

Neutropenia in Felty's syndrome successfully treated with hydroxychloroquine

Haematologica 2007; 92(7):e78-e79

Felty's syndrome (FS) is a rare disease defined by the presence of 3 conditions: rheumatoid arthritis (RA), neutropenia, and splenomegaly 1. It has been subdivided into two entities, depending on the presence or absence of large granular lymphocyte (LGL) leukaemia. LGL leukaemia is diagnosed by identifying a T cell clone with typical LGL morphology and phenotype in blood or bone marrow smears. However, both entities may be part of the same disease spectrum.^{1,2} Morbidity and mortality rates are high in FS patients, with or without LGL leukaemia, because FS patients are more susceptible to infection.^{3,4} Although little is known about the pathophysiological aspects of FS, neutropenia, a defining feature of FS, may be due to humoral and cell-mediated immune dysregulation. The treatment of FS is not well established due to its rarity and the consequent lack of prospective clinical trials. A number of drugs have been tested yielding various results,⁵⁻¹¹ but the most efficient treatment seems to be methotrexate (MTX).^{1,5,6}

We report two original cases of severe neutropenia related to FS. Both cases were successfully treated with hydroxychloroquine (HCQ) after methotrexate was withdrawn due to toxicity.

Case 1

A 42-year-old woman was referred for RA and splenomegaly. A high titre of rheumatoid factor was detected and the white blood cell count (WBC) revealed moderate neutropenia (1×10^9 PN/L). Bone marrow aspirates were normal and morphological examination of blood and marrow smears and lymphocyte immunophenotyping failed to detect large granular lymphocytes. FS was diagnosed and methotrexate was administered. Methotrexate had to be stopped after two weeks as hepatitis and thrombocytopenia were diagnosed. Salazopyrine was administered to the patient, but it was not tolerated and resulted in a skin rash. Given the absence of severe disease, symptomatic treatment was administered and marked neutropenia persisted; the resulting neutrophil count was less than $0.5 \times 10^9/L$.

The patient developed active painful synovitis in both hands after four years. Splenomegaly was continuously present from the initial diagnosis. The WBC 1.8×10^9 cells/L, the neutrophil count was $0.4 \times 10^9/L$ signalling persistent severe neutropenia, and the lymphocyte count was $0.9 \times 10^9/L$. LGL leukaemia was once again excluded as a result of peripheral blood smears and lymphocyte immunophenotyping. No circulating T-cell clones were detected by PCR amplification of the T cell receptor gene. Other causes of neutropenia were ruled out: anti-nuclear antibodies, anti-platelets, and anti-neutrophil antibodies. Erythrocyte direct antiglobulin (Coombs) tests were negative, HIV and HTLV1 tests were negative, and no drugs had been recently introduced. The patient did not receive steroids and treatment with HCQ was started at 400 mg daily. There was a dramatic increase in the neutrophil count, and normal counts were restored within 2 weeks of starting treatment. A persisting response was observed after 22 months of follow-up (Figure 1) when a relapse of active polyarthritis occurred. The neutrophil count simultaneously fell to $0.6 \times 10^9/L$. The patient had discontinued HCQ two weeks earlier because of severe gastritis, which was responsible for abdominal pain and vomiting. We measured the blood HCQ concentration using high per-

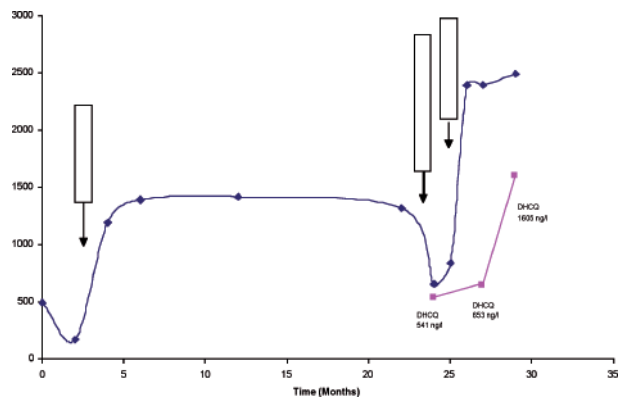


Figure 1.

formance liquid chromatography. The concentration was less than the usual therapeutic range: the desethylhydroxychloroquine (DHCQ) level was 541 ng/mL and the desethylchloroquine (DCQ) level was 99 ng/mL; HCQ is considered to be in the therapeutic range when the sum of the DHCQ level and the DCQ level is over 1000 ng/mL.¹² High-dose intra-venous methylprednisolone (500 mg daily for 2 days) was needed to control the pain and the synovitis, and a daily oral dose of 0.25 mg/kg prednisone was started. The HCQ dose was increased to 1200 mg/daily. All prior symptoms resolved, including neutropenia, as the neutrophil counts reached $2.4 \times 10^9/L$ within a week. The steroid doses were tapered and eventually stopped. Five months later, the patient was asymptomatic and both WBC and neutrophil counts were normal. DHCQ and DCQ blood levels were checked and found to be in the expected range (1605 ng/mL and 653 ng/mL respectively).

