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免疫检查点抑制剂相关内分泌不良反应的临床研究进展

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摘 要

免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)通过阻断免疫抑制、增强机体免疫实现抗肿瘤效应，显著提高了恶性肿瘤的生存率。ICIs在抗肿瘤的同时也会产生免疫相关不良反应(immune-related adverse events, irAEs)，内分泌irAEs是其中最常见的，可以累及到垂体、甲状腺、胰腺、肾上腺等。虽然内分泌irAEs通常不严重，但是也会发生危及生命的内分泌急症以及罕见的内分泌病变，因此需要得到临床的重视。目前内分泌irAEs的机制尚无定论，本文就其发病率、发病机制、临床表现、治疗作一综述。

关键词

免疫检查点抑制剂，免疫相关不良反应，内分泌病

Research Advances of Immune Checkpoint Inhibitors Related Endocrine Adverse Events

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Abstract

Immune checkpoint inhibitors (ICIs) can enhance the anti-tumor effect by blocking immunosup-

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pression and strengthening the body's immunity, which has significantly improved the survival rate of malignant tumors. However, ICIs can cause immune adverse events (irAEs) at the same time, and endocrine irAEs are the most common events and can involve the pituitary, thyroid, pancreas, adrenal glands, etc. Although endocrine irAEs are not serious generally, life-threatening endocrine emergencies as well as rare endocrinopathies can occur. Therefore, the events require clinical attention. The mechanism of endocrine irAEs is still inconclusive, and this article provides an overview of their incidence, pathogenesis, clinical manifestations, and treatment.

Keywords

Immune Checkpoint Inhibitors, Immune-Related Adverse Events, Endocrinopathy

1. 引言

肿瘤一直是危害人类健康的重大公共卫生问题。免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)的出现给肿瘤治疗带来划时代的突破，大大提高了恶性肿瘤的缓解率和生存率[1]。尽管临床实践中，化疗和放疗仍然是大多数肿瘤的常规治疗方法，但是 ICIs 已经成为各种实体肿瘤和血液肿瘤的一线治疗方案[2]，可见其在临床上的应用越来越受到重视。随着 ICIs 的大量应用，随之而出现的问题是免疫相关不良反应(immune-related adverse events, irAEs)。与传统的化疗和放疗不同，irAEs 的表现因人而异。irAEs 可以累及任何器官和系统，如免疫相关心肌炎、免疫相关肝炎、免疫相关结肠炎、免疫相关肺炎、免疫相关肌炎、免疫相关甲状腺功能障碍等，通常是比较轻微的，可以通过密切观察、对症治疗、使用糖皮质激素、激素替代治疗等得以缓解，此后可以继续使用 ICIs 药物，但是也存在一些严重的不良反应或产生不可逆转的病变，如死亡或者需要长期接受激素替代治疗等[3] [4] [5] [6] [7]，需要引起临床的高度警惕。其中，最常见的 irAEs 是累及内分泌系统的不良反应[8]。ICIs 相关的内分泌不良反应可以引起垂体、甲状腺、肾上腺、胰腺、甲状旁腺等内分泌组织和器官的功能障碍，且临床表现多样，严重的不良反应如未能及时识别，可危及生命[9] [10] [11]。因此，快速识别并处理 ICIs 相关内分泌不良反应有重要的临床意义。

2. ICIs 及内分泌 irAEs 概述

免疫检查点是人体免疫系统的负调节者，它可以介导免疫耐受，防止自身免疫，从而保护自身组织不受免疫攻击[12]。恶性肿瘤借助这个机体自我保护机制逃避免疫监视，从而进一步发生发展[13]。目前最为人熟知的免疫检查点有细胞毒性 T 淋巴细胞相关抗原(cytotoxic T lymphocyte-associated antigen 4, CTLA-4)、程序性死亡受体-1 (programmed death 1, PD-1)和程序性死亡配体-1 (programmed death-ligand 1, PD-L1)。此外，还有一些新的免疫检查点及其相关药物尚在研究中，如淋巴细胞活化基因-3 (lymphocyte activation gene-3, LAG-3)、T 细胞免疫球蛋白-3 (T cell immunoglobulin-3, TIM-3)、B7-H3 和 B7-H4 等[14]。

