

抗MDA5抗体阳性皮炎合并快速进展性 间质性肺病的影响因素分析

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【摘要】 目的 探究抗黑色素瘤分化相关基因5(melanoma differentiation-associated gene 5, MDA5)抗体阳性皮炎患者合并快速进展性间质性肺病(rapidly progressive interstitial lung disease, RPILD)的情况和影响因素分析。方法 选取四川大学华西医院2018年1月-2021年9月确诊的抗MDA5抗体阳性皮炎患者,收集一般资料和临床资料,将患者分为合并RPILD组和未合并RPILD两组,筛选出可能影响抗MDA5抗体阳性皮炎患者合并RPILD的因素,并进行二元logistic回归分析。结果 在纳入的145例抗MDA5抗体阳性皮炎患者中,共有32人(22.07%)合并RPILD,余113人(77.93%)则均为非RPILD患者。二元logistic回归分析结果显示,乳酸脱氢酶 ≥ 370 IU/L(与“ < 370 IU/L”相比,比值比=4.066,95%可信区间:1.616~10.230)、癌胚抗原 ≥ 5 ng/mL(与“ < 5 ng/mL”相比,比值比=6.070,95%可信区间:2.013~18.303)是抗MDA5抗体阳性皮炎患者合并RPILD的危险因素($P < 0.05$)。结论 建议对乳酸脱氢酶 ≥ 370 IU/L和癌胚抗原 ≥ 5 ng/mL的患者密切关注其胸部高分辨率CT和肺功能变化,如发现有肺部病变迅速进展,需要加强本病的治疗,以改善患者的预后。

【关键词】 抗MDA5抗体阳性皮炎 间质性肺病 快速进展性间质性肺病 影响因素

Risk Factors of Rapidly Progressive Interstitial Lung Disease in Patients With Anti-Melanoma Differentiation-Associated Gene 5 Antibody-Positive Dermatomyositis HAN Yuan-yuan¹, JIANG Ting¹, ZHANG Ze-hao¹, LI Wen¹, JIANG Yun-di¹, LU Chu-chu¹, FEI Yu¹, CHEN Bo^{2△}. 1. West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu 610041, China; 2. Department of Rheumatology and Immunology, West China Hospital, Sichuan University, Chengdu 610041, China

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【Abstract】 **Objective** To investigate the conditions of patients with anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive dermatomyositis combined with rapidly progressive interstitial lung disease (RPILD), and to analyze the risk factors. **Methods** A total of 145 patients diagnosed with anti-MDA5 antibody-positive dermatomyositis at West China Hospital, Sichuan University between January 2018 and September 2021 were selected, and their general and clinical data were collected. The patients were divided into two groups, a RPILD group of patients with comorbid RPILD and a non-RPILD group of those who did not have comorbid RPILD. Factors that might affect whether patients with anti-MDA5 antibody-positive dermatomyositis also had comorbid RPILD were screened out and binary logistic regression analysis was performed. **Results** Among the 145 patients with anti-MDA5 antibody-positive dermatomyositis, 32 (22.07%) patients had comorbid RPILD, while the remaining 113 (77.93%) did not have comorbid RPILD. Binary logistic regression analysis showed that lactate dehydrogenase ≥ 370 IU/L (compared with < 370 IU/L, OR=4.066, 95% CI: 1.616-10.230) and carcinoembryo antigen ≥ 5 ng/mL (compared with < 5 ng/mL, OR=6.070, 95% CI: 2.013-18.303) were risk factors for comorbid RPILD in patients with anti-MDA5 antibody-positive dermatomyositis ($\beta > 0$, OR > 1 , $P < 0.05$). **Conclusion** It is recommended that close attention be given to changes in high-resolution chest CT and pulmonary functions in patients with lactate dehydrogenase ≥ 370 IU/L and carcinoembryo antigen ≥ 5 ng/mL. If rapid progression of lung disease is detected, it is necessary to strengthen the treatment of the lung disease, thereby improving the prognosis of patients.

