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·防治实践·

光动力疗法与口服维A酸序贯治疗增殖性疣状白斑1例报道及文献回顾

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【摘要】　目的　探讨光动力疗法（photodynamic therapy，PDT）联合口服维A酸序贯治疗增殖性疣状白斑（proliferative verrucous leukoplakia，PVL）的应用，为临床提供参考。**方法**　报道1例PDT与口服维A酸序贯治疗PVL，结合文献对PVL的特点、诊断和治疗及PDT和维A酸在口腔白斑病中的应用进行回顾性分析。**结果**　1例临床诊断为PVL的患者，在行4次光动力治疗后1个月，患者口腔病损大部分消除，但是在治疗后2个月复发。随后患者接受口服维A酸治疗，剂量为10 mg/次，1次/d，睡前口服，连续用药2周后口腔病损显著减少；之后调整剂量至10 mg/次，2次/d，持续治疗3个月至病损完全消退；其后采用周期性给药方案继续予以维A酸10 mg/次，2次/d（用药3周停药1周为1个周期），共进行6个周期，停药后随访5个月未复发。文献回顾表明，PVL是一种口腔潜在恶性疾患（oral potentially malignant disorders，OPMD），具有多灶性、易复发和高恶变率的特点，目前尚无理想的治疗手段。PDT具有选择性强、微创不留疤痕、低毒、可重复操作等优点，已被推荐作为PVL的一线疗法，但由于目前光敏剂局部敷浴有效性、靶向性、渗透深度等的局限，PDT治疗PVL的疗效仍不确切。有少量文献报道口服维A酸治疗口腔白斑病，但PDT联合维A酸口服治疗PVL的文献未见报道。**结论**　PDT联合口服维A酸序惯治疗PVL是一种有效的方法。

【关键词】　增殖性疣状白斑；　口腔白斑病；　口腔潜在恶性疾患；　光动力疗法；　维A酸；　光敏剂；　激光
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Sequential treatment of proliferative verrucous leukoplakia with photodynamic therapy and orally administered retinoic acid: a case report and literature review

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【Abstract】　Objective　To explore the application of photodynamic therapy (PDT) combined with orally administered retinoic acid in the treatment of proliferative verrucous leukoplakia (PVL) and provide a reference for clinical practice. **Methods**　A case of sequential treatment of PVL with PDT and orally administered retinoic acid was reported. The characteristics, diagnosis, treatment of PVL, and the application of PDT and retinoic acid in oral leukoplakia were retrospectively analyzed based on the literature. **Results**　After four PDT sessions, a majority of the oral lesions were eliminated in a patient clinically diagnosed with PVL, but the lesions recurred two months later. Subsequently, the patient was treated with retinoic acid at a dose of 10 mg, once a day, orally before bedtime. After continuous treatment for 2 weeks, the oral lesions were significantly reduced. The dose was then adjusted to 10 mg, twice a day, and the treatment was extended for 3 months until the lesions completely disappeared. Following this, a periodic regimen was adopted to continue the administration of retinoic acid at a dose of 10 mg, twice a day (3 weeks of treat-

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ment followed by 1 week of drug withdrawal as one cycle), for a total of 6 cycles. No recurrence was observed during the 5-month follow-up after drug withdrawal. A review of the literature indicates that PVL is an oral potentially malignant disorder (OPMD) characterized by multifocality, high recurrence rate, and high malignant transformation rate. Currently, there is no ideal treatment method for PVL. PDT is advantageous because of its low toxicity. Furthermore, it is strongly selective, minimally invasive, and patients experience no scarring. Thus, it has been recommended as the first-line therapy for PVL. However, due to the limitations of local application of photosensitizers in terms of effectiveness, targeting, and penetration depth, the efficacy of PDT in treating PVL remains uncertain. There are a few reports on the treatment of oral leukoplakia with retinoic acid given by oral, but no literature has reported the combination of PDT and retinoic acid given by oral for PVL. **Conclusion**　The sequential combination of PDT and oral retinoic acid therapy is an effective treatment for PVL.

