Ann Hematol (2005) 84: 609–613
DOI 10.1007/s00277-005-1053-1

SHORT COMMUNICATION

M. Cem Ar · Teoman Soysal · Gulen Hatemi · Ayse Salihoglu · Hasan Yazici · Birsen Ulku

Successful management of cryoglobulinemia-induced leukocytoclastic vasculitis with thalidomide in a patient with multiple myeloma

Received: 13 January 2005 / Accepted: 22 April 2005 / Published online: 19 May 2005

Abstract Leukocytoclastic vasculitis (LV) is a systemic inflammatory disorder involving mostly the small vessels. It is characterised by segmental angiocentric neutrophilic inflammation, endothelial cell damage and fibrinoid necrosis. LV is related to a variety of clinical disorders including cryoglobulinemia and, very rarely, multiple myeloma (MM), among many others. The development of LV in patients with MM has been linked to cryoglobulinemia, infections, drugs and paraneoplasia. It has been speculated that myeloma patients with a poorer prognosis and progressive disease are more prone to develop LV. Thalidomide is a rediscovered old drug with anti-angiogenic, immunomodulatory and anti-inflammatory properties. It is highly effective in the treatment of MM and other clinical disorders such as leprosy, various cancers, graft-versus-host disease and autoimmune diseases. We report here a female patient with Durie–Salmon stage IIA MM who initially presented with cryoglobulinemia and LV. LV in this patient was primarily considered to be the result of progressive cryoglobulinemia, which was closely associated with MM. She was successfully managed with thalidomide and dexamethasone.

M. Cem Ar (✉) · T. Soysal · B. Ulku
Department of Internal Medicine,
Division of Haematology,
Cerrahpasa Medical Faculty,
Istanbul University,
Istanbul, Turkey
e-mail: muhcar@superonline.com

G. Hatemi · H. Yazici
Department of Internal Medicine,
Division of Rheumatology,
Cerrahpasa Medical Faculty,
Istanbul University,
Istanbul, Turkey

A. Salihoglu
Department of Internal Medicine,
Cerrahpasa Medical Faculty,
Istanbul University,
Istanbul, Turkey

Keywords Leukocytoclastic vasculitis · Thalidomide · Cryoglobulinemia · Multiple myeloma

Introduction

Leukocytoclastic vasculitis (LV) is an inflammatory disorder involving mostly the small vessels of the skin. It is usually associated with connective tissue diseases, infections, drugs, lymphoproliferative diseases and immune-complex-mediated disorders like cryoglobulinemia. Co-existence of multiple myeloma (MM) and LV has rarely been reported [3, 15, 16, 19–21, 28].

Thalidomide is an old drug with anti-angiogenic, immunomodulatory and anti-inflammatory properties. Thalidomide's activity in MM is mainly based on its anti-proliferative action, which results from various direct and indirect effects on myeloma cells, such as inhibition of angiogenesis [5] and of plasma cell adhesion [11], induction of plasma cell apoptosis [23] and stimulation of cell-mediated anti-myeloma immunity [8]. Thalidomide, as a single agent, can induce durable responses in 25–35% of patients with relapsed/refractory MM [22, 27]. Response rates are higher when thalidomide is combined with steroids (~50%) [1]. Addition of chemotherapy to thalidomide–steroid combination increases the rate of objective responses to more than 70% in refractory myeloma patients [24]. Highly encouraging results with 70% response rates were also documented in previously untreated symptomatic MM patients treated with thalidomide and dexamethasone [31].

Thalidomide has been used in various other clinical disorders such as leprosy, Behçet's disease [12], rheumatoid arthritis, systemic lupus erythematosus and graft-versus-host disease.

Here, we describe a patient who initially presented with LV and cryoglobulinemia and, 4 years later, was diagnosed to have stage IIA immunoglobulin G (IgG) kappa MM. The vasculitis was considered to be induced by the progressive cryoglobulinemia and associated with MM. She was successfully treated with thalidomide and dexamethasone.

