Lasers in Surgery and Medicine

LETTER TO THE EDITOR

Port Wine Birthmark Therapy: A New Direction

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Port wine birthmarks (PWBs) are congenital capillary malformations caused by an activating somatic mutation in GNAQ or its paralog GNA11 [1]. Since the early 1980s, standard treatment of PWBs has consisted of laser therapy, based on the concept of selective photothermolysis [2]. This works by delivery of a millisecond pulse of light that is selectively absorbed by hemoglobin species causing heating, which damages surrounding endothelial cells resulting in clot formation or vessel rupture [3]. In the 1980s, the device initially developed to target vasculature in PWBs was the 577-nm pulsed dye laser (PDL), which eventually was replaced by 585-nm and then 595-nm wavelength devices [2]. In the 1990s, cryogen spray, contact, and air cooling were introduced to protect the epidermis during PDL treatment [2]. Later, other light sources such as the 532-nm neodymium: yttrium aluminum garnet (Nd:YAG)/potassium titanyl phosphate, 755 nm alexandrite and 1064 nm Nd:YAG lasers and intense pulsed light were used [2]. Deeper penetrating wavelengths such as 755 and 1064 nm have less absorption by hemoglobin, require higher energies, and have a greater risk of scarring. Despite improvements over the past four decades, clearance of PWBs has not improved greatly as few patients achieve 100% clearance, and lesion recurrence is common if treatments are stopped [2]. The field needs to consider a new direction, one that combines laser treatment with a pathway-targeted pharmaceutical approach. Now that the genetic underpinnings of the disease are coming into focus, this approach holds great promise.

GNAQ mutation in PWBs may be exclusively present in endothelial cells, although work is ongoing [1]. GNAQ is a heterotrimeric guanine nucleotide-binding protein that can activate various downstream effectors, such as PI3K and MEK, but the involvement of many of these pathways is poorly understood [1]. Arginine-to-glutamine substitution (R183Q), or less commonly, a glutamine-to-leucine substitution (Q209L), leads to activation of GNAQ with resultant capillary overgrowth [1]. In addition, aberrant signaling in downstream effectors (e.g., upregulation of protein phosphatase 2α, diacylglycerol) may be detected in surrounding fibroblasts and pericytes in the stromal tissue [1]. Mutant GNAQ cells may be found in 6%–85% of endothelial cells in the PWB area, and a higher ratio of mutant to wild-type GNAQ cells is associated with increased severity of PWB [1].

What is not known is how the GNAQ mutant endothelial cells are distributed (Figure 1). Do all endothelial cells in the PWB carry the GNAQ mutation or is there only a subset of mutated endothelial cells? If there is a subset, what portion of the cells need to carry the mutation to cause the PWB vessel phenotype? Are there some blood vessels in PWB composed entirely of mutant endothelial cells? Is the distribution similar in all PWBs or does it vary between individuals and possibly even among different areas within a single PWB?

Using PDL, it is virtually impossible to remove all vessels in the PWB area. The light penetrates to approximately 1 mm and there is shielding that occurs from more superficial vessels, diminishing light that reaches deeper vessels—especially with vessels that are tortuous. Both help to make this procedure safer compared to, for example, photodynamic therapy, which, if not performed cautiously, can remove all vessels in a targeted area [4]. When all vessels are removed, necrosis results from ischemia, with a significant incidence of resultant scarring. If achieving long resolution of PWBs requires destruction of all mutant endothelial cells, then treatment by laser alone is almost certainly insufficient. No matter how much we improve our ability to remove the majority of the affected blood vessels, if any mutant endothelial cells remain (including those that may "hide"

