Treatment Of Schnitzler's Syndrome With Colchicine: A Case Report

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Citation

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Abstract

Schnitzler's syndrome was described in 1974(1) and is typically presents with chronic nonpruritic urticaria, bone pains, fever, and monoclonal IgM gammopathy(2). Although corticosteroids are usually used to treat these patients, long term treatment usually results in significant corticosteroid induced side effects. Other treatments that have been described include cyclosporine, thalidomide, and interferon alpha. The benefits of colchicines in this disorder have been stated by some experts to be minimal. In this report, we describe the clinical course of a patient with Schnitzler's syndrome who was treated with colchicine with marked improvement.

CASE REPORT

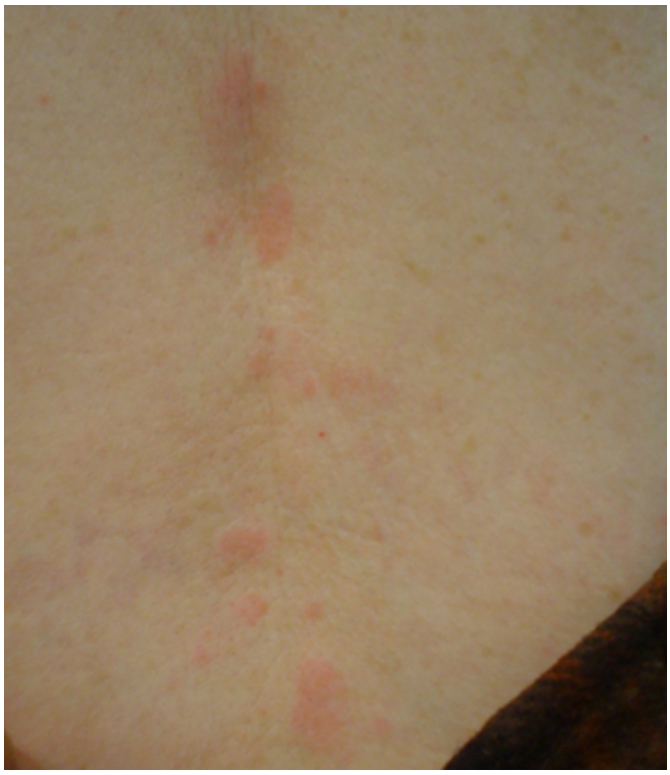
A 57 year old White female presented to the hematology department of St Vincents Hospital in December 1999 with complaints of recurrent fever and rash since 1993. She had been diagnosed as having an IgM monoclonal gammopathy at another medical facility. The patient claimed to have been treated with corticosteroids and hydroxyzine without relief. A bone marrow biopsy examination at that time showed 11% plasma cells. Serum immunfixation showed an IgM kappa band. Serum IgG was 490 mg/dL, IgA was 90 mg/dL, and IgM was 710 mg/dL. The hemoglobin was 10 g/dL. The white blood count was 16,600/mL. The serum protein was 7.7 g/dL. A left upper arm lesional skin biopsy was interpreted as being consistent with leukocytoclastic vasculitis. Linear deposition of IgM kappa chain was observed in the vicinity of the inflamed blood vessels. The patient underwent plasmapheresis, which resulted in a decreased serum IgM of 477 mg/dL Rofecoxib 25 mg daily and prednisone 60 every other day was administered. In February 2000, the rash persisted and the serum IgM rose again to 805 mg/dL Rofecoxib was increased to 50 mg/d and the patient underwent plasmapheresis on a monthly basis through May 2000, at which time pentoxifylline 800 mg/d was administered. In July 2000 the patient had a serum IgM of 671 mg/dL, a C-reactive protein level of 10.3 mg/dL, and an IL6 level of 10 pgm/mL Prednisone was continued at 60 mg every other day and cimetidine 400 mg twice daily and loratadine 10 mg/d were prescribed. celecoxib 100 mg twice daily was prescribed in place of rofecoxib. In September 2000, the patient was given etanercept 25 mg twice weekly for 10 weeks. In November 2000 the IgM rose to 1500 mg/dL. The patient continued to have rash but no fever. Rituximab 460 mg was administered intravenously on a weekly basis for 4 doses. By the middle of January 2001,.the patient reported improvement and the IgM decreased to 404 mg/dL. Prednisone was discontinued. At the end of January 2001, the fever recurred and the temperature was 38.9C (102F) and rash was noted. At that time the IgM was 240 mg/dL Prednisone was restarted at 30 mg every other day. On 4/16/01 the C-reactive protein was 9.3 mg/dL.In December 2001 the patient still reported rashes and fever that would usually recur together. The IgM was 113 mg/dL, IgA 24 mg/dL, IgG 419 mg/dL. The bone marrow biopsy examination showed 5% plasma cells.