ICIs 是针对免疫检查点研发出的药物，它可以通过阻断免疫检查点的负调节作用，从而增强机体自身免疫能力，产生抗肿瘤免疫应答[2] [8]。目前，临床上最常用的 ICIs 主要是抗 CTLA-4 单克隆抗体(anti-CTLA-4 monoclonal antibodies，下称 CTLA-4 抑制剂)和抗 PD-1/PD-L1 单克隆抗体(anti-PD-1/PD-L1 monoclonal antibodies，下称 PD-1/PD-L1 抑制剂) [1]，它们主要在与 T 细胞活化和 T 细胞耗竭相关的两个

关键信号传导途径中起作用[15]。抗肿瘤免疫应答最主要的是 T 细胞的存在，T 细胞的活化需要两步，第一步是 T 细胞受体(T cell receptor, TCR)和抗原呈递细胞(antigen-presenting cell, APC)上的主要组织相容性复合体(major histocompatibility complex, MHC)相结合，第二步是 T 细胞上的 CD28 和 APC 上的 B7 结合，从而激活 T 细胞。相较于 CD28，CTLA-4 和 B7 的亲和力更强，从而抑制 T 细胞活化，CTLA-4 抑制剂可以与 CTLA-4 结合从而使得 T 细胞激活的第二步不被干扰。而 PD-1 是 T 细胞上的一个受体，它的配体 PD-L1 在肿瘤细胞和肿瘤浸润巨噬细胞上表达，一旦 PD-1 与 PD-L1 相结合，就会引发 T 细胞抑制级联反应(T 细胞耗竭)，PD-1/PD-L1 抑制剂通过与 PD-1 或 PD-L1 结合阻断这个抑制反应，从而保留 T 细胞的抗肿瘤作用[16]。临床上用于抗肿瘤治疗的 CTLA-4 抑制剂有伊匹木单抗(Ipilimumab)，PD-1 抑制剂有纳武利尤单抗(Nivolumab)、帕博利珠单抗(Pembrolizumab)，PD-L1 抑制剂有阿特珠单抗(Atezolizumab)、阿维鲁单抗(Avelumab)、度伐利尤单抗(Durvalumab)等[8]。

内分泌 irAEs 在 ICIs 使用中很常见，发生率因文献报道的药物类型、使用方法等而有所不同，最高可近 40% [17] [18]。可以用不良事件通用术语标准 5.0 版本(Common Terminology Criteria for Adverse Events version 5.0, CTCAE 5.0)对内分泌 irAEs 进行分级，可以分为轻度、中度、严重但不会立即危及生命、危及生命、死亡五个等级[19]，可以用 Grade 1-5 (G1-5)表示。通常来说，发生内分泌 irAEs 的时间为使用药物后的 6 个月内，但具体发生时间难以预测，在使用药物的任何时间及停药后的时间里均可发生[20]。一般而言，内分泌 irAEs 的发生机制可以被理解为自身免疫耐受的消除和 T 细胞的激活，同时也与炎症反应相关，具体的各个内分泌器官的免疫相关不良反应的机制尚在研究中。垂体功能障碍多见于使用 CTLA-4 抑制剂，使用 PD-1/PD-L1 抑制剂更易发生甲状腺功能障碍，ICIs 联合用药较单药更容易出现内分泌 irAEs [15]。下文将进一步阐述各个内分泌 irAEs。

3. 免疫相关不良反应

3.1. 甲状腺功能障碍

在内分泌 irAEs 中，甲状腺功能障碍是最常见的[21]，它的发病率在不同的研究中存在差异[22]。在一项系统综述中，单用 ICIs 药物发生甲状腺功能障碍的概率最高约为 10%，其中 PD-1/PD-L1 抑制剂的发病率比 CTLA-4 抑制剂高，联合使用 ICIs 药物发生甲状腺不良反应的概率较单药高，约 10%~20% [18]。