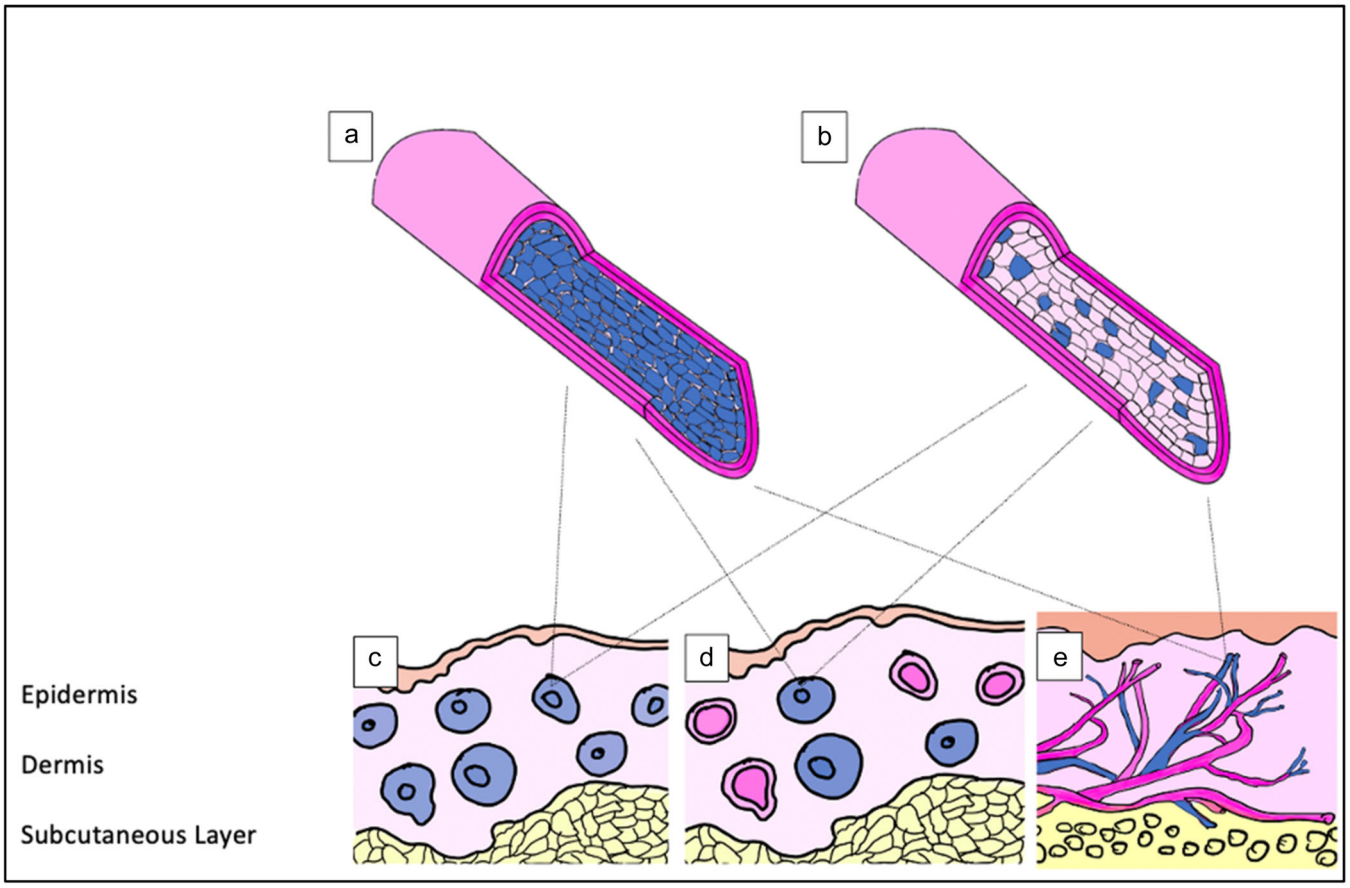

FIGURE 1 | Possibilities of GNAQ mutation distribution. Individual vessels could have all (a) or some (b) mutant endothelial cells. All vessels (c) or some vessels (d) or scattered portions of blood vessels could have mutant endothelial cells (e). (a, b) Blue endothelial cells: Mutant GNAQ; pink endothelial cells: wild-type GNAQ. (c–e) Blue blood vessels: Affected vessels with mutant GNAQ endothelial cells; pink blood vessels: unaffected vessels with wild-type GNAQ endothelial cells.

in healthy-looking vasculature), it seems likely they will continue to proliferate and result in recurrence of the PWB. This hypothesis is consistent with the behavior observed in other vascular anomalies including venous or lymphatic malformations, which are also caused by genetic changes that drive cellular proliferation and growth (commonly PiK3CA and TEK). Procedural treatments for these anomalies are also rarely curative and require serial interventions. In more refractory cases, therapy to inhibit downstream pathway proliferation can be effectively combined to improve outcomes [5].

Similar to treatment for other vascular anomalies, it is possible that combining adjuvant medical therapy with lasers or similar devices could decrease the continued molecular activity of surviving mutated endothelial cells, without resultant necrosis, improving outcomes and reducing the clinical recurrence of PWBs. Adjuvants for PWB laser treatment have been proposed in the past including imiquimod and rapamycin. While some reports demonstrated a degree of utility, neither medication dramatically increased response in a majority of patients. Of note, these treatments are antiangiogenic and unlikely GNAQ pathway-specific. The downstream activated pathways from GNAQ/GNA11 variants are an area of continued intense investigation, and targeted treatments with genetic or small-molecule inhibitors may eventually become available. Gene therapy could potentially cure PWB, but this is not a simple loss-of-function disease. One would have to replace the mutant gene or repair it. A more likely scenario would be near continuous use of a drug that suppresses or silences key pathways downstream of mutant GNAQ. At this time, candidate medications are being evaluated, although, to the authors' knowledge, a clear option has not yet been elucidated. However, there is hope. For example, Huang et al. identified the increased expression of angiopoietin-2 (Angpt2) as one of the downstream factors leading to vessel dilation in GNAQ mutant endothelial cells (R183Q) [6]. After using YM-254890, a GNAQ inhibitor, gene expression of ANGPT2 decreased and vessel dilation was reversed. In addition, using a cellular GNAQ model, Zecchin et al. recently demonstrated aberrant ligand-activated intracellular calcium signaling, which could be knocked down with targeted small interfering RNAs designed to silence the variant allele, with correction of molecular calcium signaling [7].

PWB therapy has had some advancements over the past four decades; however, to achieve consistent and complete removal of these lesions a new approach is required. With the collaboration of laser scientists, chemists, molecular biologists, geneticists, and other experts, we can work together to identify pathways to determine drug targets and ultimately cure PWB.

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