Response to «Verrucous Hemangioma Versus Microcystic Lymphatic Malformation»

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STo the Editor:

We found the letter titled "Verrucous Hemangioma Versus Microcystic Lymphatic Malformation" by Dr. del Pozo et al[1] interesting because it stimulates a reflection on the particular complexity of vascular malformations.

The characteristics of microcystic lymphatic malformations and verrucous hemangioma—also known as hyperkeratotic vascular malformation—are similar, making them hard to distinguish and the differential diagnosis is complex. For these reasons, some authors have suggested the term lymphovascular malformation to describe these lesions.[2]

Definitive diagnosis of either of the aforementioned entities requires a clinical assessment, histopathologic study, and imaging studies.

From the clinical point of view, microcystic lymphatic malformations present in the form of translucent vesicles resembling frog spawn, often on the head and particularly the neck. Episodes of pain and edema are common, and in 83% of the deep lesions, hypertrophy occurs with visible distortion in 33% of the patients.[3] In contrast, verrucous hemangiomas are usually bluish-red nodules or papules measuring from 0.4 cm to several centimeters across. They tend to be found on the legs. Trauma and superinfections are responsible for progressive transformation towards a verrucous appearance.[4]

At the histopathological level, verrucous hemangiomas have thick vascular walls containing muscle cells, as well as flattened and multilayered endothelial cells, essentially in the papillary dermis, with relatively little involvement of the reticular dermis.[5] Lymphatic malformations have irregular dilated interconnected vessels in the subcutaneous cell tissue. Both lesions can spread to the subcutaneous tissue.[3] The immunohistochemical analysis is usually negative for CD34 in lymphatic lesions[6] but positive in verrucous hemangioma.[7] Thus, when results for D2-40 are not available, CD34 positivity points to verrucous hemangioma. Furthermore, recent studies show that D2-40 has been supplanted as a lymphatic marker by Prox-1 and vascular endothelial growth factor receptor 3, which are more sensitive.[8]

In the magnetic resonance imaging studies, lymphatic malformations are characterized by well delimited multiple cysts, whereas venous vascular malformations have a serpiginous appearance defined by focal or diffuse groups of spaces of variable size separated by septa.[9]

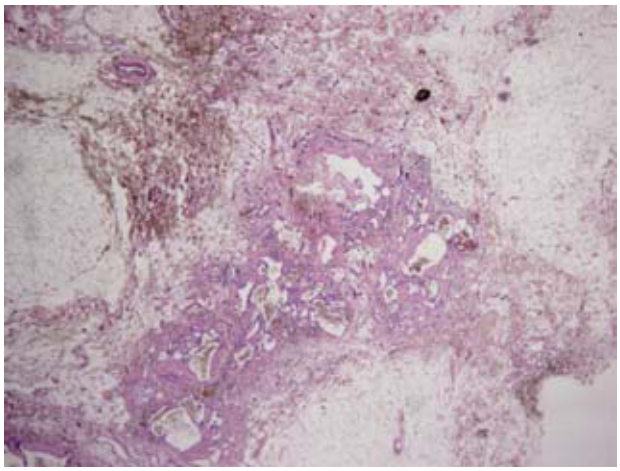

Figure 1. Venous-like dilations in the dermis (hematoxylin-eosin, ×40).

In summary, our patient had bluish-red papules on the abdomen and right leg.[10] These were asymptomatic and not accompanied by hypertrophy of the leg. Histology revealed a hyperkeratotic epidermis with venous-like dilations in the dermis (Figure), which were CD34 positive. The magnetic resonance imaging study was in agreement with the description of venous vascular malformations mentioned in the preceding paragraph. For these reasons, we believe that the lesions should be diagnosed as verrucous hemangioma rather than microcystic lymphatic malformations.

References

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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[1] 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.[2] In adults, the proliferative capacity of endothelial cells is very low compared to that of other cell lines.[2] This might be explain why, despite widespread use of erythropoietin in adults, drug-induced hemangiomas have not be reported.[3] Recently, a possible association between the use of recombinant human erythropoietin in preterm children and the appearance of both solitary[4] and multiple[3] 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.[3,4] Furthermore, in 2003, Lenczowski et al[5] 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.[2,5]

In the case presented by Vergara et al,[1] 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.[5] In addition, erythropoietin has documented proangiogenic effects.[2-4]