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过敏性紫癜性肾炎肾组织中 KIM-1 的表达与临床意义 *

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摘要 目的：探讨过敏性紫癜性肾炎肾组织中肾损伤分子 1(kidney injury molecule 1，KIM-1)的表达与临床意义。**方法：**选择 2015 年 4 月到 2018 年 1 月在我院诊治的过敏性紫癜性肾炎患者 150 例作为研究对象，采用免疫组化法检测患者肾组织中 KIM-1 表达，采用半定量评分系统进行肾脏病理损害评分，并对二者进行相关性分析。**结果：**肾炎组织与肾旁组织的 KIM-1 相对表达量分别为(9.28± 1.38)和(2.74± 1.30)，肾炎组织中 KIM-1 的表达显著高于肾旁组织(P=0.000)；肾炎组织的毛细血管外肾小球活动、系膜增殖、内皮增殖、肾间质炎症、肾小球慢性化、肾小管间质慢性化指数评分均显著高于肾旁组织(P<0.05)；肾组织 KIM-1 表达量与肾小球慢性化指数、肾间质炎症指数、肾小管间质慢性化指数均呈显著正相关性(P<0.05)。**结论：**过敏性紫癜性肾炎组织中 KIM-1 呈高表达，可能作为评估肾脏病理病变程度的参考指标。

关键词：人肾损伤分子 1；过敏性紫癜性肾炎；肾炎组织；相关性

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Expression and Clinical Significance of KIM-1 in the Henoch Schonlein Purpura Nephritis*

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ABSTRACT Objective: To investigate the expression and clinical significance of kidney injury molecule 1 (KIM-1) in the renal tissue of Henoch-Schonlein purpura nephritis (HSPN). **Methods:** 150 patients with HSPN who were treated in our hospital from April 2015 to January 2018 were selected as the research objects. The expression of KIM-1 in the renal tissue was detected by immunohistochemical method. The renal pathological damage score was evaluated by semi-quantitative scoring system. **Results:** The relative expression of KIM-1 in the nephritic tissue and paranephritic tissue were (9.28± 1.38) and (2.74± 1.30), respectively. The expression of KIM-1 in the nephritic tissue was significantly higher than that in the paranephritic tissue (P=0.000). The scores of extracapillary glomerular activity, mesangial proliferation, endothelial proliferation, interstitial inflammation, glomerular chronicity and tubulointerstitial chronicity index in the nephritic tissue were significantly higher than those in the paranephritic tissue (P<0.05). The expression of KIM-1 was positively correlated with the glomerular chronic index, renal interstitial inflammatory index and tubulointerstitial chronic index (P<0.05). **Conclusion:** KIM-1 is highly expressed in the HSPN tissue, which may serve as a reference index for evaluating the degree of renal pathological changes.

Key words: Kidney injury molecule 1; Henoch Schonlein purpura nephritis; Renal tissue; Correlation

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前言

过敏性紫癜是一种累及全身小血管的炎症性疾病[1,2]，过敏性紫癜性肾炎具体是指过敏性紫癜引起的肾实质损害，在临床上主要表现为血尿和/或蛋白尿，病理特点表现为肾脏的小血管壁上有免疫球蛋白 A 为主的免疫复合物沉积[3,4]。成人过敏性紫癜性肾炎以男性为主，预后相对比较差，病情发展为慢性肾脏病的几率超过 40%[5]。过敏性紫癜性肾炎的病因与相关发病机制还不明确，病原体包括丙型肝炎病毒、腺病毒、乙型肝炎病毒、溶血性链球等，也涉及到基因易感性、补体激活细胞因子、家族聚集、自身抗体等多个方面[6,7]。T 细胞免疫球蛋白粘蛋白(T-cell immunoglobulin mucin，TIM) 家族编码基因位于 5 号染色体，是一种Ⅰ型跨膜糖蛋白，TIM 家族具有共同的结构，包括 N 端免疫球蛋白可变区、单跨膜域、糖基化粘蛋白域和 C 端胞

