

Cerebral Venous Thrombosis Associated With Epoetin Alfa Therapy

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Background: Cerebral venous thrombosis is a rare complication of polycythemia. To our knowledge, epoetin alfa-induced polycythemia has not previously been reported in association with cerebral venous thrombosis.

Case Description: A 37-year-old patient who was receiving peritoneal dialysis and epoetin alfa (Epogen) therapy presented with a several-day history of worsening headache, and a neuroimaging scan demonstrated thrombosis of the sagittal and transverse sinus. Epoetin alfa therapy, which had been initiated 3 months earlier

according to an institutional protocol, was associated with a problematic increase in hematocrit values.

Conclusions: Headache should raise the suspicion of cerebral venous thrombosis in patients who are being treated with epoetin alfa, particularly in the presence of elevated hematocrit values. Monitoring hematocrit parameters in accordance with "standard guidelines" is recommended.

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RECOMBINANT human erythropoietin, or epoetin, has been used since the latter half of the 1980s to correct anemia with a demonstrated increased quality of life and cognitive function in patients who are receiving dialysis.^{1,2} Neurological complications of its use include seizures, visual hallucinations, headache, transient myalgia, and hypertensive posterior leukoencephalopathy.¹⁻⁴ Thrombotic events associated with this therapy include vascular access thrombosis, migratory thrombophlebitis, pulmonary embolism, retinal artery thrombosis, renal vein thrombosis, temporal vein thrombosis, transient ischemic attacks, and myocardial infarction,^{5,6} with further risk associated with higher hematocrit values.^{1,2} To our knowledge, dural sinus thrombosis, a complication of polycythemia, has not been previously reported in association with epoetin alfa therapy.

REPORT OF A CASE

A 37-year-old white woman with end-stage renal disease due to reflux nephropathy presented with a several-day history of worsening headache. When peritoneal dialysis was begun, 3 months earlier, her hematocrit value was 0.27, and as part of the routine procedure, therapy with epo-

etin alfa (Epogen) was initiated according to a pharmacy-approved standard dosing protocol. After 1 month, her hematocrit value had increased from 0.27 to 0.36, and the dosage of epoetin alfa therapy was tapered by 25%, from 7000 to 5000 U. Iron monitoring tests revealed the development of iron deficiency, so the patient was also given intravenous iron therapy. At the end of the second month of therapy, her hematocrit value had increased sharply to 0.50. Again, following the hospital protocol, the dosage of epoetin alfa therapy was reduced 50%, to 2500 U. By the end of the third month of therapy, her hematocrit value had increased to 0.55. At this point, the epoetin alfa therapy was discontinued, and about 2 weeks later, the patient developed a headache, and her hematocrit value decreased to 0.49. At first, she thought that the headache was one of her usual perimenstrual headaches, which she had had for some time, but over a period of 3 to 4 days, the headache became constant and severe.

The patient's neurological examination revealed no abnormalities, and her blood pressure readings throughout the epoetin alfa therapy were consistently 120/70 mm Hg or lower. Admission laboratory tests disclosed the following values: hematocrit, 0.49; platelet count, $149 \times 10^9/L$; white blood cell count,

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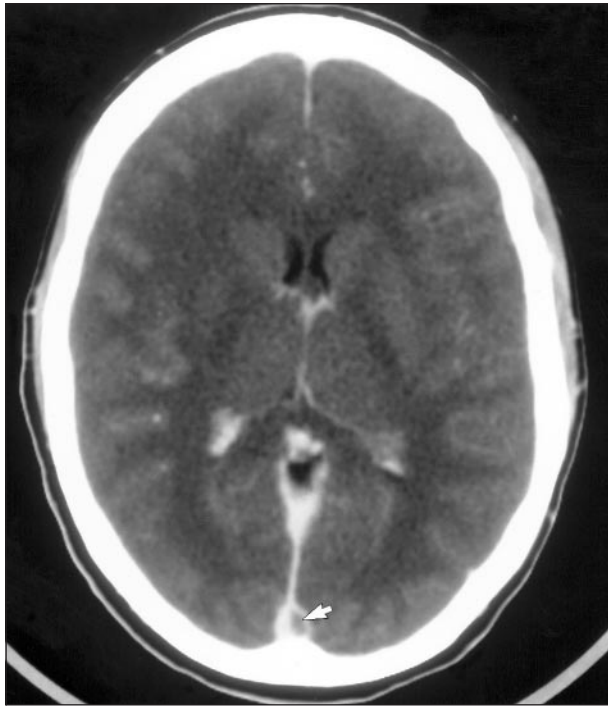


Figure 1. Enhanced computed tomographic scan with filling defect in the superior sagittal sinus with partial delta sign (arrow).