ICIs 相关甲状腺功能障碍可以分为甲状腺毒症和甲状腺功能减退两类。甲状腺毒症可以进一步分为破坏性甲状腺炎和甲状腺功能亢进症，其中破坏性甲状腺炎居多，甲状腺毒症是破坏性甲状腺炎演变成甲状腺功能减退的短暂阶段，ICIs 相关甲状腺功能亢进的报道较少[22]。一项回顾性研究发现，在 ICIs 治疗后出现甲状腺毒症的人群中，约 80%的患者最终进展为甲状腺功能减退[23]。在既往无甲状腺毒症表现的 ICIs 相关甲状腺功能减退中，有可能在随访期间未检测到一过性的甲状腺毒症。有一项前瞻性研究发现在发生 ICIs 相关甲状腺功能减退的患者中，有检测到一过性的促甲状腺激素(thyroid stimulating hormone, TSH)水平降低，甲状腺激素水平未升高的过程[24]。因此，ICIs 相关的甲状腺毒症和甲状腺功能减退有可能是同一疾病的不同发展阶段，还需要进一步研究明确其中机制。有小鼠模型研究报道，在甲状腺球蛋白免疫后 2.5 个月注射 PD-1 抑制剂诱导 CBA/J 小鼠发生严重的破坏性甲状腺炎，其中 CD4 T 细胞起到了很大的作用[25]。目前尚无明确的 CTLA-4 抑制剂的引起甲状腺 irAEs 机制研究，有小鼠实验提示 CTLA-4 在甲状腺中不表达，并且重复注射抗 CTLA-4 抗体不会诱导造血细胞浸润到甲状腺中[26]。目前，有关甲状腺 irAEs 的病理研究也较少，有一项病例报道了其甲状腺病理发现大量的坏死细胞、淋巴细胞和 CD 163 阳性组织细胞[27]，另一项研究表明其存在慢性淋巴细胞性炎症伴非坏死性肉芽肿形成，以及甲状腺滤泡破坏伴炎性浸润[28]。

ICIs 相关甲状腺功能障碍多数在治疗后 3 月内发生，但也可以发生在治疗后的任何时间[15]。甲状腺

毒症最常见的症状是体重减轻和心动过速，以及震颤、焦虑、排便过多等，体格检查可发现心动过速，皮肤温暖光滑，眼睑松弛等表现；甲状腺功能减退症最常见的症状是疲劳和体重增加，以及冷耐受不良、便秘和皮肤干燥等，体格检查可发现心动过缓、皮肤干燥粗糙、面部浮肿、眶周水肿等[8]。一般而言，甲状腺 irAEs 的临床表现是非特异性、轻中度的(大多为 G1、G2)，患者可能很少或者无症状表现，但是也有 ICIs 引起严重的危及生命的情况，如严重的甲状腺毒症引起高热伴休克的甲状腺危象、导致罕见的甲状腺风暴、严重的未经治疗的甲状腺功能减退导致粘液水肿性昏迷等[29] [30] [31]。

对于发生甲状腺毒症的患者，可以使用 β 受体阻滞剂缓解心动过速的症状，并且 2~3 周需要复查甲状腺功能；对于发生了甲状腺功能减退的患者，可以通过补充甲状腺素改善症状，起始剂量为每日 1.6 μg/kg，老年人需使用比年轻人更小的剂量，具体剂量视身体情况而定，同时一般建议每 6 周定期复查甲状腺功能调整剂量[4] [15]。一般而言，经过治疗后可再次使用 ICIs 药物。

3.2. 垂体炎

垂体炎是继甲状腺功能障碍的第二种常见的内分泌 irAEs [32]。垂体炎的发病率因不同的研究而不同，一般多见于 CTLA-4 抑制剂单药治疗或者 CLTA 抑制剂和 PD-1 抑制剂联合治疗，一项系统综述提示垂体炎最高可达到约 10%的发病率[18]，一项前瞻性研究里垂体炎的发病率可高达 14% [33]。有研究表明，男性和高龄可能是垂体炎的危险因素[34]。