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质域等[8,9]。

人肾损伤分子 1(Kidney injury molecule 1,KIM-1)为 TIM 家族的主要成员，包含 359 个氨基酸,KIM-1 的细胞外可变区参与调节细胞之间的相互作用,也具有提供细胞信号的功能[10]。KIM-1 在正常肾脏中呈现微量表达状况,而在急性肾损伤肾脏中表达显著升高,可急性肾损伤早期诊断和肾功能预后的敏感指标。KIM-1 在过敏性紫癜性肾炎发展过程中可能发挥不同的生物学作用[11],但其具体分子机制仍不清楚。本研究主要探讨了过敏性紫癜性肾炎组织中 KIM-1 的表达与临床意义，以评估患者的病情与指导治疗。现将结果总结报道如下。

1 资料与方法

1.1 研究对象

选择 2015 年 4 月到 2018 年 1 月在我院诊治的过敏性紫癜性肾炎患者 150 例作为研究对象,纳入标准:符合过敏性紫癜性肾炎的诊断标准;病理检查提示以 IgA 为主的免疫复合物在系膜区沉积;血尿;伴或者不伴水肿;年龄(18-60)岁;未经临床治疗。排除标准:继发性过敏性紫癜性肾炎患者;妊娠与哺乳期妇女。其中,男 100 例,女 50 例;年龄最小 19 岁,最大 56 岁,平均年龄(43.33± 2.48)岁;平均体重指数为(22.18± 2.84)kg/m^2;平均病程为(2.81± 0.28)年。所有患者均签署知情同意书,且本研究已获得我院医学伦理委员会批准。

1.2 试验方法

1.2.1 免疫组化法检测肾组织中 KIM-1 的表达 取肾炎组的肾炎组织与肾旁组织样本,制作成石蜡切片,厚度为(4-5)μm,置于 60℃-70℃烤片机上烘烤(20-30)min。常规脱蜡、抗原修复,滴加 3%过氧化氢溶液,孵育 15 min,滴加小鼠抗人 KIM-1 单克隆抗体,4℃孵育过夜,以 PBS 代替一抗,滴加二抗,室温孵育 20 min，滴加新配制的 3,3- 二氨基联苯胺盐酸盐显色液(DAB),苏木素复染 30s,脱水后采用二甲苯固定,用中性树胶封片,镜下观察。用显微镜拍摄 400 倍视野图像,每个样本各取 10 个不同随机视野,半定量分析 KIM-1 的表达情况。

1.2.2 肾脏病理试验 采用半定量评分系统进行肾脏病理损害评分,每张组织切片均取 10 个不同视野,记录肾脏病理(毛细血管外肾小球活动指数、系膜增殖指数、内皮增殖指数、肾间质炎症指数、肾小球慢性化指数、肾小管间质慢性化指数)评分。

1.3 检测指标

(1)肾炎组织和肾旁组织 KIM-1 表达;(2)肾炎组织和肾旁组织肾脏病理评分,毛细血管外肾小球活动指数、系膜增殖指数、内皮增殖指数、肾间质炎症指数、肾小球慢性化指数、肾小管间质慢性化指数;(3)相关性分析:分析肾组织 KIM-1 表达量与肾脏病理指标的相关性。

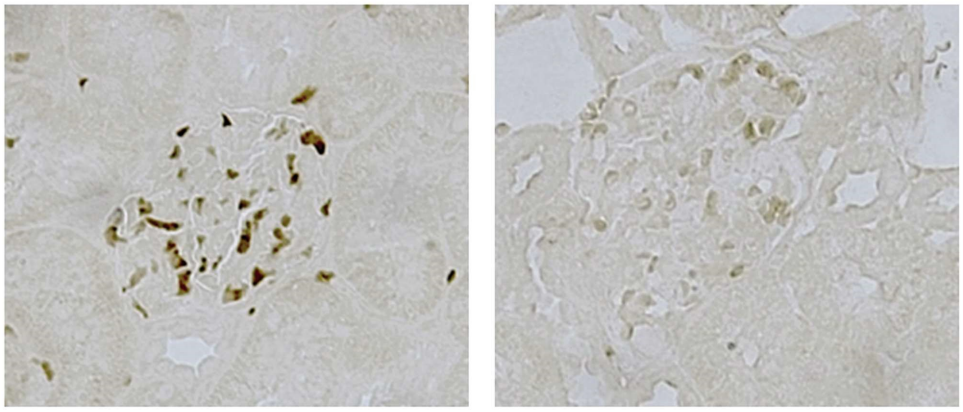
1.4 统计学方法

应用 SPSS20.00 软件对数据进行统计分析,计量数据(肾炎组织和肾旁组织 KIM-1 表达情况,肾脏病理评分)用均数± 标准差($\bar{x}$± s)表示,组间比较采用配对 t 检验;相关性分析采用 Spearman 相关分析,检验水准为α=0.05。

