Leukocytoclastic Vasculitis due to Thalidomide in Multiple Myeloma

Naciye Demirel Yildirim1, Mesut Ayer1, Reyhan Diz Küçükkaya1, Nilüfer Alpay1, Özgür Mete2, Mustafa Nuri Yenerel1, Akif Selim Yavuz1 and Meliha Nalçacı1

1Division of Hematology, Department of Internal Medicine and 2Department of Pathology, Istanbul Medical School, Istanbul University, Istanbul, Turkey

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Thalidomide is successfully used in the treatment of multiple myeloma, leprosy and various autoimmune diseases due to its anti-angiogenic, immunomodulatory and anti-inflammatory effects. Thalidomide's most common side effects are constipation, neuropathy, fatigue, sedation, rash, tremor and peripheral edema. We achieved complete response with a 400 mg/day dose thalidomide therapy in a 58-year-old male patient diagnosed with relapsing refractory multiple myeloma. While continuing thalidomide for sustainable response, the therapy was terminated at the ninth month due to development of leukocytoclastic vasculitis. We describe the case and discuss the place of thalidomide in the treatment of multiple myeloma and the rare occurrence of leukocytoclastic vasculitis during thalidomide therapy in multiple myeloma, since only one such case has been reported in the literature thus far.

Key words: leukocytoclastic vasculitis – multiple myeloma – thalidomide – zoledronic acid

INTRODUCTION

The mechanism of thalidomide effect in multiple myeloma is not yet completely clarified (1); however, it affects plasma cells both directly and indirectly, preventing their adhesion and proliferation (1,2). The mechanism of action is assumed to be as follows: it inhibits angiogenesis by preventing microvessel formation by inhibiting the release of growth factors (vascular endothelial growth factor, basic fibroblast growth factor, hepatocyte growth factor), which play crucial roles in angiogenesis, from plasma cells; it directly stimulates apoptosis or G1 arrest during the cell cycle by activating cytotoxic T (CD8) cells and natural killer (NK) cells, enabling the lysis of myeloma cells; it inhibits cell-to-cell interaction; and it inhibits the release of interleukin-6 (IL-6), one of the major growth factors that enables the proliferation and survival of plasma cells (1–3). In addition to multiple myeloma, thalidomide is also used in the treatment of skin reactions caused by leprosy, Behçet’s disease, rheumatoid arthritis, systemic lupus erythematosus and graft-vs-host disease (2,4). Leukocytoclastic vasculitis (LCV) is characterized by the aggregation of immune complexes in post-capillary venules, resulting in inflammatory infiltration, extravasation of erythrocytes, fibrinoid necrosis and leukocytoclasia on the vascular wall. Clinically, the most common outcome is palpable purpura at the lower extremities. This may be accompanied by abdominal pain, arthralgia and renal involvement (4–6). The diagnosis must be made by skin biopsy (5). Infections, drugs, chemicals, bacteria, viruses, and autoimmune and malignant diseases are all responsible for the etiology of LCV (4,5). Thalidomide’s most common side effects are sedation, fatigue, constipation, neuropathy, pruritus, rash, tremor and edema (1,2,4,7,8). In the literature, only a single case of LCV occurrence under thalidomide therapy has been reported. We herein describe this rare complication of thalidomide therapy and review the literature.

CASE REPORT

A 58-year-old male visited our clinic with low back pain in August 2003. Bone marrow was infiltrated with plasma cells (66%) and Stage II-A multiple myeloma, kappa light chain disease, without any extramedullary involvements diagnosed. The patient was given eight courses of melphalan + prednisolone treatment. After this treatment, a complete response was achieved. The patient was followed in the outpatient clinic until 2005, when a relapse occurred...
which led to a planned thalidomide + zoledronic acid therapy. However, in March 2005, bone X-ray taken due to back pain showed serious osteoporosis. In the magnetic resonance (MR) imaging of the lumbar region, compression fractures were observed in the fourth and fifth lumbar vertebrae. Ten courses of radiotherapy (total 30 Gys) were performed. The blood tests before thalidomide therapy showed Hb 7.4 g/dl, Htc 24.3%, WBC 3500/mm³, and platelets 205,000/mm³. Serum kappa light chain was 1900 mg/dl (normal value 170–370 mg/dl) and urine kappa light chain was 26 mg/dl (normal value <1.5 mg/dl). All the biochemical test results were within normal range, except for elevated serum lactate dehydrogenase (LDH) level. We could not perform cytogenetic examination for any chromosomal abnormalities. In May 2005, the patient was given thalidomide 100 mg/day, which was increased to 200 mg/day after 2 weeks. The patient tolerated this therapy well. Therefore, after one month, the thalidomide dose was increased to 400 mg/day. In addition, 4 mg zoledronic acid was applied once a month. After 8 months of therapy, the patient’s complaints were diminished. Whole blood cell counts showed: Hb 15 g/dl, Htc 44.1%, WBC 6400/mm³, platelets 360,000/mm³, and LDH 380 U/l (normal value 240–480 U/l). Kappa light chain was found to be negative by immunofixation both in the serum and urine. Bone marrow aspiration revealed 4% plasma cells and again there was no extramedullary involvement. We evaluated the patient status as complete response. At the ninth month of the thalidomide therapy a sudden purpuric exanthema occurred on the extensor sides of both lower extremities of the patient. Eruptions were bumpy and palpable, had a tendency for gathering, and did not lose color on application of pressure. The patient also described arthralgia on both knee joints. The patient was examined in the Dermatology Department and a ‘punch’ biopsy was conducted on these purpuric exanthemas. In addition, the full urine test of the patient, who described microscopic hematuria, appeared hematuric with a density of 1014 and pH 7.4, and proteinuria was positive. Microscopic examination revealed abundant erythrocytes and leukocytes. A urine culture was conducted with negative results. We did not observe any antecedent infection. Urinary system ultrasonography was performed, which showed that right and left kidney sizes, tissue characteristics, and parenchymal thickness were all within the normal range. There was no intracavitary mass formation in the urinary bladder and the vesical thickness was normal. Prostate tissue had normal size. The test conducted with benzidine for occult blood in feces was negative. Skin punch biopsy pathology was as follows: compact keratin layer involving focal parakeratosis on the surface, edema at papillary dermis, dense erythrocyte extravasation, infiltration of neutrophils, and leukocytoclasis around small blood vessels (LCV) at the superficial dermis (Figures 1 and 2). All the clinical presentations were compatible with the Schonlein–Henoch syndrome. A renal biopsy was also performed. Unfortunately, sufficient material could not be obtained and the patient refused the second biopsy. Therefore, the patient’s thalidomide therapy was stopped and methyl-prednisolone (16 mg/day) was started. After a week, arthralgia and purpuric exanthemas, and after 2 months, hematuria and proteinuria, disappeared. In this patient, after thalidomide therapy was ceased, zoledronic acid was continued. Twelve months later, he was in clinical and biochemical complete response and thalidomide was not administered again. He did not experience a recurrence of LCV during the subsequent 12 months of follow-up.

