TÜBİTAK

CASE REPORT

Turk J Med Sci
2006; 36 (4): 247-250

E-mail: medsci@tubitak.gov.tr

Arterial Thrombosis in Refractory Multiple Myeloma Patient Treated with Thalidomide and Dexamethasone: A Case Report

Dilek SOYSAL[1]
Orhan KÜÇÜKŞAHİN[1]
Ayça İNCİ[1]
Mustafa PEHLİVAN[2]

Abstract: A 48-year-old man with relapsing multiple myeloma (MM) presented with serum monoclonal protein (IgG λ) of 5.93 g/dl. He was initially treated with four cycles of VAD (vincristine, adriamycin and dexamethasone) but due to deterioration of his renal functions with disease relapse, he was placed on hemodialysis. A combined treatment with thalidomide at a daily dose of 200 mg and 4-d cycles of dexamethasone was started for relapsing MM. Thalidomide dose was increased to 400 mg after two weeks. In the second month of his treatment, the patient presented with progressive drowsiness without other symptoms. His cranial MR was suggestive of arterial thrombosis. A thrombophilia study indicated that he was heterozygous for the A1298C mutation of the MTHFR and PAI-1 genes. Thalidomide was discontinued and he was treated with anti-aggregating agents until his death from MM a month later.

Key Words: Multiple myeloma, thalidomide, arterial thrombosis

[1] Clinics of 1st Internal Medicine, Atatürk Research Hospital, İzmir - TURKEY

[2] Hematology, Atatürk Research Hospital, İzmir - TURKEY

Talidomid ve Deksametazon Tedavisi Alan Refrakter Bir Multipl Myelom Olgusunda Arter Trombozu

Özet: Kırk sekiz yaşında,erkek, 5.93g/dl serum monoklonal (IgG λ) proteini olan, nüks multipl myelom (MM) hastası. Başta 4 kür VAD tedavisi verilen hasta hastalığın nüks etmesiyle böbrek fonksiyonlarının bozulması sonucu hemodiyalize alındı. Nüks MM için talidomid 200mg/gün dozunda ve deksametazon 4 gün süreyle verilmek üzere kombine edildi. Talidomid 2 hafta içerisinde 400mg/gün dozuna çıkıldı. Tedavisinin ikinci ayında hastada başka belirtiler olmaksızın ilerleyen bir uyku hali gelişti.Beyin MR'ı arter trombozunu düşündürüyordu. Trombofiliye yönelik araştırmada hastanın PAI-1 ve MTHFR A1298C gen mutasyonları için heterozigot taşıyıcı olduğu saptandı. Talidomid tedavisi sonlandırıldı, antiagregan tedaviye başlandı. Hasta 1 ay sonra MM tablosu ile kaybedildi.

Anahtar Sözcükler: Multipl myelom, talidomid, arter trombozu

Introduction

Thrombosis is increasingly recognized as a common complication in patients with malignancy (1). Since the introduction of single-agent thalidomide for the treatment of multiple myeloma (MM), no significant cardiovascular toxicity has been observed. However, when thalidomide was subsequently combined with multi-agent chemotherapy, deep venous thrombosis (DVT) incidence rose to twice that observed in controls treated with identical chemotherapy but without thalidomide (2).

Thalidomide, a synthetic derivative of glutamic acid, is an immunomodulator that inhibits the angiogenesis induced by vascular endothelial growth factor and fibroblast growth factor (3). Thalidomide also inhibits tumor necrosis factor (TNF)-alpha synthesis, blocks the activation of nuclear factor-kappa-beta kinase activity, co-stimulates human T cells and stimulates interleukin 2 and interferon gamma production (4).

Although the exact mechanism of thalidomide in MM is unknown, a clear benefit has been demonstrated in refractory or relapsed myeloma patients (3,4).

Treatment with thalidomide should be initiated at a dose of 100 to 200 mg/day and increased weekly by 50 to 100 mg/day until reaching the final dose of 400 to 800

Received: March 09, 2006
Accepted: August 10, 2006

Correspondence
Dilek SOYSAL
Atatürk Research Hospital,
First Department of Internal Medicine,
Manolya Sokak, No: 44/4
Balçova, İzmir - TURKEY

dileksoysal@hotmail.com

mg/day. Patients receiving daily doses of 200 mg or less seem to tolerate the treatment well with few side effects (4).

The side effects of thalidomide are well recognized and include peripheral neuropathy, sedation, constipation, hypothyroidism, skin rashes and venous thrombosis (5). The incidence of thrombosis after treatment with thalidomide ranges from 2% to 23%, but is higher among patients who also receive chemotherapy (4).

The mechanism of thrombosis is not known. Thalidomide can alter the interactions between cancer cells and coagulation factors, induce prothrombotic factors, and activate platelets and vascular endothelial cells (4). Thromboembolic events usually appear early after the onset of therapy and may occur even with low-dose treatment (4). There are several reports of venous thrombotic events related to thalidomide use; however, there have been only a few patients reported who developed arterial thrombotic events while on thalidomide (6).

