·综述·

抗recoverin抗体相关副肿瘤综合征

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摘要 神经系统副肿瘤综合征（PNS）是一种复杂的临床综合征。抗recoverin抗体是一种罕见的PNS生物标志物，通常作用于癌症相关视网膜病变，少量见于其他疾病。目前还没有针对抗recoverin抗体相关疾病的既定治疗方案。本文对抗recoverin抗体相关副肿瘤综合征进行综述，增强临床工作者对此类疾病的认识与关注，并为临床治疗提供可能的启示。

关键词 副肿瘤综合征；recoverin；免疫治疗；抗体滴度；免疫检查点抑制剂
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Anti–recoverin Antibody Related Paraneoplastic Syndrome

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Abstract Paraneoplastic nervous system syndrome (PNS) is a complex clinical syndrome. Anti-recoverin antibody, a rare biomarker of PNS, usually acts on cancer- associated retinopathy and has seldom been reported in other diseases. There is no established treatment protocol for recoverin-associated diseases. This article provides a review of the anti-recoverin antibody related paraneoplastic syndrome, enhancing clinical workers' understanding and attention to this disease, and providing possible insights for clinical treatment.

Keywords paraneoplastic syndrome; recoverin; immunotherapy; antibody titers; immune checkpoint inhibitors

神经系统副肿瘤综合征（paraneoplastic neurological syndromes，PNS）是一种复杂的临床综合征，可以影响神经系统的任何部分，对外周血和脑脊液进行特异性神经元抗体检查对PNS的诊断具有重要意义。抗recoverin抗体是一种罕见的神经系统副肿瘤综合征的生物标志物，目前关于抗recoverin抗体相关疾病尚无公认的治疗方案。本文对抗recoverin抗体相关副肿瘤综合征进行介绍，增强临床工作者对此类疾病的认识与关注，并为临床治疗提供可能的建议。

1 介绍

1.1 神经系统副肿瘤综合

PNS是一种复杂的临床综合征，是由肿瘤的远程作用而非肿瘤本身、转移或其他原因引起[1,2]。PNS是较为罕见，发病率为1.6例～8.9例/百万人/年，还存在诊断率、报告率不高等问题[3]。PNS通常为亚急性发作，伴有快速进展且严重的神经系统功能障碍[4]。它可以影响神经系统的任何部分，包括中枢或周围神经系统、神经肌肉接头和肌肉。最常见的PNS包括：①Lambert-eaton肌无力综合征；②快速进展性小脑综合征，既往称为“亚急性小脑变性”；③边缘脑炎；④眼阵挛-肌阵挛；⑤视网膜病变；⑥胃肠道假性梗阻；⑦感觉神经元病；⑧脑脊髓炎[5]。癌症免疫疗法是一种新型的抗癌策略，全球已经建立了数千项研究多种不同疗法的临床试验。研究发现使用免疫检查点抑制剂可能会增加PNS的风险，尤其是对于癌症类型与PNS密切相关的患者[6,7]。

PNS是针对癌症和神经系统共有的神经抗原产生自身免疫反应的结果。因此，特征性的抗肿瘤蛋白抗体具有高特异性，是将神经系统疾病诊断为PNS的最佳方法之一[8]。PNS症状经常在诊断出早期或有限阶段的潜在肿瘤之前表现出来[6]，从而使临床医生预测特定癌症的发生。早期诊断肿瘤并进行有效的癌症治疗仍然是PNS患者神经症状最有效的治疗方法之一。

1.2 抗recoverin抗体

Thirkill博士和他的同事发现4例癌症相关性视网膜病变（cancer-associated retinopathy，CAR）患者的血清与一种视网膜蛋白发生反应[9]，随后这种蛋白被命名为“recoverin”。Recoverin是一种在光感受器中表达的钙结合蛋白，大小为23 kDa。最近的研究表明，recoverin不仅存在于视杆细胞和视锥细胞中，也存在于许多其他组织中。抗recoverin抗体相关PNS与各种癌症有关，最常见的是小细胞肺癌，其他肿瘤还包括妇科肿瘤、乳腺癌、淋巴瘤等[10]。在许多其他视网膜病变和全身疾病中，以及在没有视觉症状的癌症患者中也发现过此抗体，比如Vogt-小柳-原田综合征[11]、色素性视网膜炎[12]。有报导称recoverin单独或与其他生物标志物联合可作为肾肿瘤[13,14]和脑胶质瘤[15]诊断或判断预后的非侵入性生物标志物。

