Active Angiogenesis in an Extensive Arteriovenous Vascular Malformation

A Possible Therapeutic Target?

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Vascular malformations result from the aberrant development of vascular elements during embryogenesis and fetal maturation. Despite apparent endothelial quiescence, some vascular malformations can expand rapidly during adolescence or pregnancy, after a surgical procedure, or in response to trauma. The pathogenesis of vascular malformations is not well clarified, but their formation and progression are closely related to angiogenesis, a complicated network that is closely regulated by many angiogenic factors.1

REPORT OF A CASE

A 51-year-old man presented with an arteriovenous malformation in the left side of the trunk and arm (Figure, A). At the age of 20 years he underwent an amputation of his left arm because of incoercible repeated hemorrhagic episodes. Since then, the lesion has progressively grown, and soft, large, circumscribed blue-black tumors that repeatedly bleed have appeared.

Findings from a physical examination revealed a large vascular malformation in his trunk, thrill, and exophytic pediculated mushroomlike outgrowths. The exophytic lesions were extirpated, and findings from a biopsy specimen showed a benign vascular malformation (Figure, B and C). Serum levels of angiogenic factors are summarized in the Table. Vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9 (MMP-9) serum levels (increased ×2), angiopoietin 2 (Ang-2) levels (increased ×10), and Tie-2 (receptor tyrosine kinase-2) levels (increased ×3) were increased in comparison to the control group. Platelet-derived growth factor (PDGF) AB (PDGF-AB) and PDGF-BB levels were decreased (in one-third of the control group).

The patient died of renal and multorgan failure 3 months later while waiting for approval for bevacizumab treatment.

COMMENT

To our knowledge, there are no studies about serum angiogenic profiling in adult patients with vascular malformations. Marler et al2 showed that MMP and basic fibroblast growth factor levels are elevated in the urine of children with hemangiomas and vascular malformations when compared with controls.

Vascular endothelial growth factor, Ang-1, and Ang-2 have been reported as the most potent regulators for neovascularization. In the presence of VEGF, Ang-2 promotes a rapid increase in capillary diameter, remodeling of the basal lamina, and proliferation and migration of endothelial cells and stimulates sprouting of new blood vessels.3

In our patient, we found increased Ang-2 levels, which also occur in some brain arteriovenous malformations.4 We also detected increased levels of Tie-2 soluble receptor. Angiopoietin 2 is predominantly

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expressed in areas undergoing vascular remodeling. This could suggest that there is an abnormal disassembly level between endothelial cells and mesenchymal cells due to an abnormal balance in the Ang-2–Tie-2 system, leading to dilated vessels with insufficient mural cell components.

All capillaries are partially covered by pericytes. The pericyte-deficient mutant microvessels of PDGF-deficient embryos show endothelial cell hyperplasia, hypervascular diameter, abundant microaneurysms, and abnormal endothelial ultrastructure. Pericytes express PDGF receptor β and require PDGF-BB for their recruitment to new vessels in the course of angiogenesis. In our patient, the skin biopsy specimen demonstrated deficiency of mural cells in the newly formed exophytic lesions, in association with strikingly low serum levels of PDGF-AB and PDGF-BB.

Novel medical therapies are needed for active vascular malformations. The presence of an imbalance of angiogenic factors in this patient is in favor of their role in the pathogenesis of at least some vascular malformations. Dedicated studies with a many patients should confirm these findings, to define a therapeutic target in patients with active malformations who may be candidates for an antiangiogenic-specific medical treatment.
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