

# Increased Risk of Ischemic Stroke in Multiple Myeloma Associated With Lenalidomide Treatment: A Case Report and Review of the Literature

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**Objective:** The aim of the study was to illustrate the increased risk of ischemic stroke in the context of multiple myeloma (MM) under treatment with lenalidomide combined with dexamethasone.

**Methods:** This is a case report and literature review.

**Results:** A 62-year-old woman diagnosed with relapsed MM under treatment with lenalidomide and dexamethasone presented with acute onset disorientation, disturbed behavior, and aphasia. Cranial computed tomography scan revealed an acute cerebral infarction in the left middle cerebral artery territory, and brain magnetic resonance imaging showed additional silent ischemic lesions in other arterial territories. Common stroke etiologies were excluded after an extensive study, leading to a final diagnosis of cerebral infarction of uncommon cause probably related to MM and treatment with lenalidomide plus dexamethasone. A literature review provided 84 reports from the license holder, 2 more cases of stroke in patients with MM receiving lenalidomide and a recurrent stroke in a patient experiencing polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS syndrome) treated with lenalidomide.

**Conclusions:** Our case exemplifies the need to raise awareness about the risk of ischemic stroke associated with MM that might be increased by treatment with lenalidomide and to establish consistent recommendations regarding thromboprophylaxis to reduce comorbidities and mortality in these patients.

**Key Words:** lenalidomide, dexamethasone, ischemic stroke, hypercoagulable state, thromboprophylaxis

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Multiple myeloma (MM) is one of the most frequent hematologic malignancies, particularly in populations older than 60 years. It is characterized by a proliferation of plasma cells that cause an elevation of circulating monoclonal immunoglobulin.<sup>1</sup> The incidence of MM in the general population is approximately 3 to 4 cases per 100,000 inhabitants, and it accounts for 1% of all malignancies.<sup>2</sup> Fortunately, therapies have increased survival in patients with MM, although it still remains an incurable disease. A frequent complication of MM is venous thromboembolic disease (VTE), which occurs up to 28 times more frequently among these patients than in the general population.<sup>3</sup> Increased risk of arterial thrombosis (including coronary and cerebral ischemia) has also been reported, especially during the first year after diagnosis<sup>4</sup>; given that arterial thrombosis is associated with increased mortality,<sup>5</sup>

thromboprophylaxis is an important issue in MM management. The precise mechanisms underlying the increased thrombotic risk in patients with MM are yet unknown, although tumor-related factors, patient-specific conditions, and effects of antineoplastic treatment could be considered as potential pathogenic factors.<sup>2</sup>

Lenalidomide is a highly effective immunomodulatory drug commonly used in patients with MM. Increased risk of venous thrombosis with lenalidomide is well known, and arterial thrombosis has also been described.<sup>6–8</sup> The use of lenalidomide in combination with dexamethasone has a synergistic antitumoral effect<sup>9</sup>; thus, it is usually recommended, although it seems to increase thrombotic events.<sup>10</sup>

## METHODS

We present a novel case report and a literature review by a PubMed search using the keywords “stroke” and “lenalidomide.” We reviewed resulting articles and their references. We present a summary of the findings.

## RESULTS

### Case Report

We present the case of a 62-year-old woman diagnosed with MM type IgG  $\kappa$  stage IIIA 4 years earlier, with a relapse on treatment with lenalidomide 25 mg daily, dexamethasone 40 mg a week, darbeopetin 150 mg per month, and simvastatin 20 mg a day. She suddenly presented disorientation, disturbed behavior, and aphasia. On admission, a computed tomography (CT) scan showed an acute cerebral infarction in the left parietal lobe. After an extensive work-up study, including laboratory tests (hemogram, coagulation profiles with anticardiolipin antibodies, lipids, glycated hemoglobin), chest x-ray, transthoracic echocardiogram, 24-hour Holter electrocardiogram, and ultrasonographic study of intracranial and extracranial arteries, we ruled out significant atherosclerosis and cardiac arrhythmias. We found no signs of deep vein thrombosis, neither did there appear to be reasons to suspect a paradoxical embolism or other cardiac source of embolism on transthoracic echocardiogram. Brain magnetic resonance imaging showed the infarct previously observed in the CT scan and 2 additional ischemic lesions at the left occipital and right frontal cortex, suggesting silent infarctions in the left posterior cerebral artery and right middle cerebral artery territories (Fig. 1). After excluding other etiologies, we diagnosed the patient with cerebral infarctions of uncommon etiology probably secondary to a hypercoagulable state induced by MM and lenalidomide plus dexamethasone treatment. We interrupted chemotherapy and the patient was treated with aspirin 300 mg after hospital discharge. One month after, she still presented cognitive alterations, although language disturbances had clearly improved.

