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·综述·

糜烂型口腔扁平苔藓复发因素管理策略研究进展

李佳[1,2]，　李晓英[2]，　王诗萌[2]，　刘帆[1,3]

1.四川大学华西护理学院，四川 成都(610041)；　2.口腔疾病研究国家重点实验室 国家口腔疾病临床医学研究中心 四川大学华西口腔医院口腔黏膜病科，四川 成都(610041)；　3.口腔疾病研究国家重点实验室 国家口腔疾病临床医学研究中心 四川大学华西口腔医院护理部，四川 成都(610041)

【摘要】 口腔扁平苔藓(oral lichen planus，OLP)是一种常见的口腔黏膜慢性炎性疾病，属于口腔黏膜潜在恶性疾患。临床主要表现为双侧对称分布的珠光白色网状条纹，其亚型糜烂型口腔扁平苔藓(erosive oral lichen planus，EOLP)常伴随局部充血、糜烂及明显疼痛等症状，影响患者的进食和吞咽。口腔卫生环境因素、生活及饮食因素、心理因素、药物因素及系统性疾病因素均会导致EOLP病损迁延不愈或易复发，使其具有更高的癌变潜能，因此，预防EOLP复发及癌变的措施倍受关注。在EOLP的临床综合治疗策略中，应重视对其影响因素进行全方位的管理，从维护良好的口腔卫生环境、饮食疗法及健康生活习惯、心理疗法、全身/局部治疗指导、积极随访和治疗系统性疾病等策略出发，为患者提供多学科、多角度的口腔综合管理措施，以期减少复发、预防癌变并提高患者的生活质量。

【关键词】 口腔扁平苔藓；　糜烂型口腔扁平苔藓；　影响因素；　口腔疾病；　口腔健康；　口腔护理；　口腔管理

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Research progress on the management strategies of recurrent factors of erosive oral lichen planus

LI Jia[1,2], LI Xiaoying[2], WANG Shimeng[2], LIU Fan[1,3]. 1. West China School of Nursing, Sichuan University, Chengdu 610041, China; 2. State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases & Department of Oral Medicine, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China; 3. State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases & Department of Nursing, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China

Corresponding author: LIU Fan, Email: samotj@163.com

【Abstract】 Oral lichen planus (OLP) is a common chronic inflammatory disease and potentially malignant disorder of the oral mucosa. Clinical manifestations include bilateral symmetrical distributions of pearly white reticular streaks, and its subtype erosive oral lichen planus (EOLP) is often accompanied by local congestion, erosion, obvious pain, and other symptoms, which affects the patient′s eating and swallowing. Oral hygiene and environmental factors, lifestyle and dietary factors, psychological factors, medication factors, and systemic disease factors all contribute to the recurrence of EOLP lesions, which increases the cancer potential of this condition. Therefore, measures to prevent the recurrence and cancerous transformation of EOLP have attracted much attention. In the clinical treatment strategy for EOLP, attention should be given to its influencing factors for comprehensive management. Patients should be provided with multidisciplinary and multifaceted oral comprehensive management measures across the following strategies: maintaining a good

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【作者简介】 李佳，护师，硕士，Email：hxkqlj@outlook.com

【通信作者】 刘帆，主任护师，博士，Email：samotj@163.com

oral hygienic environment, dietary therapies and healthy living habits, psychological therapies, systemic/local therapeutic guidance, and active follow-up and treatment of systemic diseases. This article provides multidisciplinary and multifaceted comprehensive oral management measures for patients with the goal of cancer prevention, minimizing recurrence, and improving the quality of life of patients.

【Key words】 oral lichen planus; erosive oral lichen planus; influencing factor; oral diseases; oral health; oral care; oral management

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口腔扁平苔藓(oral lichen planus,OLP)是一种病因尚不明确的口腔黏膜慢性炎性疾病,好发于中老年女性,患者自觉口腔烧灼、疼痛[1],OLP属于口腔潜在恶性疾患的一种,癌变率在0.71%~1.43%,且分型为糜烂型口腔扁平苔藓(erosive oral lichen planus,EOLP)具有更高的恶变概率,文献报道为5.98%[2],约占总数的32.46%[3-4],虽然EOLP的病因尚不清楚,但其诱发和恶化因素多样,常与口腔卫生环境、生活及饮食习惯、压力性生活事件等危险因素密切相关,且其常导致病情迁延而影响患者生活质量。因此,消除疼痛症状、治愈糜烂型病损和降低恶变风险对该疾病全方位的有效管理显得尤为重要[1]。因此本文将从口腔卫生环境因素、生活及饮食习惯、药物因素、心理因素、全身系统性疾病等EOLP,发生发展中可被医护人员所控的因素进行总结,以期对疾病进行有成效的管理。

