

IgG4相关性唾液腺炎的研究进展

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收稿日期: 2024年4月7日; 录用日期: 2024年5月1日; 发布日期: 2024年5月8日

摘要

IgG4相关性疾病(immunoglobulin-G4 related disease, IgG4-RD)是一种自身免疫性的炎性罕见病, 可累及多个脏器。累及唾液腺时叫做IgG4相关性唾液腺炎(immunoglobulin G4-related sialadenitis, IgG4-RS)。本病常与唾液腺的实体肿瘤、慢性感染等临床表现相似, 临床上容易误诊。因此本文拟从IgG4相关性唾液腺炎的免疫机制、临床表现、辅助检查及诊断治疗等方面的展开综述, 以期加强临床医师对IgG4相关唾液腺炎的认识。

关键词

罕见病, IgG4相关性疾病, 唾液腺炎, 免疫机制, 临床诊断

Research Progress of IgG4-Related Salivary Gland Inflammation

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Received: Apr. 7th, 2024; accepted: May 1st, 2024; published: May 8th, 2024

Abstract

Immunoglobulin-G4 related disease (IgG4-RD) is an autoimmune inflammatory rare disease that can affect multiple organs. When the salivary glands are involved, it is called immunoglobulin G4-related sialadenitis (IgG4-RS). This disease is often similar to the clinical manifestations of solid

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文章引用: 岳蓉蓉, 龚忠诚. IgG4 相关性唾液腺炎的研究进展[J]. 临床医学进展, 2024, 14(5): 107-113.

DOI: 10.12677/acm.2024.1451403

tumors and chronic infections of the salivary glands, and is easily misdiagnosed clinically. Therefore, this article intends to review the immune mechanism, clinical manifestations, auxiliary examination, diagnosis and treatment of IgG4-related sialadenitis, in order to strengthen clinicians' understanding of IgG4-related sialadenitis.

Keywords

Rare Diseases, IgG4-Related Diseases, Salivary Gland Inflammation, Immune Mechanism, Clinical Diagnosis

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1. 引言

IgG4 相关性疾病(IgG4-RD)是一种炎性自身免疫性罕见病,可导致全身多个器官受累,包括泪腺、颌下腺、甲状腺、胰腺等[1],累及唾液腺时叫做 IgG4 相关性唾液腺炎(immunoglobulin G4-related sialadenitis, IgG4-RS)。其主要临床病理特征是唾液腺无痛性慢性肿大,以累及颌下腺最为常见,并伴有血清 IgG4 水平升高、大量 IgG4 阳性浆细胞浸润和席纹状纤维化[2]。临床应用糖皮质激素疗效显著[3]。近年来人们对该病的发病机制和临床诊疗的研究逐渐加深,因此本文现就其最新的研究进展进行综述,以期为该病的临床诊疗和研究提供帮助。

2. IgG4 相关性唾液腺炎概述

2.1. 认识历程

IgG4-RD 的不同器官的临床表现过去被认为是不同疾病而相应分别命名,如 Mikulicz 病(泪腺和腮腺受累)、Kuttner 瘤(颌下腺受累)、Riedel 甲状腺炎、1 型自身免疫性胰腺炎、Ormond 病(腹膜后纤维化) [4] 等。直到 2003 年首次提出了系统性 IgG4-RD 的概念[5]。2005 年 Yamamoto 等发现米库利兹病(Mikulicz's disease, MD)具有和 IgG4-RD 许多共同的临床和病理特征[6],因此,MD 被认为是 IgG4-RD 的一种。2011 年 Geyer 等[7]提出 IgG4-RS 的概念来描述唾液腺的 IgG4-RD,并将慢性硬化性唾液腺炎[8]和 MD 包括在内。

2.2. 流行病学

据日本学者研究报道,IgG4-RD 发病率约为 2.8~10.8/100 万[1],其中大于 90%的患者年龄 > 50 岁,男女比例约为 4:1 [9],常可累及全身各种器官。浅表器官常见于泪腺、涎腺、鼻窦[10]、皮肤等。内脏器官常见于胰腺、胆道、腹膜后、肺和前列腺等[11],男性中老年患者尤为突出。

有研究指出 IgG4 相关性的唾液腺炎占有非特异性慢性涎腺炎患者比率约 33%,而 IgG4 相关性在慢性硬化性涎腺炎中占主导地位,约 92%~100% [12]。其中,大唾液腺中以颌下腺受累最为常见(94%),次之为腮腺(29%)和舌下腺[13]。也可能发生在小唾液腺,如硬腭等部位[14]。

2.3. 发病机制

2.3.1. 遗传因素

遗传学研究表明,几种人类白细胞抗原(HLA)和非 HLA 单倍型/基因型可能与 IgG4-RD 易感性或治

疗后疾病复发相关[15]。研究表明,一些 HLA 等位基因经常与自身免疫性疾病相关,如(HLA-DQB1*04、HLA-B8、HLA-DRB1*03)。此外,有多个非 HLA 风险位点,与免疫应答、腺泡细胞损伤及抗原产生有关[16]。