【Key words】 proliferative verrucous leukoplakia;　oral leukoplakia;　oral potentially malignant disorders;　photodynamic therapy;　retinoic acid;　photosensitizer;　laser

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增殖性疣状白斑(proliferative verrucous leukoplakia,PVL)是一种进行性、持续性、多中心疣状增生的白斑病,具有多灶性、易复发和恶变率高的特点[1]。PVL病因不明,传统的手术切除方法导致严重的组织缺损和功能障碍,并且复发率高,至今尚无理想的治疗手段[2]。光动力治疗(photodynamic therapy,PDT)是一种由光敏剂介导的光化学、光生物学反应,从而对病变细胞产生杀伤作用的治疗方式。该疗法具有选择性强、微创不留疤痕、低毒、可重复操作等优点,目前被推荐作为PVL的一线疗法[3],但由于目前光敏剂局部敷浴有效性、靶向性、渗透深度等的局限以及PVL本身易复发的特性,PDT治疗PVL的疗效仍不确切;有少量文献报道口服维A酸治疗口腔白斑病,但复发率高且副作用大[4]。本文报道1例PDT与口服维A酸序贯治疗PVL,并就PVL的特点、治疗及PDT和维A酸在口腔白斑病中的应用进行相关文献回顾。

1　病例资料

1.1　一般资料

患者,男,58岁。主诉:左颊白色斑块1年。患者1年前无明显诱因出现左颊黏膜中部约直径5 mm白色斑块,稍高起于黏膜,无疼痛,未予以重视。1年来白色斑块范围呈进行性增大蔓延至口角处,遂就诊当地医院,当地医院病理活检结果示:左颊鳞状上皮中度不典型增生,上皮下结缔组织内可有慢性炎症细胞浸润。为求进一步治疗,遂来本院就诊。起病以来患者精神、饮食、睡眠一般,大小便可。否认全身系统病史和传染病史,否认药物或食物过敏史,无家族史。咀嚼槟榔10年余,约10颗/d,已戒除10年余;吸烟30年余,约20支/d。

1.2　临床检查

口腔黏膜检查:张口度约2指,左颊黏膜见大面积白色斑块,移行至左下后牙相应颊龈沟及颊侧牙龈,大小约4 cm×4 cm,表面粗糙,呈疣状稍高起于黏膜,质稍韧,无明显触痛,边界尚清;其后份约1 cm×1 cm病损较前份明显高起于黏膜;双侧颊黏膜可见苍白改变,扪及条索感(图1a)。余口腔黏膜未见明显异常。

口腔检查:全口口腔卫生不良,牙结石(++),下前牙牙龈萎缩,牙根暴露约1 mm。35、36颊侧牙尖稍锐利。

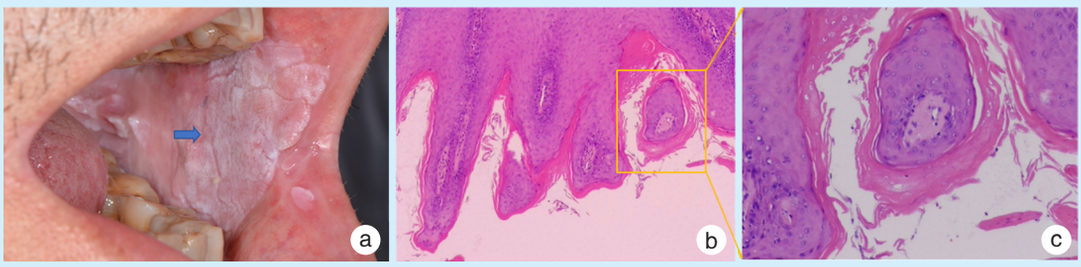
1.3　相关辅助检查

1.3.1　实验室检查　血常规、肝肾功能、血糖、凝血功能、输血前四项无明显异常。

1.3.2　心电图检查　窦性心律,正常心电图。

1.3.3　影像学检查　CBCT示全口牙槽骨呈轻度水平吸收。

1.3.4　组织病理学检查　为明确诊断,将患者外院病理切片于本院会诊。病理诊断:鳞状上皮乳头状瘤样增生,伴过度角化及角化不全,伴中度非典型增生,皮下少许淋巴细胞浸润,符合疣状白斑(图1b、1c)。



a: large white patch on the left buccal mucosa, extending to the corresponding buccal gingival sulcus and buccal gingiva of left lower posterior teeth, about 4 cm × 4 cm in size, with a rough surface, slightly raised above the mucosa in a verrucous manner (arrow). b & c: pathological results: squamous epithelial papillomatous hyperplasia with hyperkeratosis and incomplete keratinization, with moderate atypical hyperplasia; a few lymphocytes infiltrate subcutaneously, consistent with verrucous leukoplakia(scale bar, 50 μm and 10 μm)