ICIs 相关垂体炎的发病机制尚不明确，ICIs 相关尸检结果提示 IV 型(T 细胞依赖)和 II 型(IgG 依赖)超敏反应可能在其中起到重要作用[35] [36]。有研究发现在发生垂体炎的患者中检测到靶向鸟嘌呤核苷酸结合蛋白 G 亚单位 α (guanine nucleotide-binding protein G subunit α, GNAL)和整合膜蛋白 2B 的自身抗体(anti-integral membrane protein 2B, ITM2B)，这些蛋白在正常人垂体组织中表达[37]，但其中的机制尚未清楚。目前的研究表明 CTLA-4 抑制剂和 PD-1/PD-L1 抑制剂导致的垂体炎发生机制可能不同。CTLA-4 在人体和小鼠垂体中表达，在小鼠模型中注射 CTLA-4 抑制剂后小鼠出现垂体炎表现，且在脑垂体中观察到补体沉积[26] [38]。而对 PD-1 抑制剂相关的垂体炎患者尸检结果提示 T 细胞介导的 IV 型超敏反应证据[32]，也有研究表明 10%的 PD-1/PD-L1 抑制剂相关垂体炎与靶向促肾上腺皮质激素的自身免疫有关，并可能作为一种副肿瘤综合征形式发生[39]。在危险因素方面，人类白细胞抗原(human leukocyte antigen, HLAs)等位基因或 CTLA-4 基因多态性作为遗传危险因素可能参与 ICI 相关性垂体炎的发病[32]。

和甲状腺 irAEs 不同的是，大多数病人发生 ICIs 相关垂体炎是在出现症状时被发现的，严重的垂体炎(G3, G4)有较高的比例[40]。有文献报道接受 CTLA-4 抑制剂治疗的患者发生垂体炎的中位出现症状时间为 9~12 周，接受 PD-1/PD-L1 抑制剂治疗的患者为 26 周[41]。ICIs 相关垂体炎的症状多样，主要与继发性肾上腺功能不全、继发性甲状腺功能减退、性腺功能减退等有关，临床表现有头痛、疲劳、恶心呕吐、食欲不振、体重减轻、头晕、性欲减退、视物模糊、精神状态改变等，罕见但严重的症状有低血压、肾上腺危象等[42] [43]。文献报道 ICIs 垂体炎患者中，继发性肾上腺功能减退占 83%，继发性甲状腺功能减退占 77%，继发性性腺功能减退占 53% [20]。除了垂体分泌的激素分泌减退及下游腺体继发性激素分泌减退，ICIs 相关垂体炎需要完善磁共振成像(magnetic resonance imaging, MRI)明确诊断，可有垂体增大、均匀或不均匀的强化、垂体柄增厚等表现，但需要注意的是，MRI 阴性不能排除 ICIs 相关垂体炎的诊断。此外，MRI 还可以用于鉴别脑转移瘤、脑血管事件、脑膜瘤，以及区分中枢性垂体功能障碍和其他原发内分泌腺体疾病[44]。

出现 ICIs 相关垂体炎的患者建议停止 ICIs 药物使用，病情较轻者可以使用替代剂量的糖皮质激素治疗，病情较重者可能需要大剂量的糖皮质激素[19]。在伴有继发性甲状腺功能减退的患者中，直接补充甲状腺激素可能会导致肾上腺危象，因此，需要先补充糖皮质激素改善机体皮质醇功能低下的情况后再补