The patient was referred for allergy/immunology consultation in March 2002. The patient reported that she had frequent “hives” that were followed with 1-2 2 hours by sheet soaking fever with chills and severe malaise and fatigue. This sequence of symptoms occurred every 2-3 days. The patient claimed that the rash was not very pruritic and individual lesions would sometimes last for up to 2 days. The patient reported having been treated in the past with colchicine at another medical facility without improvement of symptoms. Laboratory findings showed an ESR of 65 mm/hr, CRP of 6.9 mg/dL, a CH50 of 121 CAE units, white blood count of 7.8/mm3 and a C4 of 22.7 mg/dL. No

cryoglobulins were detected in the serum. At that time she was taking prednisone 30 mg every other day, but still frequent outbreaks of rash and fever. Dapsone 100 mg per day was prescribed and the patient was instructed to reduce her prednisone dose to 25 mg every other day. The patient had little improvement and one month later the patient was observed to have slightly erythematous papules which appeared urticarial on her torso and extremities. A right forearm lesional skin biopsy taken at that time showed superficial perivascular dermatitis with no evidence of vasculitis. The patient was told to discontinue dapsone and sulfasalazine 1 gm twice daily was prescribed. The prednisone dose was continued at 30 mg every other day. Two weeks later the patient reported no improvement and hydroxychloroquine was added at 200 mg twice daily. The C-reactive protein at that time was 12.7 mg/dL. The patient reported no improvement, and began to use prednisone on the “off” day for breakthrough symptoms. In September 2002, the patient was given colchicine 1 mg twice daily. The patient claimed that her prior treatment with colchicines was at a dose lower than this. In October 2002, the patient claimed improvement and self tapered her prednisone dose to 5 mg/d. The colchicine dose was changed to .6 mg three times/day and the patient was told to continue prednisone at 5 mg/day. Over the next 6 months the patient no longer had daily fever and had discontinued prednisone and hydroxychloroquine but had 3-4 short periods of fever usually associated with chills and rash. She was treated with 20 mg prednisone for 2-3 days for each episode. By the end of 2002, she no longer required erythropoeitin injections which had been administered between 1 to 4 doses(40,000 units/dose) each month since the end of 2000 to maintain normal hemoglobin levels In March 2003, the C-reactive protein was 4.8 mg/dL. In June 2003 the patient reported being asymptomatic for 2 months off prednisone, and thus lowered the dose of colchicines she was taking. This was followed by recurrence of fever which resolved after returning to the colchicines dose prescribed. In August 2003, the patient reported being asymptomatic while taking colchicine .6 mg twice daily. She no longer required erythropoeitin injections. On August 26, 2004, the C-reactive protein was 2.06 mg/dL. Repeated bone marrow studies showed no evidence for malignant transformation. In March 2005, the patient still reported having no fever, chills while taking colchicine. The patient was still taking a non-steroidal anti-inflammatory drug for “aching” but no prednisone. At that time, the C-reactive protein was 2.98 mg/dL, the IgM was 163 mg/dL, the IgG was 407 mg/d, and the IgA was 38.3 mg/dL. On physical examination, urticaria were noted on the lower back.

Figure 1

Figure 1: Lower back of the patient



The patient admitted having urticaria intermittently but without any associated symptoms.

DISCUSSION

Colchicine is the mainstay of treatment for familial Mediterranean fever, where it markedly reduces episodes of fever and prevents amyloidosis ([3]). In Schnitzler's syndrome, the major long term complication is the development of B-lymphocyte associated malignancy, which may occur in up to 16% of patients ([4]). The patient reported here had progressive rise in monoclonal IgM levels that ultimately responded to rituximab treatment. However, the other systemic symptoms continued in spite of sustained IgM reductions. This suggests that the magnitude of gammopathy is not the key inflammatory stimulus in this disorder. No response in these symptoms occurred despite therapeutic trials with etanercept, hydroxychloroquine, sulfasalazine, and dapsone. Colchicine treatment appeared to reduce symptoms in this patient within 1 month of starting therapy. When the patient self decreased her colchicines, her symptoms exacerbated. With resumption of proper doses, her symptoms improved. The reduction of C-reactive protein and white blood count also constituted evidence the

reduction in inflammation that occurred in this treated patient. It is also of interest that erythropoeitin administration was no longer necessary after colchicine therapy was established.

The patient was still noted to have urticaria on her last examination, suggesting that her disease was not totally quiescent. Furthermore, the patient still reported the need to take non-steroidal anti-inflammatory medication for "aching". It is conceivable that this aching represented the "bone pain" that is often mentioned in Schnitzler's syndrome. Thus the disease appeared still to have some activity. Never-the-less, the patient was able to be treated with relatively non-toxic medication and did not require corticosteroids. Other successful non-steroid treatments reported, such as interferon alpha([5]), cyclosporine ([6]), and thalidomide ([7]), have significant side effects. Thus colchicine may be considered as a preferred long-term treatment modality. This case illustrates that responses may initially manifest incomplete suppression of symptoms. But with sustained long term treatment at adequate doses, the debilitating symptoms of fever were ultimately abolished. Colchicine treatment has not been uniformly successful in other reported cases. The initially lack of response to colchicines reported by the patient suggests the necessity of using adequate doses(up to 3 mg/d) similar to that observed in familiar Mediterranean fever ([3]), before attributing a response failure to this medication.

It has been proposed that interferon alpha may be beneficial in Schnitzler's syndrome because it increases IL1 antagonist levels ([5]). The patient reported here failed to respond to etanercept, suggesting that IL1 blocking mechanisms do not improve symptoms of this disorder. One characteristic of this disease is the variable presence of leukocytoclastic vasculitis ([2]), which was noted in one lesional skin biopsy from the reported patient. In serum sickness, immune complexes are thought to initiate an inflammatory cascade involving complement activation, that results in fever and small vessel vasculitis, such as leukocytoclastic vasculitis([8]). In the patient reported here, somewhat bland histopathologic findings were observed on repeat lesional biopsies despite the presence of severe systemic symptoms (fever and malaise). When the patient was free of fever, urticaria was still noted. This would suggest that skin inflammation is not a primary cause of febrile episodes in this disorder. Control of febrile episodes with continuing skin involvement has been reported in other cases ([2]).

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