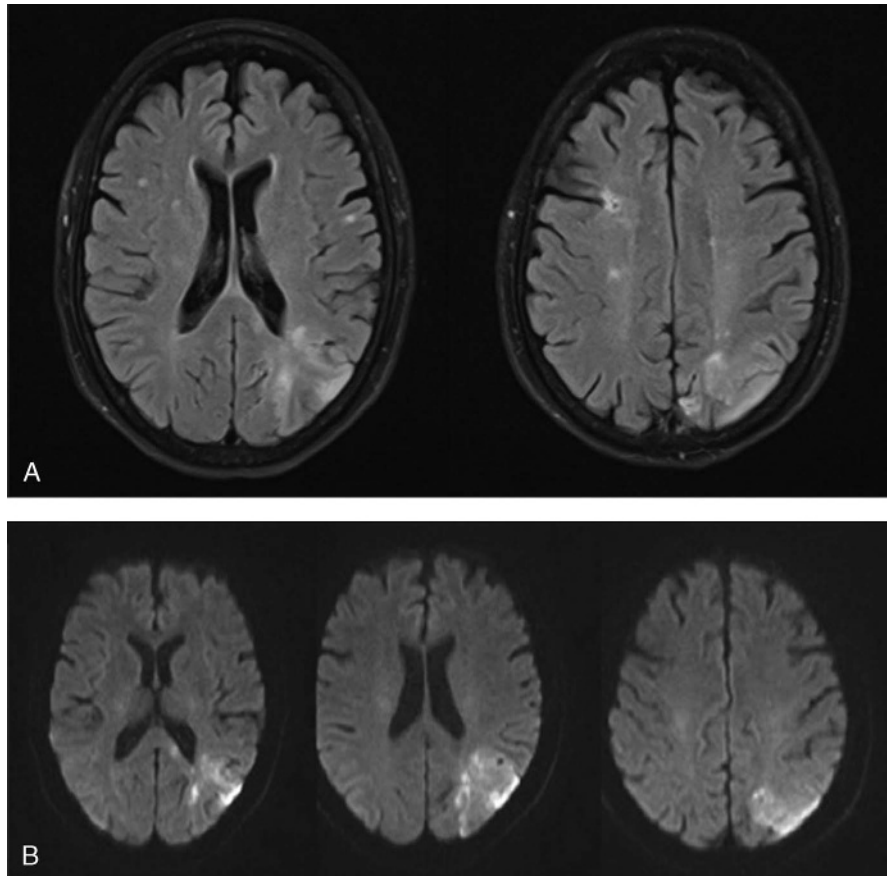
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**FIGURE 1.** Brain magnetic resonance imaging. A, FLAIR sequence showing a left middle cerebral artery infarct and laminar necrosis in the bilateral frontal cortex and left occipital cortex, suggesting silent infarctions in multiple vascular territories. B, Diffusion-weighted sequence shows restriction in middle cerebral artery territory, suggesting an acute infarction.

## Literature Review

Postmarketing data published by the Medicines and Healthcare Products Regulatory Agency in 2011 included 493 reports of arterial thrombosis in patients with MM treated with lenalidomide, representing a 0.5% rate. Most of the events were myocardial infarctions (65%), followed by cerebrovascular disease (17%), although no description of the stroke cases was provided.<sup>11</sup> The PubMed search displayed 2 more case reports: a 54-year-old woman with MM and without any other vascular risk factors who developed a fatal bilateral cerebral infarction under lenalidomide treatment without thromboprophylaxis<sup>8</sup> and a 34-year-old woman with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS syndrome) experiencing recurrent transient ischemic events with a clear temporal relationship with lenalidomide and dexamethasone treatment despite thromboprophylaxis.<sup>12</sup> In a recent phase II trial in which lenalidomide was administered together with rituximab and ibrutinib, 1 case of fatal stroke is also described.<sup>13</sup> A summary of the case reports in the literature review is found in Table 1.