2 结果

2.1 肾炎组织与肾旁组织 KIM-1 表达的对比

肾炎组织与肾旁组织的 KIM-1 相对表达量分别为(9.28± 1.38)和(2.74± 1.30),肾炎组织 KIM-1 表达显著高于肾旁组织(t=12.482,P=0.000)。



A B

图 1 KIM-1 在肾炎组织与肾旁组织中的表达

Fig.1 The expression of KIM-1 in nephritis and para renal tissues

注:A:KIM-1 在肾炎组织中的表达;B:KIM-1 在肾旁组织中的表达。

Note: A: Expression of KIM-1 in nephritic tissue; B: Expression of KIM-1 in para renal tissue.

2.2 肾炎组织与肾旁组织病理评分对比

肾炎组织的各项肾脏病理评分包括毛细血管外肾小球活动指数、系膜增殖指数、内皮增殖指数、肾间质炎症指数、肾小球慢性化指数、肾小管间质慢性化指数均显著高于肾旁组织(P<0.05),见表 1。

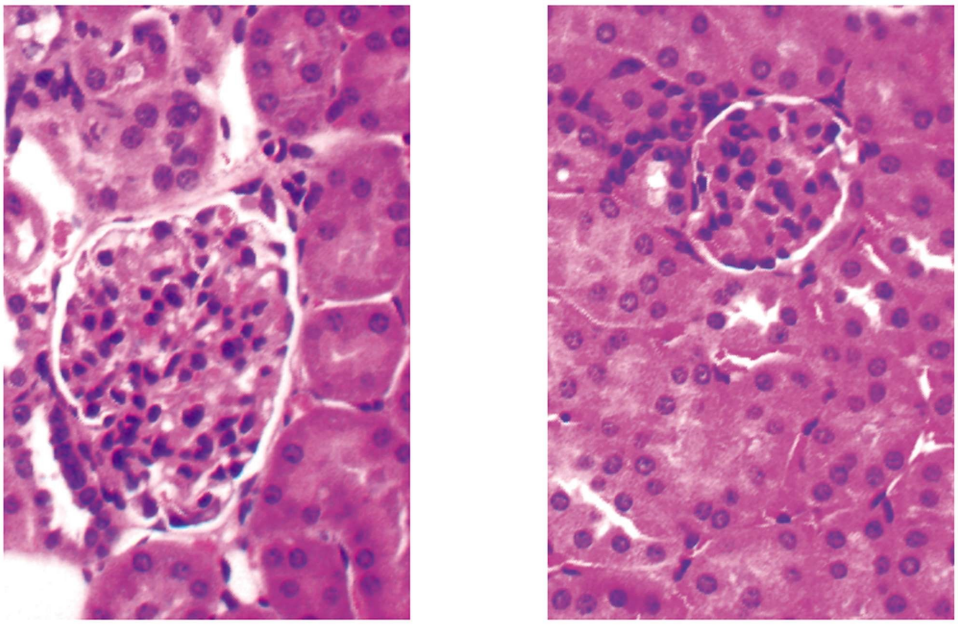
2.3 KIM-1 表达与肾组织病理评分的相关性分析

肾组织 KIM-1 表达量与肾脏病理指标 (肾间质炎症指数、肾小球慢性化指数、肾小管间质慢性化指数)均呈显著正相关性(P<0.05),见表 2。

表 1 过敏性紫癜性肾炎组织和肾旁组织患者的病理评分对比(分，$\bar{x}\pm s$)

Table 1 Comparison of the pathological scores of nephritis tissue and para renal tissue in patients with allergic purpuric nephritis (score, $\bar{x}\pm s$)