Case 2

A 35-year-old woman with a one-year history of seropositive RA with solely rheumatological manifestations was successfully treated with daily prednisone (0.5 mg/kg). Neutropenia was initially reported (0.4×10^9 cells/L); however, the patient attained normal neutrophil counts within a few days of steroid therapy. No LGL populations were identified in blood or bone marrow smears.

Methotrexate was administered one year later as a result of synovitis and morning stiffness, and prednisone was slowly tapered to 5 mg daily. The full blood count was 0.9×10^9 neutrophils/L six months after the introduction of methotrexate. Methotrexate-associated toxicity was suspected and the drug was withdrawn. However, the neutrophil count fell to $0.04 \times 10^9/L$, and the patient presented with fatigue, weight loss, acute synovitis and splenomegaly. The patient was positive for anti-CCP antibodies. Morphological examination of peripheral blood samples revealed the presence of several large granular lymphocytes with $CD3^+CD8^+CD57^+$ cell surface markers. A circulating T-cell clone was identified by PCR amplification of the T-cell receptor gene. The diagnosis was consistent with T-LGL proliferation. Treatment using a combination of steroids and granulocyte colony stimulating factor (G-CSF) was ineffective, and treatment with HCQ was started at 400 mg daily. The absolute neutrophil count (ANC) immediately increased to $1 \times 10^9/L$ and reached the normal range within four months. Treatment with HCQ has been continuously maintained over the past two years. The patient is now asymptomatic and her PN levels are still normal.

Discussion

Although the best way to treat FS is still unknown, studies of small series of patients report a frequent response to a low-dose of MTX, as in the case of classic RA.^{5,6} However, there are no alternative therapies, especially in cases of treatment failure and/or related toxicity.¹ Among other possible strategies,⁵⁻¹¹ glucocorticoids and recombinant myeloid colony stimulating factors give only transient responses, and have never been proved to induce and maintain a lasting response.^{1,8,9} Cyclophosphamide and cyclosporine-A toxicities limit their long-term use. The value of splenectomy for treating FS patients is still under debate; indeed, it must probably be reserved for the most severe cases, which have been shown to be resistant to medical treatment.^{1,9} Lastly, poor results have been observed with rituximab,¹⁰ and etanercept may worsen the neutropenia.¹¹

Here, we report two cases that have shown a lasting response to treatment with HCQ. The use of HCQ in treating FS has not been described previously. MTX was used as a first-line treatment in both cases and was withdrawn because of toxicity or inefficacy. In patient 2, treatment with HCQ was started after prednisone and GCSF failed to increase the neutrophil count. The neutrophil count increased a few days after patient 2 began treatment with HCQ and remained normal for two years. The subsequent relapse of neutropenia was clearly related to the patient not taking the medication as prescribed; this was demonstrated by a low HCQ plasma level. In patient 1, there was a dramatic increase in neutrophil counts after starting treatment with HCQ alone. A relapse of severe neutropenia occurred as the patient's HCQ blood levels fell below the therapeutic range; however, the response was restored using a higher dose of HCQ. Thus, the neutrophil count appeared to depend on the HCQ concentration in blood, and this provides strong evidence for the drug having a direct effect. It has been shown in RA that low blood concentrations of HCQ are an important marker for disease exacerbation.¹² Recently, Costedoat and colleagues have shown that low whole-blood HCQ concentrations are also associated with SLE disease activity and are a strong predictor of disease exacerbation.¹³ The close relationship observed in patient 1 between the neutrophil count and HCQ concentrations in blood strongly suggest that HCQ is effective; it also indicates that blood HCQ should be assayed in cases of apparent ineffectiveness before concluding about treatment failure.

HCQ has been reported as an effective treatment in various diseases, such as RA, SLE, ITP and sarcoidosis,^{14,15} but its mechanism of action is poorly understood. There is evidence suggesting that HCQ may interact with antigen presentation and inhibit the production of inflammation mediators, such as interleukin IL-1 and IL-6. A recent study also suggests that HCQ inhibits Toll-like Receptors.¹⁶ Its mechanism of action in FS remains to be determined.