We report a case of an arterial thrombosis in a refractory MM patient. He was a heterozygous carrier of the MTHFR A1298C and PAI-1 gene mutations and he received thalidomide in combination with dexamethasone.

Case Report

A 48-year-old man with stage IIIB IgG λ (lambda) MM was treated with four cycles of VAD (vincristine, adriamycin and dexamethasone) at diagnosis and he achieved a partial response. The disease relapsed while the patient was awaiting transfer for planned autologous peripheral stem cell transplantation at another hospital. At the time of his disease relapse, the patient presented with marrow biopsy of 35% plasma cells with atypical nuclei, serum monoclonal protein (IgGλ) of 5.93 g/dl, beta-2-microglobulin of 5.73 mg/ml (N:0.8-2.2 mg/ml) and hsCRP of 48 mg/dl (N:<5 mg/dl). Although the patient's renal functions were normal during treatment with VAD, he developed renal failure as the disease relapsed. Four hours' hemodialysis with bicarbonate in every two days was initiated in combination with thalidomide at 200 mg daily and 4-d cycles of dexamethasone. He tolerated the dose well and it was increased weekly by 100 mg, reaching the final dose of 400 mg daily, as recommended, in two weeks (4). By the second month of his treatment, while renal functions were improving, the patient presented with progressive drowsiness without other symptoms. Laboratory studies showed: hemoglobin 7.7 g/dl, platelet count 42,000/mL, and D-dimer 1500 ng/ml (N:<500 ng/ml). Leukocyte count, prothrombin time, activated partial thromboplastin time and fibrinogen levels were normal. Arterial blood gas analysis showed hypoxemia with a PaO_2 of 58.5 mmHg, hypocapnia with a $PaCO_2$ of 38 mmHg and oxygen saturation of 92%. The chest radiograph was normal and the electrocardiogram showed sinus tachycardia. There were no evident neuropathological findings except confusion. On the cranial MR, a chronic infarction of the right posterior parietal lobe suggestive of arterial thrombosis was evident (Figure 1). Except for lytic lesions of the cranial bones, the computed tomography of the cranium before treatment with thalidomide was normal. We thus searched for evidence of an underlying thrombophilic state in the patient. DNA was extracted from blood and bone marrow and analyzed for the presence of genetic mutations related with cardiovascular risks. Factor V G1691A (Leiden), factor II G20210A (prothrombin), factor V H1299R(R2), MTHFR C 677T, B-fibrinogen-455 G-A, factor XIII V34L, GPIIIa L33P (HPA-1), HFE C282Y, Apo B R3500Q and Apo E2/E3/E4 were normal. Two heterozygous mutations

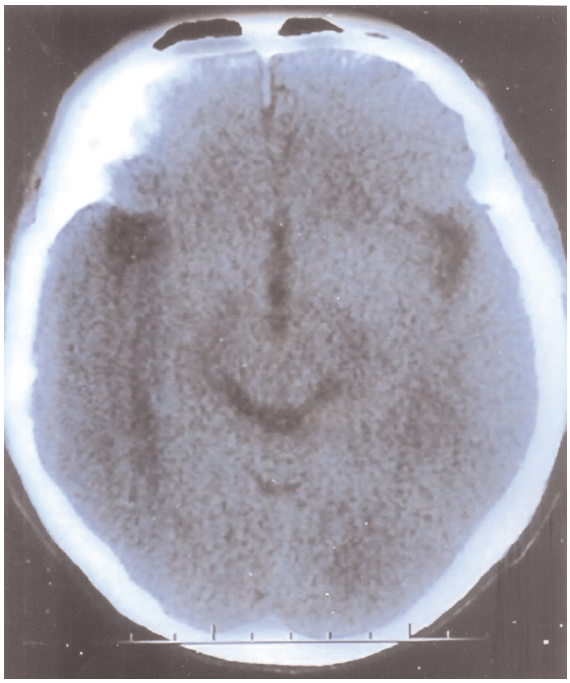

Figure 1. A chronic infarction of the right posterior parietal lobe suggestive of arterial thrombosis is evident on the cranial MR.

(MTHFR A1298C and PAI-1) were detected. Antithrombin III, and protein C and S levels were normal. Anticardiolipin antibodies were negative. Following the cerebrovascular event, thalidomide was discontinued and the patient was treated with aspirin 100 mg/d and clopidogrel 75 mg/d until his death of MM a month later.

Discussion

Thalidomide is being increasingly used in the treatment of myeloma. Response rates of up to 31% have been reported using thalidomide in refractory myeloma, and higher response rates have been reported when used in combination with dexamethasone (5).