1　EOLP发展影响因素

1.1　口腔卫生环境因素

口腔微生物是促进炎症发展和EOLP复发且持续进展的重要因素。Wang等[5]、Pouralibaba等[6]通过对EOLP患者的唾液研究发现,EOLP患者的唾液细菌数量和微生物多样性明显低于健康人,进一步机制研究显示IL-17是其重要促炎因子,可通过增强T细胞介导的免疫反应和诱导趋化因子,对占据口腔菌群中主要生态位的微生物群(优势菌群)起到保护作用,导致炎症加重,这提示口腔卫生下降诱发的口腔微生物菌群失衡是促进EOLP进展的重要因素之一,其机制可能是局部免疫应答和炎症反应的共同作用[7]。口腔微生物在OLP发展中具有重要的作用,研究表明,与健康人相比,OLP患者口腔中嗜血杆菌属、梭杆菌属、卟啉单胞菌属、罗氏菌属、放线菌属显著增加,并可导致局部免疫微环境的紊乱[8]。另一方面,EOLP患者因糜烂病损伴随的疼痛、出血等症状,影响了患者口腔正常的卫生维护,导致牙菌斑和结石沉积,微生物数量增加及微生物菌群构成的失衡[9]。

1.2　生活及饮食习惯

EOLP的复发和发展与食用辛辣刺激食物、致敏食物等饮食习惯或者接触致敏物、吸烟和饮酒等生活习惯密切相关。首先,辛辣食物如大蒜等会导致口腔黏膜化学性灼伤,引发炎症反应[10],而炎症反应中$CD8^+$ T细胞是EOLP发生反复糜烂的重要因素[11]。另外,有研究证实:饮食中的致敏因素也会引起EOLP。Chen等[12]研究发现,EOLP与口腔过敏综合征(oral allergy syndrome,OAS)相关,63%的OLP患者与OAS相关触发因素如柑橘、芥末、香料接触过后可诱发接触性过敏反应导致糜烂性病损出现,在主动避免触发因素的OLP患者中,89%的患者口腔症状改善。另一方面,接触致敏物也会诱发EOLP,最近一项病案报告表明,一位患者在长期佩戴含镍的嵌入式耳环后,这类金属致敏物将反应性淋巴细胞诱导至口腔黏膜内从而诱发EOLP发生[13]。除此之外,吸烟和饮酒等不良生活习惯也会导致EOLP持续的发展以及复发。例如:吸烟可增强OLP病变中TLR-2和CD34的表达,从而促进炎症反应[14];而酒精可通过增加上皮细胞的通透性,促进致癌物渗透,进而加速OLP的进展。微量元素也可能与EOLP复发和发展密切相关,例如:有研究表明体内维生素D水平不足会加重EOLP而诱发癌变[15]。

1.3　心理因素

焦虑、压力、抑郁等心理因素也是促进EOLP

复发和发展的重要因素。有研究发现，61.9%的患者在发病前均有焦虑症状，并且使用抗焦虑药物和心理治疗可有效缓解EOLP[16-17]。同时，有学者发现压力是EOLP急性发作的主要因素[12]。另外，EOLP患者相比无症状患者更容易发生抑郁，而心理上的焦虑和抑郁也会导致患者对保持口腔卫生的兴趣丧失，影响口腔健康进而加重EOLP的进程[18]形成恶性循环。除此之外，压力、焦虑、抑郁还会引起睡眠障碍，而睡眠是免疫过程的重要调节器，睡眠障碍会促进促炎因子表达从而导致OLP复发，反过来，这也会加重患者的抑郁症和焦虑症[19-20]。另一方面，EOLP患者口内症状会严重影响其饮食或社交活动等，与OLP相比，EOLP患者心理应激更为明显[21]，这提示心理评估同样是EOLP诊疗策略中的关键环节。值得关注的是，有研究表明EOLP患者中大多数为中年女性[16]，提示医护人员应该更加关注女性EOLP患者的心理健康状态。