【Key words】 Anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis
Interstitial lung disease Rapidly progressive interstitial lung disease Risk factors

皮炎是一类免疫介导性肌损伤特征疾病,主要累及四肢近端骨骼肌,同时伴有皮肤损害^[1]。间质性肺病(interstitial disease, ILD)是皮炎的常见并发症,也是导致皮炎患者死亡的重要原因。当合并快速进展性间质性肺病(rapidly progressive interstitial lung disease,

RPILD)时,患者常因急剧进展的ILD出现呼吸衰竭,从而导致死亡^[2],所以对患者及早识别和治疗是改善预后的关键。近年研究表明,皮炎患者体内存在某些肌炎特异性抗体,与皮炎独特的临床表现及疾病活动相关^[2],其中有关抗黑色素瘤分化相关基因5(melanoma differentiation associated gene 5, MDA5)抗体的研究^[3]提示该抗体的存在

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与无肌病性皮炎、Gottron征、关节炎、发生ILD风险高,以及死亡率较高的RPILD有关。基于以往研究结果,本研究通过对抗MDA5抗体阳性的皮炎患者进行分析,研究影响该类患者合并RPILD的危险因素,有助于对患者进行早期疾病风险评估,尽早调整治疗措施,以改善患者预后。

1 对象和方法

1.1 研究对象和资料

本研究为单中心回顾性研究,样本来自四川大学华西医院风湿免疫科和呼吸与危重症医学科于2018年1月-2021年9月确诊抗MDA5抗体阳性皮炎的患者,共纳入148例患者,经过数据整理,其中有3例患者数据缺失较为严重,最终纳入145例患者。研究内容涵盖患者一般资料(性别、年龄、吸烟情况)和临床资料(合并感染、慢性病、肌无力、呼吸困难、Ro52抗体、MDA5抗体、ANA抗体、高分辨率CT(high resolution CT, HRCT)评分、中性粒细胞/淋巴细胞比值、肌酸激酶、乳酸脱氢酶、癌胚抗原、降钙素原、C反应蛋白、D-二聚体)。本研究经四川大学华西医院生物医学伦理委员会批准(2022年审1359号)。

1.2 纳入与排除标准

纳入标准如下:①符合1997年特发性炎性肌病分级标准;②病程少于3个月。

排除标准包括:①年龄小于18岁;②诊断后1年内合并恶性肿瘤;③无空腹血糖数据;④合并其他严重疾病。

ILD诊断标准:胸部高分辨率CT所见的肺间质改变伴肺功能异常。RPILD诊断标准:从出现肺部症状到呼吸困难症状在3个月内进行性加重,伴低氧血症和放射学上的肺间质病变显著加重^[4]。所有患者参照2017年欧洲风湿病联盟/美国风湿病学会分类标准^[5]确诊为皮炎且用酶联免疫吸附测定或免疫印迹法检测抗MDA5抗体阳性^[6]。

1.3 统计学方法

采用两独立样本 t 检验或 χ^2 检验比较RPILD组和非RPILD组一般资料与临床资料的差异,将可能与RPILD相关的变量纳入二元logistic回归分析。 $\alpha_{双侧}=0.05$ 。

2 结果

2.1 基本情况

共纳入抗MDA5抗体阳性皮炎患者148例,3例数据缺失严重,有效数据145例,有效率为97.97%。其中女性患者101例(69.66%),男性患者44例(30.34%),平均年

龄为(49.39±11.23)岁。纳入的145例患者中,共有32人(22.07%)合并RPILD,余113人(77.93%)则均为非RPILD患者。

2.2 与RPILD相关的一般和临床资料分析

为探究抗MDA5抗体阳性皮炎患者合并RPILD的影响因素,采用 t 检验或 χ^2 检验进行组间差异性分析,筛选出可能与合并RPILD相关的因素,结果如表1所示,合并感染、肌无力、HRCT评分、中性粒细胞/淋巴细胞比值 ≥ 4 、乳酸脱氢酶 ≥ 370 IU/L、癌胚抗原 ≥ 5 ng/mL、C反应蛋白 ≥ 5 mg/L和RPILD均相关($P < 0.05$)。

