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· 综述 ·

皮肌炎相关的肌炎特异性自身抗体研究进展

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【摘要】 皮肌炎是自身免疫性疾病 ,以对称性四肢近端肌肉无力为特征性表现 ,通常伴有典型的皮肤损害 ,易侵犯多脏器、多系统 ,临床较复杂 ,且常伴发肿瘤。近期研究发现 ,皮肌炎患者血清中存在多种自身抗体 ,包括肌炎特异性自身抗体和肌炎相关性自身抗体 ,肌炎特异性自身抗体与某些临床表现密切相关 ,临床上通过对这些自身抗体检测可帮助疾病诊断及判断预后。

【关键词】 皮肌炎 ;自身抗体 ;抗 Mi-2 抗体 ;抗 MDA5 抗体 ;抗 SAE 抗体 ;抗 TIF1γ 抗体 ;抗 NXP2 抗体

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Research progress of dermatomyositis-related myositis-specific autoantibodies

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【**Abstract**】 Dermatomyositis (DM) is connective tissue disease characterized by symmetric proximal muscle weakness of the limbs .It is usually accompanied by typical skin rashes ,easy to invade multiple organs and systems ,complex in clinical practice ,and often accompanied by tumors .Recent research showed that there are a variety of autoantibodies in the serum of dermatomyositis patients ,including myositis-specific autoantibodies and myositis-related autoantibodies .Myositis-specific autoantibodies are closely related to some clinical manifestations .Clinical detection of these autoantibodies can help diagnose the disease and predict the prognosis .

【**Key words**】 Dermatomyositis ; Autoantibodies ; Antibodies anti-Mi-2 ; Antibodies anti-MDA5 ; Antibodies anti-SAE ; Antibodies anti-TIF1γ ; Antibodies anti-NXP2

皮肌炎易侵犯多脏器、多系统 ,临床比较复杂 ,皮肤损害是皮肌炎的一个重要特征 ,典型的皮肤损害包括眶周水肿性皮疹、Gottron 丘疹、向阳疹、披肩征、颈部“V 字征” ,常伴发肿瘤 ,因此难以早期诊断、早期治疗。近年来研究发现 ,与皮肌炎相关的肌炎特异性自身抗体与某些临床表现密切相关 ,并且不同的抗体治疗及预后情况不同 ,伴发肿瘤的风险也不同 ,临床上通过对这些自身抗体检测可帮助疾病诊断及判断预后。本文主要对皮肌炎相关的肌炎特异性自身抗体的相关研究进行综述。

1　抗 Mi-2 抗体

抗 Mi-2 抗体是皮肌炎的特异性抗体。由 REICHLIN 和 MATTIOLI 于 1976 年在 1 例 60 岁女性皮肌炎患者的血清中首次发现并报道[1]。在转录的调节中抗 Mi-2 抗体是核小体重构脱乙酰基酶复合物的基本组成成分[2]。抗 Mi-2 抗体在成年型皮肌炎中的阳性率 11% ～59%[3-5] ,在幼年型皮肌炎 (JDM)中的阳性率 4% ～10%[6,8]。抗 Mi-2 抗体在临床表现中与一系列皮肤特征显著相关 ,包括 Gottron 丘疹、向阳疹、披肩征、颈部“V 字征”和表皮过度生长 ,但肌肉的受累一般较轻[3,7]。抗 Mi-2 抗体阳性的患者发生恶性肿瘤的概率 ,目前有争议 ,BETTERIDGE 等[9]认为 ,此抗体阳性患恶性肿瘤的风险会降低 ,BENVENISTE 等[10]认为 ,此抗体阳性和恶性肿瘤相关。抗 Mi-2 抗体阳性的患者对于皮质类固醇和免疫抑制剂有良好的反应 ,对于此抗体阳性的难治性患者 ,给予利妥昔单抗治疗病情可以在短时间内得到缓解[10]。

2　抗 MDA5 抗体

临床无肌病性皮肌炎 (CADM)是皮肌炎的一种

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特殊亚型,抗 MDA5 与 CADM 密切相关。2005 年由学者 SATO 等[11]对 42 例成人皮肌炎患者进行血清检测,发现其中 8 例存在一种可识别 140 000 多肽的自身抗体,此 8 例患者均表现为 CADM,早期命名为抗 CADM-140 抗体,4 a 后该学者确定其靶抗原为 MDA5[12]。抗 MDA5 抗体阳性患者的预后不好,主要由于此抗体阳性易表现为快速进展性间质性肺病(rapidly progressive interstitial lung disease,RPILD),在 23 例抗 MDA5 阳性日本患者中,14 例(61%)表现为快速进展性间质性肺病[12]。日本皮肌炎患者中抗 MDA5 抗体阳性率为 11%[13],与西方国家(例如美国或西班牙 13%)[14-15]抗体阳性率相近,且预后不好。值得注意的是西方国家此抗体阳性主要表现为类似一种重叠综合征特征,快速进展 ILD,皮肤溃烂、机械手、可触痛的手掌丘疹等皮肤损害,还伴有口腔病变,关节痛/关节炎,脱发等症状[14-15]。抗 MDA5 抗体阳性的患者患恶性肿瘤常伴随其他抗体阳性,如 CUESTA—MATEOS 等[16]在 11 例西班牙 CADM 患者血清中发现 4 例患者抗 TIF-1Y 抗体,而抗 MDA5 抗体阳性 3 例患者,其中 1 例抗 TIF-1γ 抗体阳性的患者诊断 CADM 后 3 a 内伴发了甲状腺乳头状癌。抗 MDA5 抗体阳性患者若伴有快速进展性 ILD 和皮肤溃疡,预后非常差,约 30% 会死亡,治疗上建议给予大剂量的皮质类固醇、利妥昔单抗、钙调磷酸酶抑制剂、血浆置换积极快速的治疗[10]。