1.4　药物因素

局部糖皮质激素是EOLP治疗的一线药物[1]，但Tsushima等[22]发现在长期外用糖皮质激素治疗期间，约17.5%的患者口内会发生念珠菌感染。这是由于EOLP病损部位糜烂，黏膜完整性和口腔微环境被破坏，而糖皮质激素治疗EOLP会导致免疫抑制，为念珠菌的增殖创造理想的微环境，使得EOLP患者易受到念珠菌感染。而EOLP和念珠菌的重叠感染还会进一步加重EOLP症状，并通过产生亚硝胺或乙醛等致癌物质促进恶性转化[23]。另外，伴有丙型肝炎病毒（hepatitis C virus，HCV）感染的EOLP患者在使用干扰素治疗肝炎时会加重EOLP病损严重程度[24]。抗骨吸收药物如双膦酸盐，也会加重EOLP，造成糜烂面愈合的延迟[25-26]。这说明，对于EOLP患者在使用药物时需要更加谨慎。一些药物例如ACE抑制剂、非甾体抗炎药、磺脲类药物等被认为与OLP相关，但目前尚缺乏强力的证据支持系统性药物与EOLP的直接关联。

1.5　系统性疾病因素

众多的系统性疾病在EOLP的发生发展中扮演着重要的角色。研究发现，在伴有糖尿病的OLP患者中，其高血糖会加重细菌刺激和局部炎症从而诱发EOLP[27]，而且糖尿病引起的唾液流量减少会导致口腔菌群失衡和黏膜上皮细胞修复能力下降，进一步加重EOLP的临床症状[28]。另一方面，EOLP可能影响糖尿病患者的胰岛素敏感性，Zhao等[29]在研究中发现，在不改变患者原有控糖方案的前提下，局部糖皮质激素封闭治疗EOLP能改善患者的血糖控制情况，同时，口内糜烂面积与糖化血红蛋白的变化呈正相关。另有研究发现，幽门螺杆菌感染导致的胃内炎性细胞因子也可改变口腔黏膜局部微环境而加重局部炎症[30]。Li等[31]研究发现幽门螺杆菌的感染不是OLP发生的始动因素，但可促进EOLP的复发，提示幽门螺杆菌可能是EOLP复发的致病菌之一。此外，研究发现，HCV可直接作用于口腔黏膜上皮细胞，从而诱发EOLP，且HCV患者与EOLP的相关性显著大于非糜烂型口腔扁平苔藓[24，32]。

2　EOLP的口腔管理策略

2.1　维护良好口腔卫生环境

良好的口腔卫生环境对防止或减少EOLP复发，阻止其持续进展具有不可忽视的作用。刷牙是保持口腔卫生的基础措施。一项Meta分析指出，电动牙刷去除牙菌斑的功效比手动牙刷更为出色，使用电动牙刷后牙菌斑指数（plaque index for long-term care）降低35%～67%，因此对于EOLP患者而言，电动牙刷可能是更好的选择[33]。同时，有研究发现，牙菌斑作为牙周病的始发因素可能会阻止OLP牙龈病变愈合，进一步进展从而导致EOLP[34]，减少牙菌斑会提高牙龈的健康水平并改善牙龈微生物的细菌菌落构成，减轻牙周炎性反应和减少机会性感染，能够避免EOLP发生或延缓其发展进程[34-35]。同时，EOLP患者做好口腔卫生指导和牙周洁治等可提高糖皮质激素药物的疗效[9]。在一项针对老年女性的研究中表明，含有香芹酮成分的牙膏可导致其出现口腔屏障受损，因此，老年人应尽量避免长期使用含有此类成分的牙膏[36]。

2.2　饮食疗法及健康生活习惯

在饮食方面，健康的饮食方案（如富含新鲜水果和蔬菜、避免辛辣刺激食物等）因可提高DNA的适应性和固有的修复机制，被建议认为是一种治疗OLP的方法[37]。而对于长期嚼食槟榔、酗酒、吸烟的EOLP患者，须充分告知其戒掉上述不良生活习惯。对于过敏体质的患者，避免接触过敏源尤为重要[12]。此外，微量营养素是维持口腔黏膜正常功能的重要因素之一。研究发现，补充维生素B_{12}与免疫调节药物联合使用可有效降低OLP患者自身抗体水平、疼痛和糜烂程度[38]，提示患者日常