充甲状腺激素[4] [44] [45]。对于使用 ICIs 发生垂体炎的患者而言，在垂体炎治疗完成后可以再次评估是否可以继续 ICIs 治疗。

3.3. 糖尿病

ICIs 相关糖尿病的发病率不高，约 1%左右[46] [47]，在不同的研究中发病率略有差异。有研究指出，近些年的 ICIs 相关糖尿病的发病数量不断增多[48] [49]。ICIs 相关糖尿病通常发生在使用 PD-1/PD-L1 抑制剂的患者中，但是 PD-1/PD-L1 抑制剂联合 CTLA-4 抑制剂的用药方案其发生率高于单药治疗[50] [51]。有研究指出，更低的年龄、基础有糖尿病、CTLA-4 抑制剂联合 PD-1/PD-L1 抑制剂可能是发生 ICIs 相关糖尿病的危险因素[52]。

和经典的 1 型糖尿病类似，ICIs 相关糖尿病可能是由于胰岛 β 细胞的免疫破坏引起的[52]，理论上，PD-1/PD-L1 抑制剂可以通过活化的自身反应性 T 细胞增加胰岛 β 细胞浸润和死亡[53]。有研究表明老年小鼠和胰岛免疫浸润小鼠的胰腺 β 细胞中 PD-L1 表达增加[54] [55]，也有研究表明在非肥胖糖尿病小鼠模型中，PD1/PD-L1 信号传导的破坏可以诱导糖尿病[56] [57]。研究表明，1 型糖尿病患者胰岛中的 PD-L1 表达水平高于 2 型糖尿病患者和健康人。因此，胰腺中 PD-L1 表达的增加可能是以一种抑制炎症反应的表现。糖尿病事件一般发生在 ICI 开始后数周至数月，表明这种免疫相关型糖尿病可能需要连续事件，胰岛 β 细胞中 PD-L1 表达增加和 PD-L1/PD-1 通路阻断的两次连续打击假设可能可以解释[58]。对 ICIs 相关糖尿病的患者胰腺病理提示存在 T 淋巴细胞的浸润，且相对于 CD4+ T 细胞，CD8+ T 细胞增加，并且不存在巨噬细胞[59]，也有研究在胰腺萎缩、胰酶升高的 ICIs 相关糖尿病患者中发现胰腺炎症的证据，并且在一例死于 ICIs 相关糖尿病的患者中发现胰岛周围淋巴细胞浸润[60]。

ICIs 相关糖尿病的临床表现可以非常多样，不局限于经典的多尿、烦渴、体重减轻的症状[61]。值得重视的是，很大部分 ICIs 相关糖尿病以糖尿病酮症酸中毒为表现，其发生率可在 50%至 100%波动[62]，有研究报道其患者因疲劳，呼吸急促，意识模糊，视力模糊、体重减轻至医院就诊，其他表现还有多尿、烦渴、腹痛、恶心、呕吐和腹泻等[63] [64]。和 1 型糖尿病相比，ICIs 相关糖尿病的胰岛自身抗体阳性率较低，约 0%~71%不等，有研究发现出现 ICIs 相关糖尿病患者用药前存在胰岛自身抗体，可能提示其有成为 ICIs 相关糖尿病预测因子的可能性[65]。此外，需要注意的是，在 ICIs 药物使用中出现的 2 型糖尿病加重、类固醇性高血糖、胰腺损伤和自身免疫性脂肪萎缩等都可以出现高血糖的表现[66] [67] [68] [69]，在诊断 ICIs 相关糖尿病时，需要鉴别上述疾病以及其他引起高血糖的疾病。

对于 ICIs 相关糖尿病，胰岛素的使用原则与常见糖尿病的管理类似，视病情轻重调整胰岛素的剂量，同时，加强血糖监测对 ICIs 的管理是必要的[62]。

3.4. 其他内分泌病

内分泌 irAEs 中较少见的疾病有原发性肾上腺功能不全、尿崩症、甲状旁腺疾病、脂肪萎缩、库欣综合征、自身免疫性多内分泌腺体综合征等[70]。

有研究表明 ICIs 相关的原发性肾上腺功能不全发生率大约 1%，老年和男性是可能的危险因素，低体重是其预后不佳的因素[71]。其发生机制不明，可能与炎症和抗体介导的肾上腺免疫破坏相关[18]。ICIs 相关的原发性肾上腺功能不全临床表现是非特异的，可有休克、低血糖、低血钠、高血钾等危及生命的表现，也可有乏力、恶心呕吐、腹痛、食欲不振和体重减轻等表现，因此，需要提高临床鉴别诊断的能力[72] [73]。其治疗主要是糖皮质激素及盐皮质激素的替代治疗[74]。