2 抗recoverin抗体相关疾病

抗recoverin抗体通常作用于recoverin相关视网膜病变（recoverin-associated retinopathy，RAR），表现为无痛性单侧或双侧不对称性进行性视力丧失[16]，快速进展，可在数天至数年导致失明。视锥细胞功能障碍主要表现为视力和色觉恶化、光敏、眩光、闪烁或闪烁的灯光症状和中央盲点，视杆细胞功能障碍主要表现为暗适应障碍、夜盲症、环形盲点和外周视野缺陷[17]。目前报导的抗recoverin抗体相关中枢神经系统症状包括迟发性共济失调[18]和基底节脑炎[19]，也有副肿瘤性脊髓病的病例报导[20]，最近发现此抗体可能也与不同程度的认知障碍有关[21]。PD-1抗体治疗肝细胞癌患者后可出现CAR[22]，提示免疫检查点抑制剂治疗可能会诱发副肿瘤性抗体（如recoverin）相关的自身免疫性视网膜病变。抗recoverin抗体相关中枢神经系统PNS可能的机制有：源于肿瘤的recoverin刺激免疫系统产生特异性的自身抗体和（或）T细胞[23]，并广泛涉及中枢神经系统的各个部分。另一种可能是recoverin与中枢神经系统的内源性抗原共享交叉反应表位，抗recoverin抗体可以通过已受损的血脑屏障到达中枢神经系统[19,24]。

2.1 抗体滴度

高滴度（通常＞1:1000）抗recoverin抗体与视网膜光感受器变性相关[25]。抗recoverin抗体滴度与症状轻重有关，滴度的反弹与视觉症状的恶化有关[16,26]，治疗后滴度会降低[27]。与前列腺特异性抗原（prostate specific antigen，PSA）类似，抗recoverin抗体滴度升高5～10倍可能对肿瘤活跃生长最有预测价值[15]。抗体滴度变化的特性可能在肿瘤监测和检测治疗效果中有较好的应用价值。

2.2 治疗

目前抗recoverin抗体相关疾病尚无既定的治疗方案，治疗干预的证据基础仅包括少量回顾性病例系列和病例报告[17]。治疗目标是在不可逆损伤发生之前调节免疫系统，减少自身免疫攻击。急性期治疗包括激素冲击治疗、静脉注射免疫球蛋白（intravenous immunoglobulin，IVIG）和血浆置换治疗，有时联合使用以治疗难治性病例。维持治疗可使用口服糖皮质激素和免疫抑制剂，包括利妥昔单抗[18]、吗替麦考酚酯[27]、硫唑嘌呤[28]、他克莫司[29]。在与recoverin自身抗体介导的CAR的短期管理中，皮质类固醇被认为更有效[30]。Ramos[31]认为早期使用IVIG可能有助于稳定或改善患者的视觉症状。报导的2例recoverin抗体相关中枢神经系统疾病—迟发性共济失调和自身免疫性基底节脑炎病例，分别在用类固醇和利妥昔单抗[17]及大剂量免疫球蛋白[18]进行免疫抑制治疗后，患者症状有所改善。虽然各种方法治疗效果存在异质性，但早期开始免疫治疗对于神经系统的改善或稳定至关重要[32]。近年来已实现细胞疗法治疗退行性视网膜疾病（如老年性黄斑变性和色素性视网膜炎）[17]，未来该方法或许有望造福于包括RAR在内的所有视网膜病变患者。

2.3 预后

大多数抗视网膜抗体综合征病例的视力预后较差。未经治疗，抗recoverin抗体阳性的CAR患者会进展为严重的视力丧失，可能会发展到无光感[33]。及时识别和及早开始治疗对于视力保留至关重要。由于潜在的恶性肿瘤，CAR患者的死亡率很高。但研究表明血清抗recoverin抗体阳性的CAR患者可能有更好的生存期，可能是外周recoverin特异性细胞毒性T淋巴细胞（cytotoxic T lymphocytes，CTL）激活有益于患有CAR的癌症患者的预后[34]。

3 总结

PNS很少见且诊断困难，导致患者可能被误诊。特异性神经元抗体检查对PNS的诊断具有重要意义。抗recoverin抗体是一种罕见的PNS生物标志物，可不同程度地影响视网膜和神经系统的各个部位，抗体滴度对观察治疗效果和肿瘤是否复发可能有重要的提示意义。在对癌症患者使用免疫检查点抑制剂治疗前，进行副肿瘤抗体检测以及基线眼科检查，将有助于避免recoverin阳性患者发生CAR[22]。本综述对抗recoverin抗体相关疾病的特征、治疗与预后进行介绍，希望增强临床医师对此类疾病的认识与关注，并为临床治疗提供可能的建议。

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