需饮食均衡。研究发现，每日两次口服微量元素锌可显著减轻患者的烧灼感及病损面积[39]。部分EOLP患者可伴有血清抗胃壁细胞抗体阳性，可导致患有维生素B_{12}缺乏症或巨幼红细胞性贫血，从而表现出贫血症状，部分老年患者因其骨髓造血能力略有下降，日常代谢水平下降引起进食减少，亦会导致贫血发生，进一步提示患者多进食富含铁元素的食物[40]。

2.3　心理疗法

基于生物-心理-社会医学概念，可采用心身方法来管理与心理因素相关的皮肤及黏膜疾病，因此治疗EOLP患者时应考虑其个性特征中的尽责性和外向性及个体的心理问题[41]。值得注意的是，患者对口腔病损美观的担忧可能会使治疗依从性和有效性复杂化，进食的痛苦也会影响患者营养的摄入进而加重患者的精神障碍，这凸显了多学科管理方法的必要性，包括口腔护理、疼痛管理、心理支持和对潜在恶性转化的定期监测[42]。有研究表明，一些口腔健康相关量表（如：汉密尔顿焦虑量表和口腔健康影响程度量表14）在一定程度上能反映EOLP患者的病损严重程度和口腔健康相关生活质量水平[43-44]。正念疗法也被广泛应用到OLP的管理之中，能有效干预基于口腔病损的心身疾病[45]。研究表明瑜伽是缓解压力和焦虑的一种重要非药物治疗方式，能够有效降低压力、炎症水平及唾液粘性[46]，因此提倡患者将瑜伽作为一种非药物治疗方式应用到EOLP的管理中。

2.4　全身治疗指导

全身治疗指导在EOLP的管理过程中至关重要。对使用糖皮质激素有恐惧或焦虑的患者，可使用OLP局部类固醇恐惧量表[47]，以帮助医护人员识别和理解患者，从而提高用药的依从性和效果。免疫抑制剂如沙利度胺、羟氯喹等，在EOLP的治疗中起重要作用，激素治疗反应不佳或无法耐受激素者，可酌情使用[1]。近年来，中药治疗EOLP也被广泛应用到临床中来替代传统药物，其中，雷公藤多苷具有特殊的抗炎及免疫抑制作用，可作为对糖皮质激素抵抗的OLP患者的替代药物[48]。另外，为预防EOLP复发，使用具有较高安全性的Janus激酶（Janus kinase，JAK）抑制剂用以EOLP的治疗，现今也得到了推广[49]，然而具体何种JAK抑制剂对于EOLP的治疗最有效还需进一步证明[50]。

2.5　局部治疗指导

局部用药也是EOLP治疗的重要手段，如局部注射糖皮质激素，一方面增加了病损处的药物浓度，另一方面，避免了糖皮质激素全身用药带来的不良反应。局部应用糖皮质激素时也会受年龄增长的影响，随着年龄每增加一年，用药后病损部位不完全缓解的可能性就会增加7.9%，这可能与老年人用药依从性较低和口腔黏膜衰弱有关[51]。药物的应用方式也会影响局部用药的疗效。为避免外用药物的无靶向性、易脱落、效用低等缺点，最新研究表明氯倍他索贴剂可避免上述缺点、降低药物副作用并提高安全性[52]。最近一项病例报道将重组牛碱性成纤维细胞生长因子凝胶局部治疗儿童EOLP患者后病损愈合且无不良反应[53]。有研究将长期发展且对于常规药物治疗没有反应或治疗后复发的EOLP称为难治性OLP（refractory oral lichen planus，ROLP）[54]，PDE-4抑制剂阿普斯特用于局部湿敷可治疗ROLP[55]。对于ROLP患者可局部使用生物制剂如抗TNF-α、抗IL-2、抗IL-17药物等[56]。