2.3 RPILD相关的二元logistic回归分析

以是否发生RPILD为因变量(0=否,1=是),将可能与合并RPILD相关的变量:乳酸脱氢酶、中性粒细胞与淋巴细胞比值、癌胚抗原、C反应蛋白和肌无力等五个因素作为自变量纳入二元logistic回归分析。结果如表2所示,乳酸脱氢酶(与“ < 370 IU/L”相比,“ ≥ 370 IU/L”, $OR=4.066$,95% $CI: 1.616 \sim 10.230$)、癌胚抗原(与“ < 5 ng/mL”相比,“ ≥ 5 ng/mL”, $OR=6.070$,95% $CI: 2.013 \sim 18.303$)与RPILD相关,且差异均有统计学意义($\beta > 0$, $OR > 1$, $P < 0.05$)。

3 讨论

抗MDA5抗体阳性皮炎是一种罕见的自身免疫性疾病,主要在东亚地区有报道^[7]。抗MDA5抗体阳性皮炎患者常合并多种并发症,如皮肤溃疡、皮疹、纵膈气肿、技工手、关节炎等^[8-9],而在诸多并发症中,预后最差的并发症为ILD,ILD以进行性加重的呼吸困难、低氧血症、限制性通气功能障碍伴弥散功能降低以及影像学的双肺部慢性病变为特征。部分出现ILD的抗MDA5抗体阳性皮炎患者可进一步出现RPILD,由于RPILD治疗困难,进展迅速,导致预后极差,患者最终多死于呼吸衰竭。有研究表明^[10],抗MDA5抗体阳性皮炎患者合并RPILD在随访的一年内病死率高达71.4%,因此对于容易出现RPILD的抗MDA5抗体阳性皮炎患者的早期识别尤为重要。

本研究共纳入145例抗MDA5抗体阳性皮炎患者,并对其第一次入院时的临床指标和随访3个月内RPILD的发生情况进行分析,其中共有32例(22.07%)患者出现RPILD。本研究发现,在RPILD患者与非RPILD患者的一般和临床资料分析比较中,合并感染、ILD、肌无力、HRCT评分、中性粒细胞/淋巴细胞比值、乳酸脱氢酶、癌胚抗原、C反应蛋白均可能为抗MDA5抗体阳性皮炎患者出现RPILD的相关因素。合并感染病例数量不

表 1 RPILD与非RPILD患者的一般和临床资料分析

Table 1 General and clinical data analysis of RPILD and non-RPILD patients

Variable	Total (n=145)	Non RPILD (n=113)	RPILD (n=32)	t/χ^2	P
Age/yr., $\bar{x} \pm s$	49.39±11.23	49.22±11.37	50.00±10.86	0.345	0.730
Female/case (%)	101 (69.65)	81 (71.68)	20 (62.50)	0.995	0.384
Coinfection/case (%)	48 (33.10)	44 (38.94)	4 (12.50)	7.781	0.005
Chronic disease/case (%)	54 (37.24)	38 (33.63)	16 (50.00)	2.860	0.101
Smoke/case (%)	22 (15.17)	15 (13.27)	7 (21.89)	1.433	0.266
Myasthenia/case (%)	48 (33.10)	42 (37.17)	6 (18.75)	3.820	0.038
Dyspnea/case (%)	65 (44.83)	48 (42.48)	17 (53.13)	1.143	0.318
Ro52 antibody level/case (%)				4.764	0.190
-	62 (42.76)	46 (40.71)	16 (50.00)		
+	24 (16.55)	16 (14.16)	8 (25.00)		
++	14 (9.66)	12 (10.62)	2 (6.25)		
+++	45 (31.03)	39 (34.51)	6 (18.75)		
MDA5 antibody level/case (%)				0.782	0.676
+	55 (37.93)	45 (39.82)	10 (31.25)		
++	25 (17.24)	19 (16.81)	6 (18.75)		
+++	65 (44.83)	49 (43.36)	16 (50.00)		
ANA antibody/case (%)	60 (41.38)	51 (45.13)	9 (28.13)	2.974	0.105
HRCT score ($\bar{x} \pm s$)	87.26±39.43	80.81±37.09	110.00±39.58	3.872	<0.000
(Neutrophils/lymphocytes) ≥ 4 /case (%)	90 (62.07)	64 (56.64)	26 (81.25)	6.417	0.013
Carcinoembryonic antigen ≥ 5 (ng/mL)/case (%)	71 (48.97)	44 (38.94)	27 (84.38)	20.603	<0.000
C-reactive protein ≥ 5 (mg/L)/case (%)	79 (54.48)	55 (48.67)	24 (75.00)	6.970	0.009
Creatine kinase/(IU/L), $\bar{x} \pm s$	150.61±288.07	140.95±307.34	184.75±206.50	0.758	0.450
Lactate dehydrogenase ≥ 370 (IU/L)/case (%)	47 (32.41)	28 (24.78)	19 (59.38)	13.625	<0.000
Procalcitonin/(ng/mL), $\bar{x} \pm s$	0.50±4.00	0.56±44.51	0.29±0.64	0.343	0.732
D-dimer/(mg/I FEU), $\bar{x} \pm s$	2.08±4.99	1.44±2.09	4.34±9.64	1.687	0.101