## DISCUSSION

Multiple myeloma is a known risk factor for ischemic stroke, although the exact mechanisms underlying the increased risk are not yet well known.<sup>4</sup> Patient-dependent factors such as immobilization and advanced age, tumor-related factors such as increased plasma viscosity and hypercoagulable state and effects

of antineoplastic treatments are considered potential pathogenic factors. The risk of arterial thrombotic events is higher in the first stages of the disease and seems to be increased with lenalidomide plus high-dose dexamethasone. The incidence of cerebral vascular events in 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group studies of lenalidomide plus dexamethasone versus dexamethasone alone performed on 704 patients was 3.4% for those treated with lenalidomide and dexamethasone compared with 1.7% of those treated only with dexamethasone with placebo.<sup>11</sup> Lenalidomide alone is rarely used in MM treatment, given that concomitant use of dexamethasone has proven a synergistic antineoplastic effect. However, *in vitro* studies with endothelial cells have shown different results regarding prothrombotic effects; Valsami et al<sup>14</sup> have demonstrated increased expression of tissue factor (TF) with lenalidomide use alone, whereas Isozumi et al<sup>10</sup> did not observe significant overexpression of TF with the use of lenalidomide. In this same study, dexamethasone alone as well as in combination with lenalidomide increased TF expression on endothelial cells. Other studies<sup>15,16</sup> comparing patients with MM treated with lenalidomide plus high-dose or low-dose dexamethasone report higher rates of VTD in the high dexamethasone group. Increased risk of thrombotic events with the use of erythropoietic therapy along with lenalidomide plus dexamethasone is controversial; its effect on risk of ischemic stroke in our patient remains unclear.<sup>15,17</sup>

An associated hypercoagulable state has been suggested to be the underlying mechanism of thrombotic events in MM. An increase of inflammatory cytokines (especially interleukin 6), von

**TABLE 1.** Case Reports of Stroke in Patients Treated With Lenalidomide

Sex	Age	Underlying disease	Dexamethasone	Vascular risk factors	Thromboprophylaxis
Woman <sup>8</sup>	54	MM	Yes (40 mg/wk)	None	None
Woman <sup>11</sup>	34	POEMS syndrome	Yes (dose not specified)	None	Aspirin
Woman <sup>*11</sup>	34	POEMS syndrome	Yes (dose not specified)	None	LMWH
Woman (actual case)	62	MM	Yes (40 mg/wk)	Hyperlipidemia	None

\*Two different cerebrovascular events occurred to the same patient in a brief period of time (<3 weeks) while on lenalidomide plus dexamethasone treatment even though thromboprophylaxis with aspirin was initiated.

Willebrand factor, and coagulation factor VIII (FVIII) along with hyperviscosity has been reported in MM.<sup>2</sup> In addition, lenalidomide has been related to the increased levels of fibrinogen, P-selectin, TF, VFP, and FVIII. A prospective study found that combining lenalidomide with dexamethasone (especially pulsed dexamethasone) might increase endothelial stress.<sup>18</sup>

In the latest American Society of Clinical Oncology guidelines<sup>19,20</sup> and the guidelines of management of VTD from the International Myeloma Working Group,<sup>3</sup> thromboprophylaxis for VTD is recommended for patients with MM receiving lenalidomide. For low-risk patients (ie, those with no other prothrombotic risk factors), aspirin (81–325 mg) is recommended, whereas high-risk patients (2 or more thrombotic risk factors, such as previous thrombotic events, obesity, associated disease, or immobilization) should receive low-molecular-weight heparin (LMWH) in prophylactic doses or even vitamin K antagonists with target international normalized ratio of 2 to 3. High-dose dexamethasone, doxorubicin, or multiagent chemotherapy in combination with lenalidomide are considered additional risk factors, for which the use of LMWH or vitamin K antagonists should be considered. Individual risk factors for hemorrhage should be taken into account to decide the optimal treatment (high risk for thrombocytopenia, acquired von Willebrand disease, use of LMWH in patients with renal failure, international normalized ratio instability in patients treated with dexamethasone). Risk of thromboembolic events is higher during the first 6 months after starting treatment; thus, it is reasonable to maintain thromboprophylaxis for primary prevention of VTD during this time and to individualize further treatment based on thrombotic risk factors. There are no recommendations established for primary prevention of arterial thrombotic events due to the paucity of data in this regard. A recent study documented that only approximately 20% of patients receiving treatment with lenalidomide for MM were under correct thromboprophylaxis following recommendations of these guidelines.<sup>21</sup>

Similarly, in cases of established VTD, LMWH or vitamin K antagonist should be indicated for at least 6 months. Beyond that time, it could be maintained in high-risk patients. Treatment with LMWH has demonstrated fewer relapses of thrombotic events than vitamin K antagonists.<sup>19,22</sup> Again, no recommendations exist for secondary prevention of arterial thrombotic events.

The patient we present did not receive any prophylactic treatment before stroke; afterward, she was maintained on long-term aspirin (300 mg/d).

