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## Disseminated Lobular Capillary Angioma Induced by Erythropoietin?

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### *To the Editor:*

We read with interest the article by Vergara et al<sup>1</sup> published recently in your journal. In their letter, they present the case of a 74-year-old man with disseminated lobular capillary angiomas that had appeared over a period of 4 to 5 years. The authors suggest that the "possible trigger for the angiomatous lesions could be the multiple chronic systemic disease presented by the patient." We would like to highlight something that caught our attention. On reporting the medical history of the patient, the authors mention that he was receiving erythropoietin, among other medications, but they did not specify either the duration of treatment or the dose.

Erythropoietin is the main hormone responsible for the regulation, proliferation, differentiation, and survival of erythroid cells. Recent studies have shown that several cytokines and interleukins previously considered as specific to the hematopoietic system, such as granulocyte colony stimulating factor (GCSF), are also able to influence certain endothelial cell functions. Some studies suggest that hematopoiesis stimulating factors are also able to induce an angiogenic response in endothelial cells. This suggests that the growth and survival of endothelial cells may contribute to maintaining the bone marrow microenvironment and hematopoiesis. Erythropoietin has been shown to be able to interact directly with endothelial cells and induce an angiogenic response both in vitro and in vivo and, therefore, to act directly as an angiogenic factor.<sup>2</sup> In adults, the proliferative capacity of endothelial cells is very low compared to that of other cell lines.<sup>2</sup> This might be explain why, despite widespread use

of erythropoietin in adults, drug-induced hemangiomas have not be reported.<sup>3</sup> Recently, a possible association between the use of recombinant human erythropoietin in preterm children and the appearance of both solitary<sup>4</sup> and multiple<sup>3</sup> strawberry angiomas has been published. Both these studies consider a probable causal relationship on the basis of the temporal coincidence between starting treatment and onset of the skin lesions, and the known proliferative effect of erythropoietin on endothelial cells and its ability to induce angiogenesis. The authors of those studies believe that erythropoietin could be a potent in vivo angiogenic factor, able to trigger the development of hemangiomas in preterm neonates.<sup>3,4</sup> Furthermore, in 2003, Lenczowski et al<sup>5</sup> reported the progressive appearance over 5 years of multiple lobular capillary angiomas on the trunk and upper arms of a 25-year old immunocompromised man in treatment with GCSF. The authors attributed the appearance of lesions to use of GCSF on the basis of the progressive onset of lesions and the known stimulatory effect of the agent on endothelial proliferation in an in vivo angiogenic model.<sup>2,5</sup>

In the case presented by Vergara et al,<sup>1</sup> we think it would be interesting to know whether erythropoietin therapy began before the appearance of hemangiomas. If this were the case, we think it would be reasonable to consider a possible causal relationship between erythropoietin and skin lesions, given that there were multiple lesions that appeared progressively and that other similar lesions induced by drugs able to stimulate endothelial proliferation have been published.<sup>5</sup> In addition, erythropoietin has documented proangiogenic effects.<sup>2-4</sup>

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