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Treatment of multiple myeloma and arterial thrombosis

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Dear Editor,

In January, 2008, a 49-year-old woman presented at the emergency department of our hospital with a 2-week history of severe back pain. In three months, she had lost 10 kg in body weight. She also complained about constipation and upper abdominal pain after meals for several years. Her medical history included a popliteal artery stenosis, for which she had received conservative treatment, and Graves' disease, treated with radioactive iodine. Her only medication was levothyroxine. The patient had a smoking history of 20 pack years.

Physical examination was unremarkable apart from pain localised on the lower back when pressure was exerted. X-ray examination of skeletal structures revealed lumbar vertebrae fractures of L1, L2, and L3. Blood test results showed a hypercalcaemia of 3.24 mmol/L, C-reactive protein of 29 mg/L, haemoglobin level of 9.7 mmol/L, mean cell volume of 110 fl, platelet count of $291 \times 10^9/L$ and a leucocyte count of $6.4 \times 10^9/L$. Subsequently, tested protein electrophoresis of blood and urine showed no monoclonal protein or Bence-Jones proteinuria. Monoclonal kappa-light chains were present in urine at electrophoresis. Bone marrow biopsy revealed 64% plasma cells. Immunophenotyping showed a widespread monoclonal plasma cell population. This woman was diagnosed with non-secreting multiple myeloma (MM), Salmon–Durie stage IIIa.

Hypercalcaemia was treated with bisphosphonates and intravenous fluids. The pain was controlled with opiates. Treatment of multiple myeloma was started with vincristin, doxorubicin and dexamethasone. However, constipation remained, and she did not pass stools for 1 week. Clinical findings were consistent with a non-mechanical intestinal obstruction. The treatment with morphine was replaced by paracetamol and metamizol. In spite of the conservative treatment, the symptoms did not subside. Computed tomography showed widened small bowel loops but no signs of obstruction. C-reactive protein had risen to 378 mg/L (normal <10 mg/L) without signs of an infection or peritonitis. Serum lactate was normal (2.0 mg/L). As her situation worsened, an exploratory laparotomy was performed. At laparotomy, a greenish, full-blown ischemic bowel was observed. As there were no treatment options, the procedure was ended. The patient died within a few days. At necropsy, a necrotic small bowel and proximal colon were found, and an atherosclerotic stenosis of the inferior mesenteric artery with a secondary obstructive thrombosis was seen.

Discussion

In patients with cancer, each of the three components of Virchow's triad that predispose thrombus formation is altered and thereby induces a prothrombotic state [1]. This can explain the many venous thrombo-embolic (VTE) complications seen in patients with cancer. In multiple myeloma, additional prothrombotic coagulation abnormalities have been observed [2]. Several studies have shown that patients with multiple myeloma are especially at risk to develop thrombotic complications in the first year after diagnosis [3]. During induction chemotherapy with con-

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ventional regimens as vincristin, Adriamycin and dexamethasone (VAD), a VTE incidence of 4% has been reported. Depending on chemotherapeutic regimen and the use of thalidomide, this incidence may rise to 30% [4]. In the case described above, the patient did not receive thromboprophylaxis. At the start of induction chemotherapy with VAD, she had no conventional indications for thromboprophylaxis.