Figure 1　Intraoral photograph and pathological results in a patient with proliferative verrucous leukoplakia of the left buccal mucosa

图1　左颊黏膜增殖性疣状白斑患者口内照及病理结果

1.4　初步诊断

根据患者临床表现和组织病理学检查结果，诊断为疣状白斑，同时伴有口腔黏膜下纤维性变和慢性牙周炎。

1.5　光动力治疗与结果

疣状白斑目前无理想的治疗手段，PDT被推荐为一线疗法。在与患者充分沟通，综合考虑患者意愿与病损特点后，嘱患者戒烟，调磨35、36锐利牙尖，行全口牙周基础治疗后，分次试行光动力治疗。本研究遵循医学伦理要求，术前告知患者光动力治疗不良反应及疗效、疗程，患者签署知情同意书。

2023年8月9日首次行光动力治疗，斯康杜尼局部麻醉下采用Nd：YAG钕激光（LightWalker ST-E，M002-6A/2，Fotona激光公司，斯洛文尼亚）去除病损表面过厚的角质层，光敏剂20%盐酸氨酮戊酸外用散（上海复旦张江生物医药股份有限公司）局部湿敷2 h，使用输出激光波长为635 nm的LD600-C型半导体激光治疗仪（武汉亚格光电技术股份有限公司）照射20 min，光斑直径1.0 cm，功率密度85 mW/cm^2，能量密度100 J/cm^2，使用相同参数前后共进行了4次光动力治疗（图2），治疗从前往后，从上到下，每2~3周进行1次，每次治疗后予以康复新液10 mL含漱3次/d、裸花紫珠片0.5 g，3次/d等抗炎、镇痛和促进愈合处理。4次光动力治疗后1个月（2023年11月8日）复诊，患者疣状白斑病损大部分消除。建议患者继续光动力治疗以彻底消除白斑，患者对当时状况表示满意，要求终止光动力治疗。光动力治疗后2个月（2023年12月13日）复诊发现，原已通过光动力治疗消除的疣状白斑延咬合线出现复发（图3a）。

1.6　最终诊断

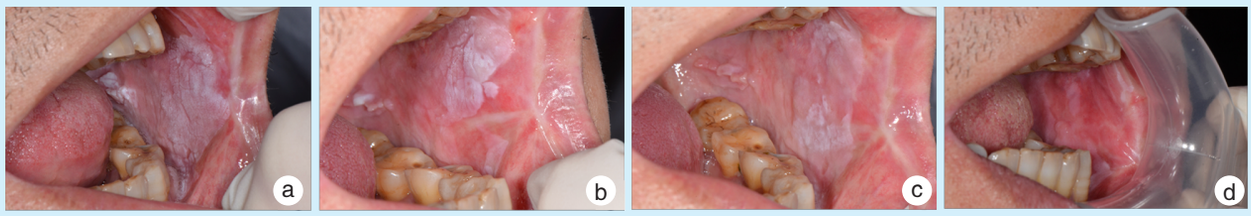
根据患者临床表现和组织病理学检查结果以及易复发病史，最终诊断为增殖性疣状白斑，同时伴有口腔黏膜下纤维性变和慢性牙周炎。

1.7　口服维A酸治疗与结果

患者因光动力治疗后疼痛等不良反应而不愿继续接受光动力治疗。进一步检查发现患者26颊尖边缘稍锐利，调磨26尖锐颊尖边缘，在与患者充分沟通并遵循患者意愿情况下，予以口服维A酸治疗。首先每晚睡前口服维A酸10 mg/次，连续2周，患者疣状白斑呈减少趋势（图3b），随后维A酸10 mg/次，2次/d，口服3个月，患者复发的疣状白斑消失（图3c），继续予以维A酸10 mg/次，2次/d，口服3周停1周循环6个周期，患者疣状白斑未复发（图3d），遂停药，随访5个月（2025年2月26日）患者疣状白斑未复发（图3e）。患者口服维A酸期间未出现头痛、脱发和唇炎等不良反应，每1~2个月复诊时检查血常规、肝功能和血脂：血常规无明显异常；口服维A酸10 mg/次，2次/d，1个月后出现甘油三酯增高，予以血脂康胶囊0.6 g/次，2次/d降脂治疗；口服维A酸10 mg/次，2次/d，3个月后出现肝功能异常，予以谷胱甘肽0.2 g/次，3次/d护肝治疗，降脂和护肝治疗持续至停止服用维A酸，期间患者血脂和肝功能恢复正常。