3 抗 SAE 抗体

抗 SAE 抗体阳性常伴有皮肤损害。由 BETTERIDGE 等[17]于 2007 年在 2 例皮肌炎患者血清中发现了一种新的 MSAs,命名为抗 SAE 抗体。这 2 例抗体阳性的患者均有典型的皮肌炎症状如皮疹,包括 Gottron 征和向阳疹。随后 BETTERIDGE 等[18]在对 266 例炎性肌病患者的研究中发现,该抗体的阳性率约 4%,其中皮肌炎患者的阳性率约 8%,该抗体阳性的皮肌炎患者皮肤黏膜损害较常见。除了典型的皮肌炎皮疹外,此抗体阳性常伴有吞咽困难和甲周改变,但与恶性肿瘤及 ILD 呈负相关。也有研究表明,抗 SAE 抗体阳性患者,会伴有轻度的 ILD(71%),但是治疗效果较好[19]。TARRICONE[23]等发现,抗 SAE 阳性患者临床中主要表现皮肤和肌肉病变,但并未出现吞咽困难、关节痛、间质性肺病等症状。抗 SAE 抗体是主要与皮肌炎相关的自身抗体,抗体阳性的患者首先会出现皮肤相关的临床表现,随后会出现严重的吞咽困难等症状。

4 抗 TIF1γ 抗体

抗 TIF1γ 抗体阳性常伴有恶性肿瘤。TARGOFF 等[20]于 2006 年发现了另一种能识别相对分子质量为 155000 和 140000 蛋白质的 MSAs,将其命名为抗 p155/140 抗体。抗 TIF1γ 抗体在儿童和成年患者中均可出现,在儿童皮肌炎中出现的频率为 32%[32],成人皮肌炎中出现的频率为 20% ~ 40%[20,33],其中 75% 的成人皮肌炎患者易合并肿瘤[20]。临床主要表现为四肢近端无力和广泛的皮肤损害,一些患者会出现银屑病样病变、手掌角化过度性丘疹、色素减退和毛细血管扩张所致的红白斑块[32-34]。此抗体与恶性肿瘤相关,儿童皮肌炎患者抗 TIF1γ 抗体阳性与恶性肿瘤没有明显关系,40 岁以下的成年人抗 TIF1γ 抗体阳性似乎不会增加恶性肿瘤风险,40 岁以上的成年人抗 TIF1γ 抗体阳性患恶性肿瘤的风险高达 75%[22]。皮肌炎患者出现抗 TIF1γ 抗体阳性时应注意对肿瘤的筛查,早发现早治疗。

5 抗 NXP2 抗体

在儿童皮肌炎患者中抗 NXP2 抗体阳性常伴有钙沉积,在成人皮肌炎患者中常伴有恶性肿瘤。ODDIS 等学者于 1997 年在青少年皮肌炎患者中发现一种抗体,将其命名为抗 MJ 抗体,直到 2007 年 TARGOFF 等[24]明确其靶抗原为核基质蛋白 2(NXP2),故将该抗体命名为抗 NXP2 抗体。随后研究发现抗 NXP2 抗体在成人患者也可出现[26]。抗 NXP2 抗体在特发性炎性肌病阳性率差异很大,报道范围在 1.6% ~ 25%[26-27]。抗 NXP2 抗体主要出现在儿童皮肌炎患者血清中,发生率为 20% ~25%;在成人皮肌炎患者血清中,发生率为 1% ~20%[10]。临床中抗 NXP2 抗体阳性患者常伴有吞咽困难和肢体水肿[26,28],儿童皮肌炎患者主要表现为严重的肌肉病变和皮肤钙沉积[21,28],成年男性皮肌炎患者有较高的癌症风险[21,25]。ICHIMURA 等[26]报道 8 例成人抗 NXP2 抗体阳性患者,3 a 内 4 例(50%)发现恶性肿瘤;ALBAYDA 等[29]对 235 例皮肌炎患者检测发现,在 56 例抗 NXP2 抗体阳性患者中 5 例(9%)合并肿瘤,较正常人群肿瘤发生风险增加 3.68 倍。抗 NXP2 抗体阳性患者,对糖皮质激素敏感,治疗效果较好[30],但对于伴有皮下钙化这类患者,单纯药物治疗对皮下钙

化无效[31],手术切除治疗可使部分患者完全缓解,但部分患者可出现钙化复发。患者血清中出现抗 NXP2 抗体阳性,应注意对肿瘤的筛查,尤其是成年男性的皮肌炎患者。

肌炎特异性自身抗体对皮肌炎的诊断具有较高的特异性,以上五种肌炎特异性自身抗体与皮肌炎密切相关,不同抗体的临床表现、治疗及预后不同,并且皮肌炎易合并肿瘤,因此早期对皮肌炎患者进行肌炎自身抗体检测对皮肌炎的诊断、分型、治疗以及预后有重要的指导意义。

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