## CONCLUSIONS

This case report adds new information to the current evidence of the increased risk of arterial thrombosis in patients with MM receiving treatment with lenalidomide and dexamethasone, given that no other cause of stroke was found after an extensive diagnostic work-up. No concomitant thromboprophylaxis was being used at the time of the event. Lenalidomide alone seems able

to cause increased risk of thrombotic events in patients with MM; however, its combination with dexamethasone (especially in high doses) can raise this risk even more. Although arterial thrombotic events have been reported previously in clinical trials and in postmarketing data, actual guidelines establish thromboprophylactic recommendations only for venous thrombotic events. Given one of the optimal treatments for MM seems to be lenalidomide in combination with dexamethasone, this case highlights the need to increase awareness about its thrombotic risks and to encourage prescription of the best thromboprophylactic regime based on individual patient risk factors. More studies with an adequate follow-up time should be performed concerning the best prophylactic strategy to prevent stroke among these patients.

## Highlights

- Multiple myeloma is related to higher thrombotic risk, especially when treated with lenalidomide and dexamethasone.
- Cases of arterial thrombosis have been described in these patients.
- Numerous mechanisms could be responsible of the hypercoagulable state in MM and lenalidomide treatment.
- Thromboprophylaxis is recommended to prevent venous thrombotic events.

## REFERENCES

- Maharaj S, Chang S, Seegobin K, et al. Increased risk of arterial thromboembolic events with combination lenalidomide/dexamethasone therapy for multiple myeloma. *Expert Rev Anticancer Ther* 2017;17: 585–591.
- Leebeek FW. Update of thrombosis in multiple myeloma. *Thromb Res* 2016(140 Suppl 1):S76–S80.
- Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia* 2008;22:414–423.
- Kristinsson SY, Pfeiffer RM, Bjorkholm M, et al. Arterial and venous thrombosis in monoclonal gammopathy of undetermined significance and multiple myeloma: a population-based study. *Blood* 2010;115: 4991–4998.
- Kristinsson SY, Pfeiffer RM, Bjorkholm M, et al. Thrombosis is associated with inferior survival in multiple myeloma. *Haematologica* 2012;97: 1603–1607.
- Li W, Cornell RF, Lenihan D, et al. Cardiovascular complications of novel multiple myeloma treatments. *Circulation* 2016;133: 908–912.
- Shridhar P, Khalil R, Lasorda D, et al. Lenalidomide induced stroke in multiple myeloma. *J Integr Cardiol* 2016;2:398–399.
- Tannemaat MR, Vries EP, Molendijk WJ, et al. Fatal ischemic stroke in a patient receiving lenalidomide for multiple myeloma. *Clin Neurol Neurosurg* 2011;113:488–489.

9. Quach H, Kalff A, Spencer A. Lenalidomide in multiple myeloma: current status and future potential. *Am J Hematol* 2012;87:1089–1095.
10. Iozumi Y, Arai R, Fujimoto K, et al. Activation of coagulation by lenalidomide-based regimens for the treatment of multiple myeloma. *PLoS One* 2013;8:e64369.
11. Medicines and Healthcare products Regulatory Agency: lenalidomide: risk of thrombosis and thromboembolism. Available at: <https://www.gov.uk/drug-safety-update/lenalidomide-risk-of-thrombosis-and-thromboembolism>. Accessed July 2018.
12. Mitsutake A, Matsumoto H, Hatano K, et al. Lenalidomide-induced ischemic cerebrovascular disease in polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome. *J Stroke Cerebrovasc Dis* 2018;27:e102–e103.
13. Jerkeman M, Eskelund CW, Hutchings M, et al. Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Haematol* 2018;5:e109–e116.
14. Valsami S, Ruf W, Leikauf MS, et al. Immunomodulatory drugs increase endothelial tissue factor expression in vitro. *Thromb Res* 2011;127:264–271.
15. Menon SP, Rajkumar SV, Lacy M, et al. Thromboembolic events with lenalidomide-based therapy for multiple myeloma. *Cancer* 2008;112:1522–1528.
16. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol* 2010;11:29–37.
17. Chen C, Reece DE, Siegel D, et al. Expanded safety experience with lenalidomide plus dexamethasone in relapsed or refractory multiple myeloma. *Br J Haematol* 2009;146:164–170.
18. Rosovsky R, Hong F, Tocco D, et al. Endothelial stress products and coagulation markers in patients with multiple myeloma treated with lenalidomide plus dexamethasone: an observational study. *Br J Haematol* 2013;160:351–358.
19. Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014. *J Clin Oncol* 2015;33:654–656.
20. Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013;31:2189–2204.
21. Anderson SM, Beck B, Sterud S, et al. Evaluating the use of appropriate anticoagulation with lenalidomide and pomalidomide in patients with multiple myeloma. *J Oncol Pharm Pract* 2018;1078155218758500.
22. Farge D, Bounameaux H, Brenner B, et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol* 2016;17:e452–e466.