Case report

In March 2000, a 51-year-old woman was admitted to the Rheumatology Division of Cerrahpasa Medical Faculty, Istanbul University, due to the recent onset of migratory arthralgias and palpable purpura symmetrically distributed on both legs and buttocks. She had no abdominal pain. Results of her physical examination were otherwise unremarkable. Histological examination of the skin lesions revealed leukocytoclastic vasculitis. Results of complete blood count and blood chemical analysis including renal function tests were within normal limits. Anti-nuclear antibody was positive and anti-double-stranded DNA was found to be 1.108 U/l (N<0.9). A high level of cryoglobulins was detected. Hepatitis virus-related cryoglobulinemia was excluded by the negative results of serologic tests for hepatitis B and C. Results of the serum protein electrophoresis showed hypogammaglobulinemia. No immunoelectrophoresis was performed. The patient was diagnosed as having vasculitis and was started on prednisolone in combination with hydroxychloroquine in March 2000 at a dose of 15 and 400 mg/day, respectively. The disease seemed to be under control until January 2003 when she presented with ulcerative lesions on both legs and increased levels of cryoglobulins. Her blood counts and blood chemical analysis were normal except for the persisting hypogammaglobulinemia. The serum immunofixation electrophoresis depicted an IgG, kappa monoclonal protein. A bone marrow biopsy was performed. The morphological and immunohistochemical examination of the bone marrow trephine revealed mature-appearing IgG, kappa (+) monoclonal plasma cell infiltration in interstitial spaces. On bone marrow smears, the number of plasma cells was found slightly increased (8% of all nucleated cells). Her blood counts, serum calcium level and results of renal function tests were normal. No lytic bone lesions were identified (Table 1). Based on these findings, the patient was diagnosed to have a monoclonal gammopathy of undetermined significance (MGUS). No major change in the treatment plan was considered. She continued to take 10 mg prednisolone with 400 mg hydroxychloroquine daily until February 2004 when she presented again with skin infarctions and a high level of cryoglobulins of IgG class (type I). She did not respond to high-dose (1 g/day) pulse methylprednisolone repeated three times. Anaemia was established (Table 1). After exclusion of blood loss and hemolysis, a bone marrow biopsy was performed that displayed a prominent increase in IgG kappa (+) monoclonal plasma cells (32% of all nucleated cells). Due to technical reasons, cytogenetic analysis could not be performed. Re-evaluation of bone X-rays revealed multiple, occipital lytic lesions. She was diagnosed to have Durie–Salmon stage IIA MM. In March 2004, after written informed consent was obtained, she was begun with high-dose (32 mg) dexamethasone (D1–4, D9–12, D17–20) in combination with low-dose thalidomide (initiated with 100 mg/day, increased to 200 mg/day after 2 weeks). After 2 months of treatment, tests for cryoglobulins gave negative results and the skin lesions were healed. Between March and August 2004, the patient received four cycles of high-dose dexa-

Table 1 Laboratory and clinical features of the patient before different treatment courses

Parameter	March 2000	January 2003	February 2004	July 2004	March 2005
Haemoglobin (g/dl)	11.4	12.2	9.1	11.3	12.7
Haematocrit (%)	33.5	35.9	26.9	33.9	38.1
WBC ($\times 10^9$/l)	6.7	9.3	10.5	5.3	4.4
Platelets ($\times 10^9$/l)	269.0	218.0	169.0	293.0	256.0
ESR (mm/h)	72	56	26	7	9
Total protein (g/dl)	7.79	7.14	6.59	6.02	6.20
Albumin (g/dl)	4.81	4.15	4.07	3.98	3.80
IgG (g/dl)[a]	NP	0.530	0.517	0.800	0.889
IgA (g/dl)[a]	NP	0.053	0.037	0.046	0.073
IgM (g/dl)[a]	NP	0.085	0.072	0.057	0.071
β_2-Microglobulin[a] (ng/ml)	NP	2.47	1.80	1.77	1.59
Cryoglobulins[b]	0.500	0.77	0.64	Negative	Negative
Bone lesions	NP	Absent	Present	Stable	Stable
Plasma cells in BM (%)	NP	8	32	2	NP
Skin lesions (vasculitis)	Present	Relapsed	Relapsed	Absent	Absent
Treatment given	Prednisolone/ hydroxychloroquine	High-dose methylprednisolone	High-dose dexamethasone/ thalidomide	Thalidomide	Thalidomide

WBC White blood cells, *ESR* erythrocyte sedimentation rate, *Ig* immunoglobulin, *BM* bone marrow, *NP* not performed
[a]Normal values: IgG, 0.7–1.6 g/dl; IgA, 0.07–0.4 g/dl; IgM, 0.04–0.23 g/dl; β_2-microglobulin, 1.2–2.5 ng/ml
[b]Spectrophotometrically measured; values <0.02 not detected

methasone (32 mg; D1–4, D9–12, D17–20 every 4–6 weeks), concomitant with continuous low-dose thalidomide (200 mg daily). A response assessment was done in July 2004, after the third cycle of dexamethasone (Table 1). The bone marrow biopsy showed no increase in plasma cells. Monoclonal paraprotein disappeared in serum; serum immunoglobulins and haemoglobin increased to normal levels. There were no additional bone lesions. Based on these findings, the patient was considered to be in complete remission. After having completed the fourth cycle in August 2004, the patient had been solely using thalidomide (200 mg/day). On the eighth month of thalidomide monotheraphy, the remission was still maintained for all three conditions: the cryoglobulinemia, the vasculitis and myeloma (Table 1).