2.3.2. B 细胞

IgG4-RD 是由成熟的自身反应性 B 细胞活化所产生的针对自身抗原的自身免疫性体液反应产生的。在 IgG4-RD 患者血液和病理组织中可观察到 IgG4 阳性 B 细胞的寡克隆扩增[17]。活化 B 细胞的扩增与疾病进展性,受累器官数目[18]相关,治疗预后[19]及复发相关。成熟的 B 细胞可能通过表达血小板衍生生长因子(PDGF)来激活成纤维细胞,从而促进组织的纤维化[20]。

2.3.3. T 细胞

1) TFH 细胞: T 细胞亚群参与了 IgG4-RD 的发病。其中共表达碱性亮氨酸拉链 ATF 样转录因子(BATF)和白介素 4 (IL-4)的循环滤泡辅助性 T 细胞(TFH)的特定亚群的水平与疾病涉及的器官数量、循环浆母细胞数量以及血清中 IgG4 和 IL-4 的浓度[21]相关。TFH2 细胞释放的细胞因子可以促进 B 细胞分化为抗体分泌细胞[22],并诱导 B 细胞抗体向 IgG4 和 IgE 的类别转换。分泌 IL-4 的 TFH2 细胞的组织浸润程度与同一组织内 IgG4 阳性 B 细胞的数量和血清 IgG4 水平相关[23]。表达 IL21 的 TFH 细胞亚群与疾病活动性和对糖皮质激素的反应有关[24]。

2) TFR 细胞分泌 IL10 的滤泡调节性 T (TFR)细胞,可能在以 IgG4-RD 为标志的免疫球蛋白类别转换中发挥作用;此外, TFR 细胞数量与血清中的 TFR 水平与疾病受累器官数目有关[25]。

3) CD4+细胞毒性 T 淋巴细胞(cytotoxic T lymphocytes, CTLs):被认为是 IgG4-RD 的患者病理组织中最具代表性的 CD4+T 细胞亚群[26]。在成熟 B 细胞产生 C-C 趋化因子配体 5 (C-C motif chemokine ligand 5, CCL5)后, CD4+CTL 被募集到病理组织内[20],诱导组织驻留细胞凋亡[27],并通过表达转化生长因子 β (transforming growth factor β , TGF β)、干扰素 γ (interferon γ , IFN γ)和 IL-1 β 激活驻留成纤维细胞,最终诱导细胞外基质广泛沉积[28]。研究发现 CD8+CTLs 也有可能通过诱导病理组织中的细胞死亡在 IgG4-RD 中发挥致病作用[27]。

2.3.4. 巨噬细胞

在 IgG4-RD 患者的组织中,巨噬细胞可能参与了纤维化的发生[29]。不仅通过胞葬作用清除凋亡细胞,而且表达多种促纤维化分子,如 IL-1 β 、IL-10、IL-33、TGF β 和 CC18 [30] [31]。它在受累组织的纤维化区域有聚集倾向,且与组织纤维化程度相关[32] [33]。

2.4. 临床表现

IgG4-RS 常表现为唾液腺(尤其是下颌下腺)单侧或双侧对称性、持续性和无痛性肿胀、可能伴随腺体肿大[34],病程常超过 3 个月。通常唾液分泌正常或伴有轻度减少,约 30%的患者出现口干症。分泌障碍在下颌下腺中更为严重,早期类固醇治疗可改善[35]。IgG4-RS 应与其他主要唾液腺肿大的疾病相鉴别,如干燥综合征、慢性阻塞性下颌下唾液腺炎和嗜酸性粒细胞增生性淋巴肉芽肿等[36]。

2.5. 辅助检查

2.5.1. 血清学

血清 IgG4 水平检测较为快捷、方便且敏感度高,可为 IgG4-RS 的临床诊断和疗效观察提供一定依据。研究发现,血清 IgG4 水平升高也可见于少数健康人群、过敏性疾病等患者和部分自身免疫性疾病(自身免疫性肝病、急性胰腺炎、炎性肠病以及原发性肾小球病等) [37],因此,学者提出血清 IgG4 临界值为

1.35 g/L 时来诊断 IgG4-RD 的特异度不高, 可能会增加临床误诊率, 并提出以血清 IgG4 $\geq$ 2.07 g/L 作为 IgG4 的参考值上限时, 其对 IgG4-RD 与其他自身免疫性疾病的鉴别诊断具有较高的敏感度和特异度[38], 与 IgG4/IgG 联合作为 IgG4-RD 与其他自身免疫性疾病的鉴别诊断指标时, 能够进一步提高诊断效能。