The mechanism of thalidomide-associated thromboembolism is not known (4,6). The thrombotic mechanism seems to be multifactorial in arterial thrombosis and in DVT patients. In our patient, the potential risk factors were paraproteinemia, relative immobility, genetic factors (heterozygosity for MTHFR A1298C and PAI-1 gene mutations) and renal failure, in addition to the treatment with thalidomide and dexamethasone. Renal failure is a common complication of myeloma and is associated with a poor prognosis (5). Though not definitively proven, thalidomide may be responsible for hyperkalemia, thus caution is recommended when used in patients with moderate-to-severe renal failure or in those on dialysis (5). We did not observe hyperkalemia or any other electrolyte imbalance during treatment with thalidomide, but we were aware of the complications of dialysis such as dehydration and central venous catheters (CVCs), which also contribute to thrombosis risk (2,6). In a review of 2,075 adverse events regarding treatment with thalidomide, 67 patients had thromboembolic events, such as DVT and pulmonary embolism (7). The events occurred at a mean of two months of thalidomide therapy, as observed in our patient, with a marked increase when chemotherapy including glucocorticoid therapy was concomitantly administered.

In another study by Zangari et al. (2), the association between DVT and chemotherapy with thalidomide was significantly high in MM patients. The median time to development of DVT was 78 days and most thromboses were localized at the site of the CVCs (2). Bowcock et al. (8) suggested that thalidomide might predispose to thromboembolism at even lower doses than previously reported. In their study, the median time to thromboembolic events after starting thalidomide was 3.5 months. They reported arterial thromboembolism with cerebral arterial ischemia as well as venous thromboembolism. Their patients had no thrombophilic tendency and were using low-dose thalidomide.

Age, surgery, smoking, drug therapies as well as CVCs, immobility, hypertension, dehydration, diabetes mellitus, obesity, heart failure, left ventricular dysfunction, oral contraceptives, acquired activated protein C resistance (APCR), and plasma level of factor VIII:C are regarded as acquired risk factors for thrombosis (3,6).

In view of the pre-existing risk factors (paraproteinemia, immobility, renal failure and genetic mutations) in our patient, we cannot conclude whether or not thalidomide contributed to his arterial thrombosis. The dose we used was high, at 400 mg daily, as in the study of Zangari et al. (9), who recorded no arterial events.

The most common genetic risk factors for thrombosis were investigated in our patient. Plasma homocysteine with MTHFR C677T, factor V Leiden, factor V H1299R (R2), factor II G20201A (prothrombin), β-fibrinogen-455 G-A, factor XIII V34L, Gp IIIa L33P, Apo B R3500Q and Apo E2/E3/E4 were normal. Other rare deficiencies of natural coagulation inhibitors such as antithrombin III, and proteins S and C were not present. The patient was negative for anticardiolipin antibodies and had no family history of thrombosis.

Although venous and arterial thromboembolisms are considered to have different pathophysiologies, they occur together in disorders such as the antiphospholipid syndrome (2) and hyperhomocysteinemia (8). All forms of malignancy increase the likelihood of thrombosis and in general there is no increased thromboembolic predisposition in MM patients when compared with patients with other malignancies (1,6). MM, in the absence of hyperviscosity, is not associated with a particularly high risk for thromboembolism (1). The results in different studies indicate that when combinations of chemotherapy and thalidomide are used, effective prophylactic anticoagulation should be implemented in all, at least during the first few cycles of treatment (2,3,4,6,9). For the known contribution of increased platelet activity in malignancy, antiplatelet therapy as an additional or alternative strategy to warfarin should be tested during thalidomide therapy (6).

References

1. Baron JA, Gridley G, Weiderpass E, Nyren O, Linet M. Venous thromboembolism and cancer. Lancet 1998; 351: 1077-1080.
2. Zangari M, Barlogie B, Anaissie E, Saghafifar F, Eddlemon P, Jacobson J et al. Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemotherapy: effects of prophylactic and therapeutic anticoagulation. Br J Haematol 2004; 126: 715-721.
3. Santos AB, Llamas P, Roman A, Prieto E, De Ona R, De Velasco JF et al. Evaluation of thrombophilic states in myeloma patients receiving thalidomide: a reasonable doubt. Br J Haematol 2003; 122: 159-160.
4. Dimopoulos MA, Eleutherakis-Papaiakovou V. Adverse effects of thalidomide administration in patients with neoplastic diseases. Am J Med 2004; 117: 508-515.
5. Harris E, Behrens J, Samson D, Rahemtulla A, Russell NH, Byrne JL. Use of thalidomide in patients with myeloma and renal failure may be associated with unexplained hyperkalaemia. Br J Haemotol 2003; 122: 160-161.
6. Scarpace SL, Hahn T, Roy H, Brown K, Paplham P, Chanan-Khan A et al. Arterial thrombosis in four patients treated with thalidomide. Leuk Lymphoma 2005; 46: 239-242.
7. Bennet C, Schumock G, Desai A, Kwaan H, Raisch D, Newlin R. Thalidomide-associated deep vein thrombosis and pulmonary embolism. Am J Med 2002; 113: 603-606.
8. Bowcock SJ, Rassam SMV, Ward SM, Turner JT, Laffan M. Thromboembolism in patients on thalidomide for myeloma. Hematology 2002; 7: 51-53.
9. Zangari M, Anaissie E, Barlogie B, Badros A, Desikan R, Gopal AV et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood 2001; 98: 1614-1615.