Discussion

Leukocytoclastic vasculitis is an inflammatory disease of the small vessels. Arthralgias and/or arthritis and fever are the most common systemic manifestations. Renal, gastrointestinal and neurological involvement may occur during the course of the disease. Histologically, it is characterised by segmental neutrophilic inflammation of vessel walls leading to endothelial swelling and fibrinoid necrosis in the post-capillary venules. Immune complex deposition resulting in complement activation and neutrophil chemotaxis in the involved vessels has been thought to be the underlying pathogenesis [18]. As neutrophils migrate and invade the vessel walls to phagocytose the immune complexes, they damage endothelial cells via the released lysosomal enzymes. Clinically, LV appears as palpable purpura mostly on the lower extremities.

LV has been reported in association with infections, medications, chemicals and various disease states. It is also the most frequent form of vasculitis accompanying malignancies. LV in its paraneoplastic form appears to be mostly related to haematological malignancies, in particular to lymphoproliferative disorders [10]. Vasculitis in the course of MM is rare [3, 10, 16, 18, 19, 21, 28]. When present, vasculitis is much more linked to cryoglobulinemia rather than myeloma itself [4].

Cryoglobulins are immunoglobulins that undergo reversible precipitation when exposed to cold. Pathologic cryoglobulinemia can be related to a variety of clinical conditions including lymphoproliferative disorders, autoimmune diseases and infections, particularly hepatitis C virus infection. Type I cryoglobulins account for 10–15% of all cryoglobulins. They are almost only associated with MM, Waldenström's macroglobulinemia or chronic lymphocytic leukaemia and consist usually of monoclonal IgM or IgG fractions. Type I cryoglobulinemias are usually defined to be clinically indistinguishable from immunoproliferative diseases such as MM in which the presence of cryoglobulins is not an unexpected finding [7].

Cutaneous diseases including LV in MM has recently been extensively reviewed [3, 4, 28]. A retrospective analysis of more than 2,300 myeloma cases revealed only eight patients with coexisting LV [4]. It has been speculated that patients with a poorer prognosis or those who are at a later stage of MM are more likely to develop LV [3]. Time between the onset of vasculitis and occurrence of malignancy varies greatly. LV has been reported to precede or follow the diagnosis of MM in a wide range of months to years [28].

Thalidomide's mechanisms of action are not completely understood. It has some direct and indirect effects on myeloma cells. It has been shown that thalidomide directly acts on myeloma cells to induce growth arrest during the G_1 phase of the cell cycle and apoptosis by activation of caspase 8 [14, 23]. Although solid evidence is lacking, thalidomide also seems to exert its anti-myeloma effect in part by inhibiting tumor angiogenesis through modulating the action of cytokines such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor [17, 26, 29]. It has been recently reported that ceramide and sphingosine-1-phosphate exclusively play a role in thalidomide-induced anti-angiogenic action through the regulation of VEGF receptors [33]. In addition, thalidomide has been shown to down-regulate the expression of cytokines implicated in myeloma cell proliferation and survival, such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-6 and VEGF. Consequently, the expression of adhesion molecules on myeloma and bone marrow stromal cells decreases, resulting in inhibition of the interaction of myeloma cells with their micro-environment. Myeloma cells cannot survive in the absence of essential proliferative stimuli from marrow stromal cells [6, 11, 25, 30]. Thalidomide also exhibits potent immunomodulatory effects by inducing secretion of IL-2 and interferon gamma (INF-γ) and proliferation of CD8 (+) T cells and natural killer cells that might result in the lysis of myeloma cells [8, 13]. These findings provided the background for the clinical use of thalidomide in MM. Since the first report by Singhal et al. [29], thalidomide has been repetitively and consistently shown to be effective in the management of myeloma.