2　讨　论

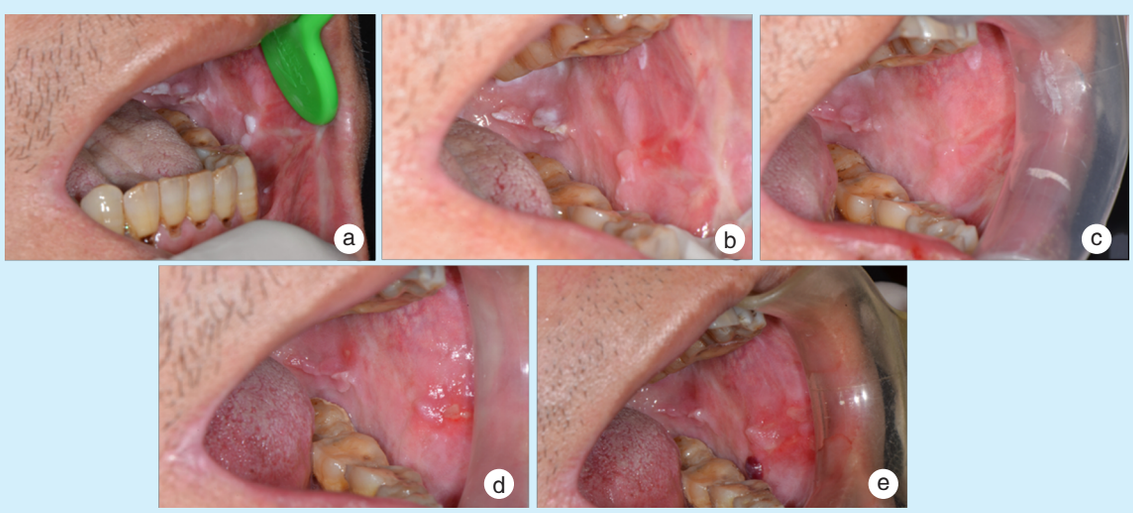
PVL作为口腔白斑病的一种独特类型，于1985



Under local anesthesia, the excessive keratin layer on the surface of the verrucous leukoplakia lesions on the left cheek of the patient was removed using an Nd: YAG laser. Then, 20% ALA was applied locally for 2 hours, followed by irradiation with a 635 nm semiconductor laser for 20 minutes. Four sessions of photodynamic therapy (PDT) were conducted. a: two weeks after the first PDT (August 23, 2023), the verrucous leukoplakia in the left corner of the mouth disappeared. b: three weeks after the second PDT (September 18, 2023), the verrucous leukoplakia in the lower anterior part of the left cheek disappeared. c: three weeks after the third PDT (October 11, 2023), the verrucous leukoplakia on the left cheek further reduced. d: four weeks after the fourth PDT (November 8, 2023), most of the verrucous leukoplakia on the left cheek was eliminated

Figure 2　The condition of verrucous leukoplakia lesions in a patient with proliferative verrucous leukoplakia of the left buccal mucosa after four photodynamic therapy sessions

图2　左颊黏膜增殖性疣状白斑患者4次光动力治疗后疣状白斑病损愈合情况



a: 2 months after four photodynamic therapies, white plaques were recurred on the mucosa near the left cheek bite line, rising from the mucosal surface. b: retinoic acid treatment (10 mg orally at bedtime for 2 weeks). c: retinoic acid treatment (10 mg twice a day for 3 months). d: six cycles of retinoic acid 10 mg twice a day for 3 weeks, followed by 1 week of drug withdrawal. e: after drug withdrawal for 5 months, the patient's verrucous leukoplakia did not recur

Figure 3　The timeline of retinoic acid treatment for a patient with proliferative verrucous leukoplakia of the left buccal mucosa