2.5.2. 病理学

IgG4-RS 患者下颌下腺组织的病理学特点: 可见小叶结构、小叶间广泛纤维化、淋巴浆细胞浸润明显、淋巴滤泡形成、腺泡萎缩和闭塞性静脉炎[36]。免疫染色可见大量 IgG4+ 浆细胞浸润, IgG4 与 IgG 阳性细胞比例 $> 40\%$, 每个高倍视野下 IgG4 阳性细胞超过 10 个[35]。部分患者可能具有一种或几种上述组织病理表现, 因此, IgG4-RS 还应与良性淋巴上皮病变、淋巴瘤及炎性肌纤维母细胞性肿瘤等疾病鉴别[39]。对于唇腺组织的病理学表现, 其病理学形态与下颌下腺组织存在明显差异[40] [41]。少部分患者可形成淋巴滤泡、席纹状纤维化不明显, 且几乎无闭塞性静脉炎。因唇腺活检组织病理学特征往往不典型, 当临床高度怀疑 IgG4-RS 时, 建议首选下颌下腺组织行活检。到目前为止, 活检仍然是诊断 IgG4-RS 的金标准。

2.5.3. 影像学

超声检查是使用最广泛的技术。因其对患者的无创性和高耐受性, 以及低成本。超声下可见腺体增大, 双侧下颌下腺或腮腺内回声不均匀或低回声[42]。MRI 是诊断唾液腺肿胀的常用有用技术, 常表现为 T1WI 等信号或低信号, 肿块均匀强化[43]。对比增强的 T1 加权图像显示肿胀的下颌下腺网状增强。影像学和病理学相关性显示, 特征性网状增强与纤维化和小叶间隔和下颌下腺导管周围区域的炎性细胞浸润相对应[44]。

2.6. 诊断标准

2011 年日本学者确立了 IgG4-RD 的综合性诊断标准[45], 并在 2020 年制定了修订版诊断标准[46]: ① 临床表现: 单个或多个器官弥漫性/局限性肿胀或肿块形成; ② 血液学检查: 血清 IgG4 ≥ 135 mg/dL 以上; ③ 组织病理学: 受累组织中大量淋巴细胞、浆细胞浸润伴纤维化; IgG4 阳性浆细胞浸润; IgG4/IgG 阳性细胞比大于 40% 以上且 IgG4 阳性浆细胞超过 10/HPF。① + ② + ③: 确诊组; ① + ③: 拟确诊组; ① + ②: 疑诊组。确诊组即确诊 IgG4-RD [47]。在拟确诊组、疑诊组中, 需要结合各个器官的特异性诊断标准进一步诊断。该标准目前被大多数临床医师所接纳, 但由于病理活检的弊端, 有一定局限性。

2019 年 ACR-EULAR 制定了 IgG4-RD 的新的分类标准, 只有严格遵守纳入标准和排除标准, 且当纳入标准条目积分大于等于 20 分时才可进行诊断[48]。该标准不仅提高了诊断的特异性, 而且无需病理结果即可获得特异性较高的诊断, 符合当前临床的需要。

3. 治疗及预后

3.1. 手术

目前认为 IgG4-RS 患者均需治疗, 但对于一些无症状的淋巴结病损及轻微的颌下腺肿胀可以考虑随访观察[49]。对于一些高度纤维化且常规治疗疗效不佳的病灶, 可选择手术切除腺体, 解决局部症状, 但会造成腺体唾液分泌功能丧失, 并可能发生全身其他腺体及各脏器继续受累的情况[50]。

3.2. 糖皮质激素(Glucocorticoid, GC)是所有活动性

IgG4-RS 患者诱导缓解的一线药物[51]。通常应用 GC 治疗后起效迅速, 且有效率达 90% 以上[49]。

泼尼松龙初始治疗至少 40 mg, 应持续 4 周。临床上需要根据年龄、病情等进行调整剂量。病情控制后可规律减量, 后续随访中根据病情和复发风险再考虑逐渐减停或长期维持治疗。

3.3. 免疫制剂

常用的免疫抑制剂有吗替麦考酚酯、硫唑嘌呤、甲氨蝶呤、来氟米特、环磷酰胺、环孢素、他克莫司等。临床上应用最为广泛的是吗替麦考酚酯和硫唑嘌呤[3]。IgG4-RS 患者对免疫抑制剂治疗表现出良好的反应[52], 常与 GC 联合应用以提高疗效并减少复发[53]。

3.4. 生物制剂

目前, 生物靶向治疗在 IgG4-RD 中的应用正在被广泛研究, 目前有应用前景的生物靶向治疗包括: B 细胞清除治疗、靶向 T 淋巴细胞和靶向细胞内信号通路 JAK 抑制剂等。根据现有研究, 利妥昔单抗将来可能成为 IgG4-RD 的首选治疗方法[54]。对于常规治疗失败, 类固醇减量期间复发, 类固醇耐药或不耐受的患者, 可考虑使用利妥昔单抗, 长期使用这些药物可能会增加感染的风险[55]。

4. 总结

综上所述, IgG4-RS 的临床表现和病理特征有一定特点, 因此需要综合病史、临床表现、辅助检查和病理学表现来诊断该疾病, 降低临床误诊率, 制定最佳治疗策略。糖皮质激素是目前该病的首选药物, 可结合免疫抑制剂提高疗效并减少复发。随着对该病发病机制的研究深入, 对于 IgG4-RS 患者的个体化的精准治疗是今后该领域的发展方向。

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