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Reply:

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Reply:

We thank Drs. Schwartz, Mulkern, and Vajapeyam for their comments and find the case they demonstrate to be quite interesting. We indeed agree with the need for caution in interpreting information with respect to posterior reversible encephalopathy syndrome (PRES). Their case is of interest for several reasons.

Aside from the arbitrary nature of color windowing in relative cerebral blood volume (rCBV) maps, rCBV data are "relative" and do not represent an absolute measurement of CBV. These are, essentially, an integration of the area under the negative enhancement curve and not a specific measure of perfusion. This is one of the reasons we chose to reference PRES regions relative to areas of the normal appearing cortex. Remember, rCBV is typically used to assess low-flow states such as stroke and ischemia, including assessment of the ischemic penumbra.

Interpretation of hyperperfusion on the initial imaging, when the patient's blood pressure was 150/90 mmHg, in our opinion is likely overzealous.

The second scan, obtained approximately 1 hour after the patient's blood pressure reached 230/130 mm Hg, though, is quite interesting. Presumably, the severe hypertension was quickly treated after being recognized.

If the "systemic" toxicity process ultimately responsible for PRES results in the development of T-cell activation and trafficking, endothelial activation, and vasoconstriction (as occurs systemically in the conditions prone to develop PRES), several consequences would occur.

Endothelial activation and vasculopathy (vasoconstriction) would likely render feeding arterioles and the microvasculature less compliant and with luminal narrowing. In addition, trafficking T-cells (T-cell to endothelial adhesion with transluminal migration) would further obstruct flow in the microvascular bed. The end point of these combined effects would be restricted blood flow, relative hypoperfusion, and potential hypoxemia. In addition, as might be present in this case, the immunosuppressive drugs cyclosporine and tacrolimus exert a vasoconstrictive effect in many vascular beds, potentially worsening restricted brain perfusion.

The acute increase in blood pressure could be related to a systemic change in the toxicity process, a Cushing response to tissue hypoxemia, or both. Systemic increase in blood pressure could even augment brain autoregulatory vasoconstriction.

The observed rCBV result may depend on when the imaging examination is performed.

If the patient undergoes an imaging examination while at maximal hypertension, the increase in systemic pressure would confront markedly altered brain vascular "impedance" (both altered compliance and resistance).

With increase in systemic blood pressure, distension of noncompliant narrowed vessels (feeding arterioles and microvascular endothelium) and dislodgement of adhering T-cells would improve cerebral blood flow but not necessarily to normal levels. Transit time of contrast-laden blood across the capillary bed may remain delayed with prolongation of flow. Such prolonged and somewhat reduced flow could easily lead to a prolongation of the negative enhancement curve/integral, increase in perceived rCBV "as calculated," but not reflect an actual increase in cerebral blood flow.

If the patient undergoes imaging examination after partial reduction of blood pressure in the setting of cerebral blood flow restriction from endothelial activation, T-cell trafficking, and vasoconstriction, cerebral blood flow might be inadequate. The brain's vascular response, in this setting, might be partial relaxation of autoregulatory vasoconstriction, again with some reduced flow but prolonged transit, resulting in an increase in perceived rCBV.

There are other circumstances in which rCBV can be increased but cerebral blood flow is not increased. The effect can be observed in the ischemic penumbra where rCBV may be increased, in particular with some relative hypertension, but transit time is delayed, and, in actuality, the brain tissue is hypoperfused and the patient is at risk for stroke.

The time course of toxicity in the presented case is also of interest. The PRES process is clearly developing, even when blood pressure is only minimally increased. If endothelial activation and trafficking is developing, areas of reduced perfusion and delayed transit may already exist. Features suggested as "hyperperfusion" on the initial rCBV scan could already represent areas of reduced flow. An important question here is why did hypertension accelerate? This patient had an "unrelated" bone marrow transplant and therefore has an extremely complex immune state. Was there an acceleration of graft-versus-host disease, multiorgan involvement, systemic vasoconstriction and systemic organ hypoperfusion, platelet adherence and endothelin upregulation? The PRES toxicity process tends not to be "isolated hypertension with brain changes" but usually is identified in patients with a complex systemic process.

More confident understanding of the state of brain blood flow in PRES will likely require a better understanding of brain pathologic processes in PRES and quantitative assessment of cerebral blood flow at toxicity.

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