Expression of Phosphodiesterase-5 in Lymphatic Malformation Tissue

Lymphatic malformations (LMs) are uncommon and sometimes debilitating congenital vascular anomalies that presumably arise because of developmental dysplasia of the lymphatic network in utero. They comprise primitive lymphatic sacs surrounded by a thickened layer of connective tissue and interspersed muscle fibers. Current treatments for LM are palliative and only partially successful and include compression, surgical resection, laser ablation, and sclerotherapy. A recent report by Swetman and colleagues noted marked reductions in LM size in 3 children after starting treatment with oral sildenafil citrate, an inhibitor of phosphodiesterase isoform 5 (PDE5). The localization of PDE5 in LM tissue and the mechanism of the effect of sildenafil on LM is unknown. To further investigate PDE5 localization within LM tissue, we performed immunohistochemical studies to identify the presence and relative location of PDE5 expression in vascular smooth muscle, vascular endothelium, and lymphatic endothelium.

Methods | Study samples were collected with approval of the Colorado Multiple Institutional Review Board. Fourteen cases of LM (both microcystic and macrocystic forms) were selected at random from all archived specimens submitted to the Children’s Hospital Colorado Department of Pathology between 1995 and 2011, for which either a diagnosis of lymphangioma or LM was assigned. Medical records were reviewed to confirm the clinical diagnosis, and an experienced dermatopathologist (L.P.) verified that the original histologic features (Figure, A) were consistent with LM. Additional sections from each case were obtained for immunohistochemistry to demonstrate the following proteins: CD34, D240, smooth muscle (smooth muscle actin [SMA]), and PDE5. Expression of each protein was assessed by 2 investigators independently (J.S.G. and L.P.).

Results | As expected, vascular endothelium expressed CD34 (Figure, B); lymphatic endothelium expressed D240 but not CD34 (Figure, C); and perivascular smooth muscle expressed SMA (not shown). Expression of PDE5 was demonstrated in vascular smooth muscle adjacent to lymphatic spaces (Figure, D) and interspersed among adipocytes in subcutaneous tissue, but none of the 14 cases demonstrated staining for PDE5 in LM endothelia or in the surrounding connective tissue stroma.

Discussion | Phosphodiesterase-5 is expressed within smooth muscle in a wide variety of tissues, where its primary function is to break down guanosine-3′-5′ cyclic monophosphate (cGMP), which is generated in vascular smooth muscle by the diffusion of nitric oxide from adjacent vascular endothelial cells. Phosphodiesterase-5 inhibitors such as sildenafil inhibit breakdown of cGMP, resulting in smooth muscle relaxation and vascular dilation; high concentrations of PDE5 in pulmonary arteries and the corpus cavernosum are implicated in the pathogenesis of 2 conditions for which sildenafil has gained Food and Drug Administration approval, pulmonary hypertension and erectile dysfunction.

Herein, we demonstrate that within LM tissue, PDE5 expression is localized to perivascular smooth muscle adjacent to lymphatic spaces. A hypothesis for the cause of the clinical effect of sildenafil on LM may be that relaxation of perivascular smooth muscle allows collected lymphatic fluid to empty into the venous system, leading to LM...
decompression. Another possible explanation includes induction of nitric oxide synthase by sildenafil, stimulating further cGMP-mediated vasodilation, permitting lymphatic dilatation and enhanced lymphatic drainage; endothelial nitric oxide synthase has also been shown to mediate lymphangiogenesis. Novel effects of sildenafil on LM tissue should also be considered. A lack of PDE5 expression in LM endothelium in our study suggests that sildenafil is likely to produce decompression of LM via indirect effects on adjacent smooth muscle. We propose that sildenafil may mediate relaxation of perivascular smooth muscle in LM tissue, allowing decompression of dilated lymphatic spaces; additional studies to elucidate specific physiologic effects of sildenafil in LM are warranted.

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Published Online: January 1, 2014.

Author Contributions: Drs Green and Prok had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition of data: Green, Prok.

Analysis and interpretation of data: Green, Prok.

Drafting of the manuscript: Green, Bruckner.

Critical revision of the manuscript for important intellectual content: Prok, Bruckner.

Conflict of Interest Disclosures: None reported.


Multibranched Acquired Periungual Fibrokeratoma

We have encountered a case of multibranched acquired periungual fibrokeratoma (APF).

Report of a Case | A man in the sixth decade of life consulted us for an evaluation of small rodlike nodules at the proximal nail fold on his left fifth finger in May 2012. Six months previously, he noticed a small rodlike nodule, and 3 months later, he noticed another near the first nodule. Because the nodules had progressively enlarged, he sought medical advice. He reported no history of trauma before the onset of

Figure 1. Clinical Presentation of Acquired Periungual Fibrokeratoma

A. At presentation, 2 branching asymptomatic, small, firm, flesh-colored rodlike nodules arise beneath the proximal nail fold. B. At total excision, a third 2-mm small nodule, which branched off the other nodules, was found under the nail fold (arrowhead).