Our report suggests that HCQ could be an effective, inexpensive and safe alternative to MTX for the management of FS, and may be considered as a first-line treatment for patients with FS, with no or few articular manifestations. Monitoring HCQ concentrations may be of great help in cases of relapse or the absence of response.

Matthieu Mahévas,¹ Sylvain Audia,² Victoire De Lastours,¹
Marc Michel,¹ Bernard Bonotte,² Bertrand Godeau

¹Department of Internal Medicine, Hôpital Henri Mondor,
Assistance Publique Hôpitaux de Paris, Créteil, France;

²Department of Internal Medicine. Hôpital du Bocage. BP 1542
21034 DIJON CEDEX.

Correspondence: Mahévas matthieu,

Department of Internal Medicine, Hôpital Henri Mondor, 51 avenue
du marechal delattre de tassigny Assistance Publique Hôpitaux de
Paris, Créteil, France

Tel : 33 1 0149812076

Fax : 33 1 01 49 81 27 72

E-mail: mahevasm@yahoo.fr

Keywords: Rheumatoid arthritis, Felty's syndrome, Treatment,
Hydroxychloroquine.

References

- Burks EJ, Loughran TP, Jr. Pathogenesis of neutropenia in large granular lymphocyte leukemia and Felty syndrome. *Blood Rev* 2006;20(5):245-66.
- Semenzato G, Zambello R, Starkebaum G, Oshimi K, Loughran TP, Jr. The lymphoproliferative disease of granular lymphocytes: updated criteria for diagnosis. *Blood* 1997;89(1):256-60.
- Campion G, Maddison PJ, Goulding N, et al. The Felty syndrome: a case-matched study of clinical manifestations and outcome, serologic features, and immunogenetic associations. *Medicine (Baltimore)* 1990;69(2):69-80.
- Breedveld FC, Fibbe WE, Hermans J, van der Meer JW, Cats A. Factors influencing the incidence of infections in Felty's syndrome. *Arch Intern Med* 1987;147(5):915-20.
- Loughran TP, Jr, Kidd PG, Starkebaum G. Treatment of large granular lymphocyte leukemia with oral low-dose methotrexate. *Blood* 1994;84(7):2164-70.
- Wassenberg S, Herborn G, Rau R. Methotrexate treatment in Felty's syndrome. *Br J Rheumatol* 1998;37(8):908-11.
- Sood R, Stewart CC, Aplan PD, et al. Neutropenia associated with T-cell large granular lymphocyte leukemia: long-term response to cyclosporine therapy despite persistence of abnormal cells. *Blood* 1998;91(9):3372-8.
- Hellmich B, Schnabel A, Gross WL. Treatment of severe neutropenia due to Felty's syndrome or systemic lupus erythematosus with granulocyte colony-stimulating factor. *Semin Arthritis Rheum* 1999;29(2):82-99.
- Rashba EJ, Rowe JM, Packman CH. Treatment of the neutropenia of Felty syndrome. *Blood Rev* 1996;10(3):177-84.
- Sordet C, Gottenberg JE, Hellmich B, Kieffer P, Mariette X, Sibilia J. Lack of efficacy of rituximab in Felty's syndrome. *Ann Rheum Dis* 2005;64(2):332-3.
- Ghavami A, Genevay S, Fulpius T, Gabay C. Etanercept in treatment of Felty's syndrome. *Ann Rheum Dis* 2005;64(7):1090-1.
- Munster T, Gibbs JP, Shen D, et al. Hydroxychloroquine concentration-response relationships in patients with rheumatoid arthritis. *Arthritis Rheum* 2002;46(6):1460-9.
- Costedoat-Chalumeau N, Amoura Z, Hulot JS, et al. Low blood concentration of hydroxychloroquine is a marker for and predictor of disease exacerbations in patients with systemic lupus erythematosus. *Arthritis Rheum* 2006;54(10):3284-90.
- Arnal C, Piette JC, Leone J et al. Treatment of severe immune thrombocytopenia associated with systemic lupus erythematosus: 59 cases. *J Rheumatol* 2002;29(1):75-83.
- Baltzan M, Mehta S, Kirkham TH, Cosio MG. Randomized trial of prolonged chloroquine therapy in advanced pulmonary sarcoidosis. *Am J Respir Crit Care Med* 1999;160(1):192-7.
- Lafyatis R, York M, Marshak-Rothstein A. Antimalarial agents: closing the gate on Toll-like receptors? *Arthritis Rheum* 2006;54(10):3068-70.