

Autoimmune neutropaenia complicating Sjögren's Syndrome: haematological and clinical improvement with granulocyte colony stimulating factor

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Date accepted for publication 16 April 2007

Abstract

Connective tissue diseases are associated with granulocyte-specific autoantibodies and autoimmune neutropaenia. Reduced levels of circulating neutrophils may predispose to recurrent infections, particularly of the respiratory tract, although severe and opportunistic infections have also been reported. There is only one previous description of the use of granulocyte colony stimulating factor (GCSF) in Sjögren's Syndrome complicated by autoimmune neutropaenia, reporting poor response and tolerability. We present here the successful use of GCSF in a 42-year-old woman with Sjögren's Syndrome, autoimmune neutropaenia and chronic mastoiditis.

Keywords

Autoimmune neutropaenia; Sjögren's Syndrome; granulocyte colony stimulating factor.

Case report

A 42-year-old white British woman was referred to the Immunology Clinic for evaluation. She had a history of chronic suppurative otitis media of the left ear since infancy, and recurrent urinary tract infections since childhood. Following a mastoidectomy at the age of 30, she required three further debridements with skin grafting and four hospital admissions for severe ear infections. She was diagnosed with Sjögren's Syndrome at the age of 18 on the basis of arthralgia, Raynaud's, kerato-conjunctivitis sicca, xerostomia and a positive Schirmer's test, and was treated with artificial tears and hydroxychloroquine 200 mg twice daily. In addition, she was known to have medullary sponge kidney, manifesting as recurrent urinary tract infections and renal calculi. Physical examination showed a thin woman with active suppuration in the left mastoid cavity. Urinalysis was negative for blood and protein.

The neutrophil count was reduced and averaged $1.2-1.5 \times 10^6/l$ ($2-7.5 \times 10^9/l$), in the presence of active infection; the remainder of the blood count was normal. The erythrocyte sedimentation rate was elevated at 60 mm/h. Levels of IgG, IgA and IgM were raised in keeping

with chronic inflammation. Levels of antibodies directed against tetanus, haemophilus and pneumococcus were protective. Functional complement studies and lymphocyte subset analysis were within the normal ranges. We confirmed the presence of antinuclear antibody, with specificity for Ro and La. Antibodies against double-stranded DNA were not detected, and rheumatoid factor was negative. She had mild renal impairment (creatinine of 132 $\mu\text{mol/l}$ (79–118)).

Our patient's clinical and serological features satisfy the revised version of the European criteria proposed by the American-European Consensus Group for the classification of Sjögren's syndrome^[1].

A bone marrow aspirate and trephine demonstrated normal erythroid and megakaryocytic lineages, and granulocytes and their precursors were plentiful. Granulocyte-specific antibodies of both IgG and IgM isotype were present, supporting a diagnosis of autoimmune neutropaenia. We suspected that the poor resolution of her middle ear infection was related to mild neutropaenia, and commenced a trial of granulocyte colony stimulating factor (GCSF) (filgrastim) at a dose of 30 million units twice weekly, which was well-tolerated and normalised her absolute neutrophil count. The average neutrophil count rose from 1.2–1.5 to 3.0–4.0 $\times 10^9/\text{l}$. This resulted in a marked reduction in the frequency and severity of infective episodes (from one episode a month to one every 6–9 months), although the mastoiditis is well established and unfortunately has not resolved. A subsequent attempt to reduce the frequency of GCSF to weekly was associated with a fall in the absolute neutrophil count to 1.3 $\times 10^9/\text{l}$ and recurrent infection of the middle ear. There has been no apparent reduction in the frequency of urinary tract infections. Our patient did not suffer any significant side effects from filgrastim.

Discussion

Granulocyte-specific antibodies are a well-recognised cause of neutropaenia in infants and children (in whom the condition is usually primary) as well as in adults (in whom the condition is usually associated with other pathologies, e.g. connective tissue disease, viral infection and autoimmune haemolytic anaemia)^[2]. Granulocyte-specific antibodies, generally of IgG but sometimes of IgM specificity, are directed against a variety of antigens. The condition presents with recurrent infection, with a frequency and severity relating to the degree of neutropaenia; as neutrophil counts are often in the mild to moderate range, severe and opportunistic infections are uncommon. Autoimmune neutropaenia is well recognised in Sjögren's Syndrome and may affect up to 10% of patients^[3–7]; most individuals have mild neutropaenia and are asymptomatic^[8], but severe sepsis and infection with opportunistic organisms have occasionally been reported^[9]. GCSF has been demonstrated to improve neutrophil count and reduce the infection rate in autoimmune neutropaenia^[10], although steroids have documented efficacy in the context of Sjögren's Syndrome^[4,9] and high-dose immunoglobulin infusion has been used in other contexts^[11]. There have only been two previous reports of the use of GCSF in autoimmune neutropaenia complicating Sjögren's Syndrome^[8,9]; in one report short courses of subcutaneous GCSF produced a transient and mild response in all three patients^[8], and in another, a 58-year-old woman presented with severe neutropaenia, fever and pseudomonal conjunctivitis^[9]. The response was suboptimal despite adequate dosing, and treatment was complicated by anaemia and thrombocytopenia, prompting the discontinuation of GCSF and the successful use of corticosteroids. By contrast, treatment was well tolerated in our patient, with sustained clinical and haematological response.

We are unsure of the duration of this patient's neutropaenia, but suspect that it may have been longstanding; Schattner et al.^[5] reported autoimmune cytopaenias preceding the onset of connective tissue disease, and infection of the middle ear and upper respiratory tract were the commonest presenting features in a study of 240 infants^[12].

Teaching point

The presence of neutropaenia in connective tissue disease should prompt assay of anti-granulocyte antibodies. Prompt treatment of intercurrent infections is important, and may need to be continued for longer than normal. For symptomatic patients, treatment with GCSF may be beneficial and less toxic than alternatives.

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