图3　左颊黏膜增殖性疣状白斑患者口服维A酸治疗疣状白斑过程

年被Hansen等[5]首次描述。该病的白斑病损呈疣状，并具有病损面积和病损区域进行性增加以及术后易复发的特点[6]。该病好发于50岁以上的女性，最常见的受累部位为牙龈，其次为颊黏膜和舌侧缘。PVL病因不明，镜下改变为角化不良、锐利侧缘、角化不全、角蛋白增加，典型特征为疣状结构并伴有较少细胞异型性的波纹状过度正角化或不全角化[7]。PVL至今仍无公认临床诊断标准，研究发现，对最终确诊为PVL的患者，其初诊时满足Cerero-Lapiedra等[8-9]提出的诊断标准[主要标准：①两处以上病损；②疣状；③逐渐扩大；④有复发；⑤组织学表现：单纯上皮过角化到疣状增生或疣状癌或口腔鳞状细胞癌。次要标准：①病损面积至少3 cm^2；②女性；③不吸烟；④进展超5年。满足3个主要标准(有⑤)或2个主要标准(有⑤)+2个次要标准则可诊断为PVL]的比例为60%。本文中病例病损累及左颊和左下后牙龈两处病损；疣状；逐渐扩大；光动力治疗后复发；病理检查符合

疣状白斑;病损面积大于3 cm^2,因此可以诊断为PVL。

PVL是口腔潜在恶性疾病之一。一项系统的文献回顾和荟萃分析报告PVL癌变率高达44.5%[10],另一项文献回顾报告PVL癌变率为49.5%,而所有口腔潜在恶性疾病的总癌变率为7.9%[11]。由于PVL病损的进行性和广泛性,传统的手术切除方法导致严重的组织缺损和功能障碍,并且复发率高,目前尚无理想的治疗方法[12]。PDT是一种联合利用光敏剂、光和氧分子,通过光动力效应进行疾病治疗的一种医学新技术,是一种新型的非侵入性疗法[13]。该疗法在口腔癌前病变甚至癌变中均取得良好效果[14],被推荐作为口腔疣状增生的一线疗法。其治疗白斑的原理是经光敏剂处理过的白斑病变部位在特定波长的光照下,通过一系列光反应,使组织内的氧分子转化为活性氧,导致光敏剂富集的异常增生活跃的细胞发生凋亡、自噬或坏死等不可逆的损伤[15]。该疗法具有选择性强、微创不留疤痕、低毒、可重复操作不影响后续治疗等优点,已广泛应用于口腔白斑病的治疗[16]。光敏剂现已发展到第三代。用于口腔白斑病的第一代光敏剂Photofrin是一种全身性光敏剂[17],因其化学纯度低、半衰期长、在健康的组织中消除缓慢、副作用较大、缺乏特异性、激发波长在可见光区域和难以穿透深层组织等缺点而被第二代光敏剂取代。用于口腔白斑病的第二代光敏剂有5-氨基酮戊酸(5-aminolevulinic acid,ALA)(Han等[18]研究发现ALA-PDT治疗口腔白斑病的总体缓解率为86.2%,其中包括55.2%的完全缓解和31.0%的部分缓解)、甲苯胺蓝(对15处口腔白斑病变使用2.5%的甲苯胺蓝溶液,并结合630 nm波长的LED光源进行PDT,结果6处病变完全缓解,7处病变部分缓解[19])和亚甲蓝[口腔白斑细胞MSK-Leuk1通过亚甲蓝光动力治疗后,其基质金属蛋白酶-9(matrix metalloproteinase-9,MMP-9)的基因表达显著下调]等[20]。第三代光敏剂为靶向光敏剂,尚处于基础研究阶段[21]。目前PDT治疗口腔白斑病最常用的光敏剂为20% ALA,给药方式为局部湿敷或局部注射[22]。由于ALA对组织的渗透深度仅1~2 mm[23],因此对角化程度较高的白斑病损进行PDT前预处理有利于提高疗效。微针、激光等预处理方法被证实明显提高PDT治疗口腔白斑病的效果[24-25]。PDT治疗口腔白斑病常用的光源有激光,如半导体激光、氦-氖激光等[26-27],另外,LED光也常被选择为PDT治疗光源[28],这些光源的治疗波长为(630±5)nm[29]。照光时间(s)=能量密度(J/cm^2)/功率密度(W/cm^2)[30],或者通过公式光子积分通量=4×(功率密度×照光时间)/(π×光斑直径^2)[31]进行确定。研究表明,经过完整疗程的PDT治疗可显著降低白斑恶变的风险,尤其对于有恶变危险因素的患者[32]。