**DISCUSSION**

Today, thalidomide is one of the therapy options for the treatment of multiple myeloma in addition to various other...
LCV due to thalidomide

diseases (4). In the treatment of relapsed or refractory multiple myeloma, 30% response is achieved when thalidomide is given solely, and 50% response is achieved when it is combined with dexamethasone. In patients recently diagnosed who have not been treated, this response rate can reach 70% (1). Toxic effects due to thalidomide have been shown to occur in 5% of the cases at 800 mg/day doses, and most occurred at 400 mg/day dosage rates. The most common side effects were sedation and somnolence (25%), constipation (16%), sensory neuropathy (9%) and deep vein thrombosis (2%) (9–11). Rare side effects reported are peripheral edema, tremor, bradycardia, hypothyroidism, neutropenia and increase in hepatic enzymes (1,8). The rates of thromboembolic complications with combined therapy regimens of thalidomide and doxorubicin were reported to range from 2 to 16% (1,9,11). The combined use of thalidomide with dexamethasone was reported to cause Stevens–Johnson syndrome very rarely (8). Glasmacher et al. reported a multicenter study on 1674 patients with relapsed and refractory multiple myeloma for whom thalidomide was used as a single agent (12). Complete or partial (>50% reduced monoclonal protein) response was 29.4%, minor response 13.8%, stable disease 11%, and progression of the sickness under therapy 9.9%, with average survival of 14 months (12). The same study described the side effects of thalidomide usage as somnolence (11%), constipation (16%), neuropathy (6%), rash (3%), thromboembolism (3%) and cardiac (2%) (12). Hattori et al. reported somnolence, vertigo, headache, peripheral neuropathy, and tremor in 75% of the cases as the most common neurological side effects of thalidomide (1). The same authors reported gastrointestinal symptoms including nausea, emesis and constipation in 66% of the cases; general symptoms such as fatigue, weight loss, and fever in 60%; dermatological side effects such as skin rash, dry skin, and dry mouth in 16%; and leukopenia and deep vein thrombosis in less than 5% of the cases (1). We achieved complete response in a relapsed and refractory multiple myeloma patient with 400 mg/day thalidomide therapy, but in the ninth month we observed LCV development due to thalidomide therapy. Recently, Witzens et al. (4) reported that in a refractory multiple myeloma case, in the third month of 400 mg/day thalidomide therapy, LCV occurred. The therapy was stopped and prednisolone started, and LCV disappeared in 7 days. We also stopped thalidomide therapy and changed to methyl-prednisolone (16 mg/day). One week later, arthralgia and purpuric exanthemas, and 2 months later, hematuria and proteinuria, disappeared. On the other hand, Cem Ar et al. (2) achieved complete response in a case of LCV caused by cryoglobulinemia due to multiple myeloma with 200 mg/day thalidomide and high-dose dexamethasone 32 mg/day, combined in four cycles and given for 12 days a month in total. Afterwards, under only thalidomide 200 mg/day, the patient’s response continued in cryoglobulinemia, vasculitis and myeloma within 8 months of therapy. However, in this reported case, the disappearance of LCV may be attributed to the high-dose dexamethasone rather than thalidomide. LCV is also reported to occur in progressive multiple myeloma cases, although very rarely (6,13). Bayer-Garner et al. (6) reported in a study of 2357 patients with progressive multiple myeloma that only eight patients developed LCV. However, kappa-light chain was negative in serum and urine immunofixation and no extra-medullary plasmacytoma or infection was detected when the LCV developed in our patient. Only 4% of plasma cells were detected in the sample of bone marrow aspiration. We concluded that the LCV was not related to the multiple myeloma itself. Zoledronic acid was the only drug other than thalidomide and might have been responsible for the LCV. However, to our knowledge, there has been no report which suggests zoledronic acid caused LCV. Thalidomide is reported to be successfully used in the treatment of LCV and other autoimmune diseases, but it should be kept in mind that, although very rarely, it can cause various autoimmune diseases such as LCV (2). In contrast to the situation in patients with nonmalignant disorders, in the context of malignant diseases, thalidomide might induce an immune stimulatory effect that leads to autoimmune disease (4). LCV is an extremely rare complication of thalidomide therapy, but the autoimmune phenomenon that can occur during treatment with this drug remains to be evaluated.

Conflicts of interest statement
None declared.

References