The prothrombotic coagulation abnormalities in patients with untreated multiple myeloma are also associated with disease stage [5]. Notably, factor VIII and von Willebrand factor (vWF) antigen levels are higher and correlate with disease stage. Recent studies suggest that treatment of multiple myeloma with dexamethasone and Adriamycin combined with either vincristin (VAD), thalidomide or bortezomib (PAD) result in an augmented prothrombotic coagulation state with significantly higher levels of factor VIII, vWF and fibrinogen. In patients with multiple myeloma, levels of these pro-coagulant factors are elevated at presentation and increase with induction therapy [6]. Higher levels of clotting factors are known to be associated with increased risk of thrombotic events in the general population [7]. Consequently, multiple myeloma patients receiving induction chemotherapy are at increased risk of thrombo-embolic complications. In most cases, patients experience venous thrombo-embolic complications, and rare arterial thrombotic complications, as was seen in our patient, have been reported [8]. Taking all this into account, one should consider preventive measures to reduce thrombotic complications in multiple myeloma patients receiving chemotherapy, especially when combined with thalidomide. Currently, there are only recommendations on thromboprophylaxis for multiple myeloma patients who are treated with thalidomide- or lenalidomide-containing regimens [10]. In these patients, thromboprophylaxis with low molecular weight heparin (LMWH) is effective in reducing thrombotic complications [9]. Several studies have shown that aspirin is also effective in reducing thrombotic events [10]. In a recent prospective, multicenter study, low-dose warfarin, LMWH and aspirin were compared in patients treated for newly diagnosed multiple myeloma. The incidence of VTE was comparable for all groups [11]. Whether thromboprophylaxis will also reduce the risk of arterial thrombotic complications is unknown; however, this complication is only rarely observed and predominantly reported in patients treated with thalidomide [8]. Based on the recent reports of the frequency of venous thrombotic complications and the occurrence, although rare, of arterial thrombotic complications in multiple myeloma patients

receiving induction chemotherapy not containing thalidomide or lenalidomide, giving thromboprophylaxis with aspirin also to these individuals [3, 9].

Our patient's medical history was positive for cardiovascular disease. At presentation, she was diagnosed with multiple myeloma at advanced stage. Before treatment started, she was dehydrated due to hypercalcaemia. Lethal arterial thrombosis was diagnosed after the first induction chemotherapy. In our opinion, this case is a dramatic example of the prothrombotic predispositions as reviewed in Virchow's triad.

In conclusion, we report a case of mesenteric artery thrombosis in a patient treated for multiple myeloma. Taken together with the previously reported patients with arterial thrombosis, i.e. stroke and acute myocardial infarction, this suggests that patient with MM are not only at risk for venous thrombo-embolism but also of arterial thrombotic complications.

References

1. Lip YH, Chin BSP, Blann AD (2002) Cancer and the prothrombotic state. *Lancet Oncol* 3:27–34
2. Zangari M, Elice F, Fink L et al (2007) Thrombosis in multiple myeloma. *Expert Rev Anticancer Ther* 7:307–315
3. Kristinsson SY, Fears RH, Gridley G et al (2008) Deep vein thrombosis after monoclonal gammopathy of undetermined significance and multiple myeloma. *Blood* 112:3582–3586
4. Barlogie B, Tricot G, Anaissie E et al (2006) Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* 354:1021–1030
5. Auwerda JJA, Sonneveld P, de Maat MPM et al (2007) *Haematologica* 92:279–280
6. Marion AMW, Auwerda JJA, Lisman T et al (2008) Prospective evaluation of coagulopathy in multiple myeloma patients before, during and after various chemotherapeutic regimens. *Leuk Res* 32:1078–1084
7. Kyrle PA, Minar E, Hirschl M et al (2000) High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. *N Engl J Med* 343:457–462
8. Goz M, Nesimi Eren M, Cakir O (2008) Arterial thrombosis and thalidomide. *J Thromb Thrombolysis* 25:224–226
9. Minnema MC, Breikreuz I, Auwerda JJA et al (2004) Prevention of venous thromboembolism with low molecular-weight heparin in patients with multiple myeloma treated with thalidomide and chemotherapy. *Leukemia* 18:2044–2046
10. Palumbo A, Rajkumar SV, Dimopoulos MA et al (2008) Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia* 22:414–423
11. Palumbo A, Cavo M, Bringhen S et al (2008) Enoxin versus aspirin versus low-fixed-dose of warfarin in newly diagnosed myeloma patients treated with thalidomide containing regimens: a randomized controlled trial. *Haematologica* 93(suppl 1):0910