There is also accumulating evidence that thalidomide exerts anti-inflammatory effects by inhibiting leukocyte chemotaxis, reducing polymorphonuclear phagocytic activity, suppressing TNF-α and altering the density of TNF-α-induced adhesion molecules on leukocytes [2, 9, 11]. These may explain its action in inflammatory processes such as vasculitis.

Considering the aforementioned properties of thalidomide and current experience on its usefulness in the management of inflammatory disorders and myeloma, we considered it the most appropriate choice of treatment for the patient, as we presented here, to use a regimen containing thalidomide and dexamethasone. As we suggested, we observed a marked improvement in vasculitic lesions shortly after the beginning of the treatment. The response was very striking as compared with other forms of established therapies such as low- and high-dose steroids, which were rendered ineffective in this particular patient. After a few months of therapy, cryoglobulins in the serum and monoclonal plasma cell infiltration in the bone marrow

disappeared as well. The well-known anti-inflammatory and anti-myeloma effects of high-dose dexamethasone alone probably did not contribute much to this remarkable response because the patient had used high-dose steroids earlier in the course of the disease without much success. Consequently, we reasoned that thalidomide, with its immunomodulatory and anti-inflammatory effects, reduced the immune-complex-mediated vasculitis and suppressed myeloma probably in synergy with dexamethasone. Indirect evidence supporting the efficacy of thalidomide is that during follow-up the patient is still symptomless under thalidomide monotherapy.

Recently, Witzens et al. published a case report in which they described the development of thalidomide-induced LV in a patient with MM [32]. We were not aware of that publication at the time we started to treat our patient with thalidomide. Admittedly, had we been aware of this publication, we would have probably avoided using thalidomide in our case in the first place.

On the other hand, the probability also exists that the LV in the patient reported by Witzens et al. was a part of the clinical picture rather than a drug effect. The development of LV in patients with MM has been linked to cryoglobulinemia, infections, drugs and paraneoplasia. Details are lacking to fully discuss the potential differences between our patient and the Witzens' case. However, the most important difference seems to be the presence of cryoglobulinemia in our patient. There is no information on whether Witzens et al. checked the presence of cryoglobulins in their case, which might be one of the underlying causes in LV other than drug effect.

LV has been reported to develop in progressive MM [3, 28]. The Witzens' case had a progressive myeloma for which he received a thalidomide-added chemotherapy regimen. He tolerated the drug up to a dose of 400 mg/day for the first few months, after which he developed LV. Considering that LV is more likely to occur in patients with progressive disease and the use of thalidomide was not initially associated with LV in the described patient, it can be argued that the progressive myeloma itself or other coincidental insults, such as an undiagnosed infection, might have led to the development of LV.

As discussed by Witzens et al., thalidomide's immunomodulatory activity has been reported to range from stimulatory immune responses to inhibitory effects depending on the micro-environmental interactions and cytokine secretion. We assume that certain clinical conditions, infections or concomitant use of other drugs such as chemotherapeutics may alter thalidomide's immune functions by changing the milieu in which the drug acts. This may explain the different responses of thalidomide, i.e. suppressing vasculitis in one patient while inducing autoimmunity in the other.

We demonstrated here that cryoglobulinemia/myeloma-induced LV can successfully and effectively be treated with thalidomide, but more experience is clearly needed before announcing this drug as an alternative therapy for cryoglobulinemia-induced LV.

Acknowledgements We thank Prof. H.M. Moutsopoulos (Athens, Greece) for his help in the management of this patient.

