd}$ day. There was no longer detectable monoclonal protein. In February 2011, there was still no detectable monoclonal protein and the C-reactive protein was 0.1 mg/dL. In March 2011 the patient developed noticeable submental adenopathy. She claimed that she had increased bacterial vaginosis symptoms and treatment requirements since starting the anakinra, the dosing for which was then increased to every 2 days. Because of persistent adenopathy, a fine need biopsy of a cervical lymph node was performed in April 2011, which showed no evidence for lymphoma. In August 2011, the patient again developed increasing adenopathy (neck and groin), as well as some thigh pain and mild rash while attempting to decrease the anakinra dosing interval to every 6 days but she reverted to every 2 days more recently. At that time the C-reactive protein level was 0.4 mg/dL. There was no monoclonal band, no serum free light chain alterations, and no T or B cell gene rearrangements. By November 2011 the patient was self-injecting anakinra every 1-2 days and still at that time had no monoclonal protein detectable; the C-reactive protein was <0.1 mg/dL. In January 2012, the patient had a brief febrile illness which was associated with a mild rash on the wrist. She thereafter continued to self-inject anakinra every 2 days with no recurrence of fever or rash.

## DISCUSSION

The hallmark of Schnitzler syndrome is the presence of a monoclonal band, typically IgM(3). There may also be recurrent febrile rash, joint and/or bone pain, enlarged lymph nodes, fatigue, leukocytosis and systemic inflammatory response (3). The rash, typically described as urticarial, and the monoclonal band are required elements of the diagnostic criteria put forth by Lipsker (3). This author is aware of two reports of Schnitzler syndrome without monoclonal antibody (4,5). Although this is stated to be rare, this author believes that the present case demonstrates that monoclonal protein can sometimes be transient. A recent review by Lipsker stated that in early disease, the monoclonal band can be faint (3). The currently described patient has had the disease for 2 years and has not had detectable band since anakinra was started, suggesting that therapy may also influence the ability to detect monoclonal protein. Lipsker (3) also states that an elevated sedimentation rate is universally seen in Schnitzer syndrome. There was never erythrocyte sedimentation elevation in the currently described patient. One might consider an approach analogous with temporal arteritis where either sedimentation rate or C-reactive protein increases can be used to assess systemic inflammation in diagnosing the disorder (6).

The prognosis for those with Schnitzler syndrome is generally good, with at least 80% having no lymphoproliferative or myeloid malignant transformation (3). Anakinra appears to the most effective treatment to date. However it is conceivable that the more convenient dosing interval for canakinumab (monoclonal anti IL-1 antibody) may make this more popular in the future.

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