维A酸是维生素A的衍生物,可通过调节上皮细胞增生、分化及较明显的角质溶解等代谢作用,防止上皮过度角化而用于治疗口腔白斑病[33]。由于口腔处于湿润环境,局部涂搽维A酸易被唾液稀释冲刷而影响疗效,且局部涂搽只能作用于白斑表面角化层,临床观察发现停止局部涂搽后白斑很容易复发。全身使用维A酸可维持正常基因如表皮生长因子(epidermal growth factor,EGF)、转化生长因子-α(transforming growth factor -α, TGF-α)、p53等的表达,调节细胞生长和分化,诱导细胞凋亡,促进分裂细胞成熟,并作为抗氧化剂减少自由基,降低DNA突变及酶功能改变的概率。Hong等[4]研究显示,口服异维A酸1~2 mg/kg/d治疗口腔白斑病3个月,临床总反应率为67%,而对照组为10%,但是在异维A酸停用2~3个月复发率高达56%,而且大剂量异维A酸所导致的唇炎、高脂血症等副作用严重。该团队基于这两个问题展开进一步研究,纳入70例口腔白斑患者,最开始口服异维A酸,剂量是1.5 mg/kg/d,进行3个月诱导。后期将有临床反应及疾病稳定的患者随机贯序给予0.5 mg/kg/d的异维A酸或30 mg/d的胡萝卜素,治疗9个月,结果显示维持期异维A酸组复发率仅为8%,而胡萝卜素组为55%,说明长期使用小剂量异维A酸可以预防口腔白斑的进展与复发,且副作用相对较小[34]。国内有荟萃分析显示维A酸联合塞来昔布治疗口腔白斑,可提高治疗有效率[35]。

本病例通过临床表现和组织病理学明确了PVL的诊断,其病损累及大面积左颊黏膜,并移行至左下颊龈沟和牙龈,如果手术完整切除将需要植皮,手术创伤大,面容和口腔功能都将受到影响,且PVL容易复发,复发后二次治疗比较棘手,因此需要寻找更合适的治疗方式。光动力治疗作为PVL的一线推荐治疗方法,优势明显,副作用较少。在与患者充分沟通,综合考虑患者意愿与病损特点,去除局部刺激因素(嘱患者戒烟,调磨35、36锐利牙尖,行全口牙周基础治疗)后,分次进行光动力治疗。该病例病损总面积较大,单个有效

输出功率光斑无法完全覆盖，且单次治疗创面过大不利于愈合，因此分次进行治疗，治疗时光斑覆盖病损及其周围正常黏膜3~5 mm的区域，每次治疗区域与之前有一定的重叠。由于该病损疣状增生较厚，在ALA局部湿敷前采用激光去除病损过厚角化层有助于促进光敏剂的组织渗透，从而增强光效应，提高临床治愈率。通过4次PDT，患者病损大部分消除，且无明显瘢痕形成，获得满意的临床疗效。但由于PVL易复发的特性，患者PVL 2个月后复发。此时患者因光动力治疗后疼痛等不良反应而不愿接受继续光动力治疗，在与患者充分沟通并遵循患者意愿情况下，予以口服维A酸治疗。由于该药首次大剂量服用会出现头痛等副作用，因此先予以10 mg/d诱导治疗2周，患者耐受后予以10 mg/次，2次/d，缓解治疗3个月，患者复发病损完全消除，继续予以10 mg/次，2次/d，口服3周停1周循环巩固治疗6个周期后停药，随访5个月患者疣状白斑未复发。由于目前光敏剂局部敷浴有效性、靶向性、渗透深度等的局限，单纯PDT治疗PVL仍有较高的复发率；口服维A酸可能出现头痛、脱发、唇炎、白细胞减少、肝功能异常和高血脂等不良反应和毒副作用，临床上不推荐长期大剂量使用[36]。本研究PVL患者采用PDT与小剂量口服维A酸序贯治疗，病损完全消除，且停药至今未复发，为PVL的有效治疗提供了新的思路。

【Author contributions】 Yu HQ designed the study, wrote the article. Yang ZN and He YL collected and analyzed the data. Wu YF designed the study, guided and critically reviewed the article structures. All authors read and approved the final manuscript as submitted.

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