References

1. Anagnostopoulos A, Weber D, Rankin K et al (2003) Thalidomide and dexamethasone for resistant multiple myeloma. Br J Haematol 121:768–769
2. Barnhill RL, Doll NJ, Millikan LE et al (1984) Studies on the anti-inflammatory properties of thalidomide: effects on polymorphonuclear leukocytes and monocytes. J Am Acad Dermatol 11:814–819
3. Bayer-Garner IB, Smoller BR (2003) Leukocytoclastic (small vessel) vasculitis in multiple myeloma. Clin Exp Dermatol 28: 521–524
4. Bayer-Garner IB, Smoller BR (2003) The spectrum of cutaneous disease in multiple myeloma. J Am Acad Dermatol 48: 497–507
5. D'Amato RJ, Loughnan MS, Flynn E et al (1994) Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci U S A 91:4082–4085
6. Damiano JS, Cress AE, Hazlehurst LA et al (1999) Cell adhesion mediated drug resistance (CAM-DR): role of integrins and resistance to apoptosis in human myeloma cell lines. Blood 93:1658–1667
7. Dammacco F, Sansonno D, Piccoli C et al (2001) The cryoglobulins: an overview. Eur J Clin Investig 31:628–638
8. Davies FE, Raje N, Hideshima T et al (2001) Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. Blood 98:210–216
9. Faure M, Thivolet J, Gaucherand M (1980) Inhibition of polymorphonuclear leukocytes chemotaxis by thalidomide. Arch Dermatol Res 269:275–280
10. Garcia-Porrua C, Gonzales-Gay MA (1998) Cutaneous vasculitis as paraneoplastic syndrome in adults. Arthritis Rheum 41:1133–1136
11. Geitz H, Handt S, Zwingerberger K (1996) Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. Immunopharmacology 31: 213–221
12. Hamuryudan V, Mat C, Saip S et al (1998) Thalidomide in the treatment of the mucocutaneous lesions of Behçet's syndrome: a randomized, double-blind, placebo controlled trial. Ann Intern Med 128:443–459
13. Haslett PA, Corral LG, Albert M et al (1998) Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic reponses in the CD8+ subset. J Exp Med 187:1885–1892
14. Hideshima T, Chauhan D, Shima Y et al (2000) Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood 96:2943–2950
15. Highet AS (1980) Urticarial vasculitis and IgA myeloma. Br J Dermatol 102:355–357
16. Kois JM, Sexton FM, Lookingbill DP et al (1991) Cutaneous manifestations of multiple myeloma. Arch Dermatol 127:69–74
17. Li X, Liu X, Wang J et al (2003) Thalidomide down-regulates the expression of VEGF and b-FGF in cisplatin-resistant human lung carcinoma cells. Anticancer Res 23:2481–2487
18. Lotti T, Ghersetich I, Comacchi C et al (1998) Cutaneous small-vessel vasculitis. J Am Acad Dermatol 39:667–687
19. Lucas E, Martinez A, Guerao MR et al (1997) Hypersensitivity vasculitis as the first manifestation of a multiple myeloma. An Med Interna 14:374–375
20. McMillen JJ, Krueger SK, Dyer GA (1986) Leukocytoclastic vasculitis in association with immunoglobulin A myeloma. Ann Intern Med 105:709–710
21. Means RT, Greer JP, Sergent JS et al (1987) Leukocytoclastic vasculitis and multiple myeloma. Ann Intern Med 106:329–331

22. Mileshkin L, Biagi JJ, Mitchell P et al (2003) A multi-center phase II trial of thalidomide in relapsed/refractory multiple myeloma: adverse prognostic impact of advanced age. Blood 102:69–77
23. Mitsiades N, Mitsiades CS, Poulaki V et al (2002) Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. Blood 99:4525–4530
24. Moehler TM, Neben K, Benner A et al (2001) Salvage therapy for multiple myeloma with thalidomide and CED chemotherapy. Blood 98:3846–3848
25. Moriera AL, Sampaio EP, Zmuidzinas A et al (1993) Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. J Exp Med 177:1675–1680
26. Neben K, Moehler T, Kraemer A et al (2001) Response to thalidomide in progressive multiple myeloma is not mediated by inhibition of angiogenic cytokine secretion. Br J Haematol 115:605–608
27. Neben K, Moehler T, Benner A et al (2002) Dose-dependent effect of thalidomide on overall survival in relapsed multiple myeloma. Clin Cancer Res 8:3377–3382
28. Sanchez NB, Canedo IF, Garcia-Patos PE et al (2004) Paraneoplastic vasculitis associated with multiple myeloma. J Eur Acad Dermatol Venereol 18:731–735
29. Singhal S, Mehta J, Desikan R et al (1999) Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 341:1565–1571
30. Turk BE, Jiang H, Liu JO (1996) Binding of thalidomide to alpha 1-acid glycoprotein may be involved in its inhibition of tumor necrosis factor alpha production. Proc Natl Acad Sci U S A 93:7552–7556
31. Weber D, Rankin K, Gavino M et al (2003) Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol 21:16–19
32. Witzens M, Moehler T, Neben K et al (2004) Development of leukocytoclastic vasculitis in a patient with multiple myeloma during treatment with thalidomide. Ann Hematol 83:467–470
33. Yabu T, Tomimoto H, Taguchi Y et al (2005) Thalidomide-induced anti-angiogenic action is mediated by ceramide through depletion of VEGF receptors, and antagonized by sphingosine-1-phosphate. Blood (prepublished online March 1, 2005; DOI 10.1182/blood-2004-09-3679)