Figure 2. Magnetic resonance angiogram midline sagittal reformat of coronal 2-dimensional time-of-flight image showing no flow in the superior sagittal sinus (arrows) and impaired flow in the lower straight sinus, indicative of sinus thrombosis.

$14.1 \times 10^9/L$; serum urea nitrogen, 15.4 mmol/L (43 mg/dL); and serum creatinine, 566 $\mu\text{mol/L}$ (6.4 mg/dL). The prothrombin time, partial thromboplastin time, serum homocysteine level, international normalization ratio, protein C and S activity, antithrombin activity, and results of polymerase chain reaction for activated protein C resistance were all in the normal range. A nonenhanced computed tomographic scan showed increased attenuation in the region of the straight and right transverse sinus, and an enhanced computed tomographic scan showed a filling defect in the superior sagittal sinus with a partial delta sign (**Figure 1**). A magnetic resonance (MR) imaging scan showed no parenchymal or vascular abnormality, and MR angiographic phase contrast and 2-dimensional time-of-flight images showed absence of flow in the superior sagittal sinus and torcular area and impaired flow in the lower straight sinus, indicative of sinus thrombosis (**Figure 2**).

The patient was admitted to the hospital, and intravenous heparin sodium therapy was initiated. Over the next 10 days, the patient's headache responded to treatment with analgesics; however, her course was complicated by a retroperitoneal hemorrhage that occurred while she was receiving therapeutic levels of heparin. She had an uneventful recovery and was discharged to her home on a 6-month oral regimen of warfarin sodium (Coumadin). At her request, epoetin alfa therapy has not been reintroduced.

COMMENT

Patients who are receiving long-term dialysis frequently experience hemorrhagic complications. However, with

the advent of epoetin alfa therapy, thrombotic events involving various organ systems have been reported.^{2,5} Of 118 patients who had anemia due to end-stage renal disease, but who were not at risk for thrombovascular disease, and who were treated with dialysis and epoetin alfa, 22 experienced thrombovascular complications: 17 developed fistula thromboses and 5 experienced systemic events (3 cerebral strokes, 1 pulmonary embolism, and 1 myocardial infarction).⁵ Factors predisposing to thrombovascular complications, in association with epoetin alfa therapy, include increased blood viscosity due to the rise in hematocrit, normalization of bleeding time, improvement in platelet function, and reduction in protein C and protein S levels.²

The dosage of our patient's epoetin alfa therapy was determined according to an institutional protocol, with a target hematocrit range of 0.32 to 0.36 but with limited provision for the discontinuation of the therapy with higher levels or an excessive rate of increase. As such, the hematocrit increased faster in rate and absolute value than is suggested by the drug manufacturer and National Kidney Foundation guidelines.^{6,7} In contrast to our protocol, the National Kidney Foundation guidelines would have suspended the epoetin alfa therapy when the hematocrit was 0.50. Also, if polycythemia is of concern, phlebotomy is suggested to decrease the hematocrit.⁶

Cerebral venous thrombosis, a rare complication of polycythemia,⁸⁻¹⁰ has not been reported with epoetin alfa therapy, to our knowledge. The reason that cerebral venous thrombosis has occurred with epoetin therapy may relate to the use of dosing guidelines that suspend therapy at a certain hematocrit level. In our patient, no other medi-

cation, disease, or predisposing factor known to be associated with cerebral venous thrombosis was identified. Hyperviscosity due to polycythemia either alone or in conjunction with associated factors that affect coagulation with epoetin alfa therapy is thought to be responsible for the dural sinus thrombosis in our patient, in whom the hematocrit value more than doubled in less than 2 months, reaching 0.55. Importantly, although headache is a noted adverse effect of epoetin alfa therapy, this symptom should raise the suspicion of cerebral venous thrombosis, particularly in the presence of an elevated hematocrit value. Despite the neuroimaging abnormalities noted initially in this case, it should be emphasized that the combined use of MR imaging and MR angiography is necessary, as MR imaging may not reveal abnormalities in the acute phase.

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