Sample	n	Glomeru-lonephritis pellet activity index	Mesangial proliferation index	Endothelial proliferation index	Renal interstitial inflammation index	Glomerular chronicity index	Renal tubulointerstitial chronicity index
Nephritis tissue	150	3.22± 0.45	3.32± 0.22	2.98± 0.41	3.29± 0.56	3.67± 0.47	3.61± 0.55
Para renal tissue	150	1.87± 0.63	2.10± 0.63	2.00± 0.72	2.78± 0.61	2.81± 0.56	2.81± 0.44
t		7.409	5.355	4.294	3.884	6.793	5.014
P		0.002	0.010	0.017	0.023	0.008	0.019



C D

图 2 肾炎组织和肾旁组织 HE 染色表现(× 400)

Fig.2 HE staining of nephritis and para renal tissues (× 400)

注：C:肾炎组织；D:肾旁组织。

Note: C: nephritic tissue; D: para renal tissue.

表 2 过敏性紫癜性肾炎患者肾组织 KIM-1 的表达与肾脏病理评分的相关性(n=150)

Table 2 Correlation between KIM-1 expression in the renal tissues and the renal pathological parameters in patients with allergic purpuric nephritis (n=150)

Index	r	*P*
Glomerulonephritis pellet activity index	0.092	0.553
Mesangial proliferation index	0.087	0.671
Endothelial proliferation index	0.133	0.365
Renal interstitial inflammation index	0.533	0.000
Glomerular chronicity index	0.419	0.002
Renal tubulointerstitial chronicity index	0.482	0.000

3 讨论

过敏性紫癜是一种以小血管炎性反应为主要病理改变的全身性血管炎综合征，可有一个或多个器官损害，病情常反复迁延[12-14]。过敏性紫癜性肾炎是影响过敏性紫癜预后的主要因素之一，是过敏性紫癜最严重的并发症。过敏性紫癜性肾炎的确切的病因及发病机制至今虽尚未完全明确。感染、毒物和药物等可能是重要病因[15-17]。在肾功能衰竭患者和许多肾功能衰竭动物模型中，KIM-1 表达量与疾病的严重性、治疗预后有较好的相关性[18,19]。KIM-1 作为一种磷酯酰丝氨酸受体，能够介导肾小管上皮细胞吞噬凋亡小体，抑制损伤引起的免疫反应[20]。但血清 KIM-1 在反映肾损伤方面存在一点的缺陷，其浓度差

异不能很好地反映肾脏病理的变化,机体的各个环节可影响血清中的 KIM-1 浓度[21]。本研究显示肾炎组织 KIM-1 相对表达显著高于肾旁组织。肾小管上皮细胞损伤后极性丧失,KIM-1 可直接释放入肾间质;肾损伤引起肾脏微血管内皮细胞肌动蛋白等细胞骨架破坏,使微血管通透性增加;肾小管上皮细胞损伤引起跨上皮细胞通透性升高,肾小管内的 KIM-1 可回漏到肾间质[22,23]。肾脏病理仍然是各种肾脏病诊断及评估肾脏损伤情况的主要标准,本研究显示肾炎组织的肾脏病理评分均显著高于肾旁组织。但有时病理检查所取的肾组织有时不能代表肾脏的整体损伤情况,在评估肾脏损伤病情的特异性和敏感性还有待进一步提高。

KIM-1 能促进肾间质炎症和肾间质纤维化,并能通过分泌趋化因子调节炎症细胞的免疫反应[24,25]。有研究显示在局灶节段肾小球硬化、肾移植急慢性排斥、糖尿病肾病、高血压肾损害 IgA 肾病、膜性肾病患者中,肾脏 KIM-1 的表达显著升高,KIM-1 主要表达在肾间质炎症、纤维化周围的肾小管上皮细胞等[26-28]。本研究结果显示过敏性紫癜性肾炎患者的肾组织 KIM-1 表达量与临床病理指标有显著正相关性。有研究表明 KIM- 还可通过诱导肾间质炎细胞浸润,从而促进慢性肾脏病的进展[29-31]。随着肾炎组织病情的加重,肾小管间质化加重,肾小球间质纤维化,炎细胞侵润逐渐增加,肾小管萎缩加重至完全萎缩,KIM-1 表达量降低。总之,过敏性紫癜性肾炎组织中 KIM-1 呈高表达,可能作为评估肾脏病理病变程度的参考指标。但本研究也具有一些局限性,其为描述性研究,KIM-1 在过敏性紫癜性肾炎的作用和具体机制还需要进行深入分析。

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