ICIs 相关尿崩症有少数报道，目前病因不明，主要表现为多尿多饮[75] [76] [77]，可以合并有垂体前叶功能减退的表现，需与有类似症状的疾病相鉴别[70]，可以使用去氨加压素治疗[78]。ICIs 相关甲状旁

腺功能减退也有报道，通常表现为低钙血症症状，如肌肉抽搐、全身无力、便秘等，通过静脉补钙，后口服补钙剂骨化三醇可得到缓解[79] [80] [81]，一般不建议补充甲状旁腺素[82]。

脂肪萎缩是 ICIs 治疗中非常罕见的不良反应，有使用了 PD-1 抑制剂导致脂肪萎缩病例报道，其特征是全身皮下脂肪的损失，可以继发高脂血症和胰岛素抵抗，患者可因肝脏、肾脏和心血管疾病死亡，且患者一般不能从脂肪萎缩状态恢复[66] [67] [83] [84]。有研究报道了 ICIs 相关库欣综合征，患者在使用 ICIs 药物联合治疗后出现高皮质醇血症，头颅磁共振证明促肾上腺皮质激素的增多来源于垂体，暂停 ICIs 药物后血皮质醇降低[85]。

ICIs 药物治疗可能会引起多个内分泌腺体的不良反应，可起病急、发病重，称之为 ICIs 相关自身免疫性多内分泌腺体综合征(autoimmune polyglandular syndromes, APS)，对其大致有 3 种分型，1 型 APS 是一种罕见的单基因病变，其特征为艾迪生病(原发性肾上腺功能不全)、甲状旁腺功能减退和粘膜皮肤念珠菌病，2 型 APS 是更常见的多基因病变，其特征是满足艾迪生病、自身免疫性甲状腺疾病、1 型糖尿病三者中的至少两种疾病，3 型 APS 可以认为是共存的多种累及其他器官组织的 irAEs (包含内分泌 irAEs) [70] [86] [87]。

4. 临床管理现状和展望

内分泌 irAEs 的治疗主要是症状控制与激素替代[8]，一般而言，可以通过治疗得到明显的改善后继续 ICIs 药物治疗。由于内分泌 irAEs 的发生时间可以在用药后的任何时间，因此需要加强用药前基线状态及用药后定期的内分泌相关检验检查的监测，遵照相关用药及毒性管理指南，以避免危及生命的内分泌急症出现。有研究表明用药前甲状腺抗体阳性、甲状腺彩超有异常表现的患者使用 ICIs 后更易发生甲状腺功能障碍[24] [88] [89] [90]，这提示在用药前可能需要强调完善甲状腺抗体和甲状腺彩超的检查，更多关于 ICIs 相关甲状腺及其他内分泌腺体的危险筛查因素研究还需要进一步开展。还有一些研究表明内分泌 irAEs 的发生和疾病更好的预后相关。例如，有前瞻性研究提示发生甲状腺功能障碍、垂体功能障碍和更长的总生存期(overall survival, OS)存在相关性[91] [92]。这可能说明发生内分泌 irAEs 的患者使用 ICIs 药物的获益更大，可能可以为临床抗肿瘤治疗的药物决策提供新的支持。

5. 结语

ICIs 药物的作用在肿瘤治疗方面日益突出，随着其使用增多，需要警惕内分泌 irAEs 的发生。内分泌 irAEs 的发病机制尚不明确，在此方面更多的研究有助于对疾病的监测和管理。对临床医生而言，ICIs 相关的内分泌功能障碍常见且可控，但需要及时识别罕见的内分泌危重症，这需要肿瘤科医生和内分泌科医生的重视和协作，从而提高抗肿瘤免疫治疗的安全性和有效性。

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