RPILD: rapidly progressive interstitial lung disease; MDA5: melanoma differentiation associated gene 5; HRCT: high-resolution CT.

表 2 RPILD相关因素的二元logistic回归分析

Table 2 Binary logistic regression analysis of RPILD-related factors

Variable	β	SE	Wald χ^2	OR (95% CI)	P
Lactate dehydrogenase (≥ 370 IU/L)	1.403	0.471	8.878	4.066 (1.616-10.230)	0.003
Myasthenia (yes)	-0.649	0.554	1.373	0.522 (0.176-1.548)	0.241
C-reactive protein (≥ 5 mg/L)	0.512	0.527	0.942	1.668 (0.594-4.688)	0.332
Carcinoembryonic antigen (≥ 5 ng/mL)	1.803	0.563	10.253	6.070 (2.013-18.303)	0.001
Neutrophil/lymphocyte ratio (≥ 4)	0.636	0.573	1.230	1.888 (0.614-5.804)	0.267

RPILD: rapidly progressive interstitial lung disease; β : partial regression coefficient; SE: standard error; OR: odds ratio; CI: confidence interval.

多且在影像学上和ILD鉴别困难,中心粒细胞/淋巴细胞比值受到激素影响较大,因此这两项指标未纳入多因素分析。多因素logistic回归分析结果表明,乳酸脱氢酶 ≥ 370 IU/L、癌胚抗原 ≥ 5 ng/mL对于RPILD发生有意义,因此推测具有这些临床特征的患者将来进展为RPILD的可能性大,故需要对入院时相关指标升高的患者给予密切

随访,如有肺部病变快速进展则给予激素联合免疫抑制剂加强治疗,推荐将糖皮质激素联合钙调磷酸酶抑制剂,或联合环磷酰胺的三联方案被报道有效。对于难治性患者,还可选择利妥昔单抗、丙种球蛋白、血浆置换或者肺移植等治疗方案,以提高患者的生存率^[11]。此前有文献表明^[12-13],癌胚抗原升高是抗MDA5抗体阳性皮炎患者

下肺区实变的独立预测因子,并且在合并ILD的皮炎患者中,死亡组的乳酸脱氢酶水平显著高于生存组的乳酸脱氢酶水平,并将乳酸脱氢酶指标纳入ILD相关的皮炎死亡率风险预测模型当中。以上研究凸显出了癌胚抗原以及乳酸脱氢酶在皮炎患者的肺部病变与预后预测方面具有一定意义。值得注意的是,与既往部分研究结论不同,该研究发现不管是组间差异比较还是多因素logistic回归分析,MDA5抗体滴度高低均与RPILD的发生无关。

综上所述,本研究的结果表明,患者入院时癌胚抗原或乳酸脱氢酶水平偏高与合并RPILD相关。因此推测患者在第一次入院时,如检查结果提示癌胚抗原或乳酸脱氢酶水平较高,未来发生RPILD风险可能增高,应密切观察患者体征变化,加强胸部影像学 and 肺功能监测,如肺部病变进展迅速需要加强本病的治疗,以改善患者的预后。

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利益冲突 所有作者均声明不存在利益冲突

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