Erythropoietin-Induced Deep Vein Thrombosis in Myelodysplastic Syndrome

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Abstract
We report a rare case of deep vein thrombosis (DVT) secondary to erythropoietin (EPO) in an 89-year-old patient with myelodysplastic syndrome (MDS). The incidence of EPO-induced thrombotic episode increases with an absolute increase of hemoglobin (Hb) beyond >12 gm/dL or rate of increase of Hb level >1 gm/dL every 2 weeks. ©

INTRODUCTION
Erythropoietin (EPO), a glycoprotein hormone stimulates erythropoesis by binding to the receptors of erythroid progenitors. EPO is used in the treatment of refractory anaemia secondary to chronic renal failure (CRF), post-chemotherapy and myelodysplasia. Increased incidence of thrombotic events has been reported in the literature in patients receiving EPO for anaemia secondary to myelodysplastic syndrome. Rise in the absolute Hb level >12 gm/dL or rate of increase of Hb >1 gm/dL every 2 weeks sharply increase the incidence of thrombosis.

CASE REPORT
The patient, 89-years Kuwaiti male with history of refractory anaemia secondary to myelodysplastic syndrome (MDS) was initiated with EPO 40,000 IU subcutaneously thrice weekly in 2000. He was advised to reduce the dose gradually according to Hb level. He had been treated recently for haemorrhagic cerebral infarct. Six weeks later he was admitted with swelling of the right calf while on Eprex® 40,000 IU subcutaneously once weekly. There was a circumferential difference of 3 cm at the right mid calf and mid thigh level, compared to left side. All peripheral pulses were well felt. Investigation revealed Hb level 15 g/dL, ESR 59 mm in first hour and platelets 198x10⁹/L. The coagulation profile revealed raised D-dimer and INR 1.36. Doppler ultrasonography (USG) revealed extensive DVT involving right common femoral vein, superficial femoral vein, popliteal vein, proximal third of right anterior tibial vein and posterior tibial vein. Abdomino-pelvic CT angiogram revealed thrombosis extending to right external iliac vein. In view of a recent cerebral haemorrhagic infarct, warfarin was avoided and he was treated with LMWH (Clexane®) alone. Two weeks later, the left lower limb became swollen too and Doppler USG confirmed evidence of extensive thrombosis up to left external iliac vein. He underwent inferior vena cava (IVC) filter insertion in view of bilateral extensive DVT and advised to continue Clexane for 6 weeks followed by a plan to restart Warfarin. There was no clinical evidence of pulmonary embolism during his 5 weeks stay in hospital. There was a reduction of the circumferences of 1.5 cm in both lower limbs at mid calf as well as mid thigh level, with the above mentioned treatment. He was advised to restart Eprex if Hb level dropped below 8gm/dL in order to keep Hb level between 10-12 gm/dL. The patient remained asymptomatic thereafter with further reduction of lower limb swelling since the time of discharge.

DISCUSSION
The myelodysplastic syndromes (MDS) are a group of disorders characterised by one or more peripheral blood cytopenias secondary to bone marrow dysfunction. Anaemia, bleeding and fatigue are the common presenting features. MDS may be primary or secondary to treatment with chemotherapy/radiation therapy. MDS is commonly seen in elderly patients usually >60 yrs, but it can occur in any age group. The mainstay of treatment of MDS has traditionally been supportive care. Anaemia secondary to MDS are generally treated with red blood cell transfusions. The use of recombinant human erythropoietin (rHuEpo) has revolutionised the treatment of refractory anaemia secondary to MDS. Meta-analyses show an overall response rate approaching 33%, although this figure exceeds 50% among transfusion-independent persons who have refractory anemia with ringed sideroblasts.
Erythropoietin, a glycoprotein hormone secreted from kidneys is crucial to the regulation of erythropoiesis; it stimulates red cell production by stimulating erythroid progenitors. There have been rare reports of unusual thromboembolic events including migratory thrombophlebitis, microvascular thrombosis, pulmonary thrombo-embolism, DVT and thrombosis of the temporal veins. Erythropoietin can be used to improve anemia.

Although old age increases the risk of thrombotic events in MDS, the risk of thrombosis is increased significantly if absolute Hb level exceeds 12 g/dL or there is an increase in Hb > 1.0 g/dL during any 2 week time period of EPO use. In this patient, absolute Hb level was much higher than the recommended value of 12 gm/dL for sufficient period predisposing to DVT (Fig. 1). Various recommendations available in the literature for prevention of venous thrombo-embolism secondary to EPO treatment in MDS are as follows: (1) Target Hb level should be kept ≤ 12 gm/dL, (2) EPO dose should be reduced by 25% if Hb level approaches 12 gm/dL or increase by >1 gm/dL in any 2 weeks of treatment period, (3) If Hb continues to increase >12 gm/dL doses should be suspended temporarily and be reinitiated when haemoglobin begins to decrease, at a dosage that is 25% lower, (4) Dosage should be increased by 25% at a frequency of at least 4 weeks interval, (5) The maximal target haemoglobin level should be 12 gm/dL, however the goal should be individualized.

This patient responded well to EPO treatment. However the haemoglobin level exceeded the recommended level of 12gm/dL, which predisposed to venous thrombosis. We emphasize that physicians should monitor Hb level closely and follow the guidelines during EPO treatment in patients with refractory anemia in MDS.

REFERENCES
6. Hellstrom-Lindberg E. Efficacy of erythropoietin in the myelodysplastic syndromes: a meta-analysis of 205 patients from