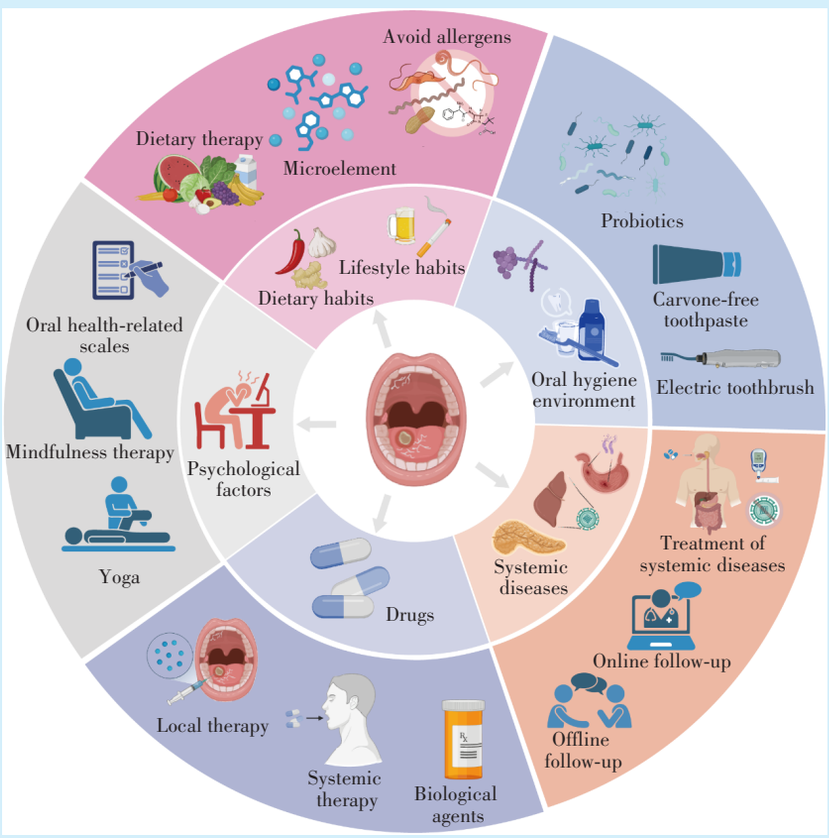
2.6　积极随访和治疗系统性疾病

由于EOLP是一种慢性疾病且存在恶变可能，患者更需要对病情进行长期的管理，因此，积极随访尤为重要。医护人员可通过皮肤镜或唾液等无创手段进行监控[57]。值得注意的是，有研究表明，当观察到EOLP病损局部发红时，应当给予组织活检术以明确病损性质[3]。此外，在随访期间，医护人员也应当密切关注EOLP患者系统性疾病的情况。一方面，系统性疾病可能会影响EOLP病损进展，如：高脂血症与EOLP严重程度呈正相关，因此患者随访时应当检测血脂情况[58]；自身免疫性疾病如乳糜泻、桥本氏甲状腺炎、甲状腺功能减退症等可显著增加OLP风险[59]。因此，应将早期排查自身免疫性疾病纳入EOLP的管理中。另一方面，EOLP也可能会引起系统性疾病，因而医护人员应当定期检测EOLP患者的相应指标。对于部分高龄EOLP患者，无法定期线下就诊，医护人员可通过利用新式通讯方式进行远程随访。

3　小　结

综上，EOLP的发生发展与口腔卫生环境、饮食生活习惯、精神心理因素、药物因素、系统性疾病因素等密切相关。基于上述因素，除给予常规用药指导外，还需对EOLP患者进行多学科、多角

度管理，因此，本文提出了口腔环境卫生护理、健康生活方式及饮食疗法、心理疗法、全身/局部治疗指导及预防潜在恶性转化的管理手段（图1）。但EOLP复发因素管理策略的研究较少，在未来，需要针对上述手段开展更高质量的临床研究。



The recurrence of erosive oral lichen planus is related to oral hygiene and environmental factors, lifestyle and dietary factors, psychological factors, medication factors, and systemic factors. This article reviews these five major factors and summarizes the corresponding management measures including improvement of oral hygiene, promoting healthy diet and lifestyle habits, psychological therapy, systemic/local treatment guidance, and active follow-up and treatment of systemic diseases

Figure 1　Factors for recurrence of erosive oral lichen planus and management strategies

图1　糜烂型口腔扁平苔藓的复发因素及其管理策略

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