

结缔组织病伴免疫性血小板减少症的诊断治疗进展

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摘要 免疫性血小板减少症 (ITP) 为免疫介导的疾病,分为原发性 ITP 和继发性 ITP。结缔组织病 (CTD) 是一组主要侵犯全身结缔组织的系统性自身免疫性疾病,容易合并继发性 ITP 的疾病包括系统性红斑狼疮、原发性干燥综合征、抗心磷脂抗体综合征等。CTD-ITP 患者出血倾向增加,严重者可致内脏出血,病死率高,是影响 CTD 患者预后的重要因素。近年来有关 CTD-ITP 的发病机制、临床表现、治疗方法的研究取得了较大进展,新型生物制剂和促血小板生成药物的使用让更多患者获益。早期诊断、出血程度分级、风险判断以及个性化达标治疗是获得良好预后的关键。

关键词 结缔组织疾病;免疫性血小板减少症

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Progress in the diagnosis and treatment of connective tissue disease associated with immune thrombocytopenia

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Abstract Immunological thrombocytopenia (ITP) is an immune-mediated disease, divided into primary ITP and secondary ITP. Connective tissue disease (CTD) is a group of systemic autoimmune diseases that mainly invade the whole body's connective tissue. It is the most common disease to combine with secondary ITP, including systemic lupus erythematosus, primary Sjogren syndrome, and antiphospholipid antibody syndrome. CTD-ITP patients have an increased tendency for bleeding, and in severe cases, it can lead to visceral bleeding with a high mortality rate, which is an important factor affecting the prognosis of CTD patients. In recent years, significant progress has been made in the research on the pathogenesis, clinical manifestations, and treatments of CTD-ITP. The use of new biological agents and platelet promoting drugs has benefited patients more. Early diagnosis, grading of bleeding severity and risk assessment, as well as personalized and standardized treatment are key to achieve a good prognosis.

Key words Connective tissue disease; Immune thrombocytopenia

免疫性血小板减少症 (immune thrombocytopenia, ITP) 为免疫介导的血小板破坏性疾病,以血小板计数减少为主要特点^[1]。国际上通常将血小板计数 $< 100 \times 10^9/L$ 定义为血小板减少。成人 ITP 年发病率约为 2~5/10 万^[2,3]。根据是否有原发病存在可将 ITP 分为原发性 ITP 和继发性 ITP。结缔组织病 (connective tissue disease, CTD) 是一类免疫介导的累及多器官多系统结缔组织的自身免疫性疾病,是发生继发性 ITP 的常见疾病^[4~6]。CTD-ITP 临床表现异质性极大,轻者仅为无症状血小板减少或皮肤黏膜出血,重者可出现严重内脏出血,病死率高^[4,5]。尽管进行充分的免疫抑制治疗,仍有部分

患者的血小板不能得到有效的提升,其复发性、难治性使 CTD-ITP 患者的临床管理面临巨大挑战。

目前,关于 ITP 发病机制及治疗方法的研究主要关注于原发性 ITP,其研究进展亦为 CTD-ITP 的诊治提供了新的思路。我们中心对 CTD-ITP 的回顾性分析显示,ITP 主要继发于系统性红斑狼疮 (systemic lupus erythematosus, SLE)、干燥综合征 (primary Sjogren syndrome, pSS) 及抗心磷脂抗体综合征 (antiphospholipid antibody syndrome, APS)^[7]。本文对 SLE、pSS、APS 合并 ITP 诊治新进展的研究进行综述,旨在促进对 CTD-ITP 的认识及管理。

一、发病机制

近年来 ITP 发病机制在体液免疫和细胞免疫机制方面取得了重要进展。在体液免疫机制方面:ITP 患者体内存在血小板膜蛋白特异性 IgG 抗体^[8],它与纤维蛋白受体 GP II b ~ III a、VWF 受体 GP I b-IX 以及胶原受体 GP I a ~ II a 等结合,通过巨噬细胞 FC 受体介导的调理作用或者抗原抗体复合物激活补体对血小板和/或巨核细胞进行吞噬破坏^[9,10]。ITP 细胞免疫异常包括辅助性 T 细胞 Th1/ Th2、Th17/调节性 T 细胞 (regulatory T cell, Treg) 的失衡,抗原呈递细胞的功能异常,细胞毒性 T 细胞对血小板的直接杀伤,调节性 B 细胞 (regulatory B cell, Breg) 的免疫耐受功能缺陷等^[11~14]。研究发现体外 Breg 调节活性需要通过 CD40L 与 CD40 结合激活,而血小板表面表达 CD40L,血小板数量的增加可提高 ITP 患者 Breg 的活性,证实了抗 CD40L 自身抗体、Breg 均与血小板减少症有关^[15,16]。同时研究表明 ITP 患者血小板生成素 (thrombopoietin, TPO) 水平正常或仅轻度升高 (TPO 水平相对不足),可能为影响血小板生成的重要因素^[17]。

CTD-ITP 发病机制是血小板被抗血小板自身抗体破坏,其方式与经典 ITP 类似,但区别于原发性 ITP,CTD 患者除了存在抗血小板抗体外,还可出现抗磷脂抗体等,这些抗体可直接与血小板结合,因此 CTD-ITP 发病机制更为复杂^[18,19]。

部分 SLE 患者骨髓中的血小板生成受损或脾脏中的血小板隔离增加,这两种过程都会导致血小板减少^[18]。此外,在许多 SLE 病例中发现高水平的含 IgG 的免疫复合物^[20],它可以通过 Fc γ RIIA 受体启动血小板活化^[21]。Fc γ RIIA 通过免疫复合物激活的血小板释放血清素,并可暂时隔离在狭窄的血管床中,例如脑和肺血管^[22]。我们的研究也表明 CTD-ITP 患者血小板与 B 细胞百分比之间存在明显的负相关,证实了 B 细胞在 ITP 发病机制中的作用^[7]。SLE 中其他报道的血小板通路包括 Toll 样受体激活、补体激活、细胞外囊泡脱落以及与雷诺现象相关的缺血再灌注^[19,23]。

自身免疫因素同样是导致 pSS-ITP 主要原因^[24]。pSS 患者的 T 细胞和 B 细胞活化、增殖后,产生多种自身抗体,抗体吸附于血小板表面后可破坏血小板膜的结构和完整性。脾功能亢进情况下,免疫复合物的血小板在脾脏内破坏过多。研究证实,pSS-ITP 与骨髓巨核细胞产血小板功能异常密切相关,体液免疫和细胞免疫失调均可参与并加重巨核细胞产板不良^[25]。

APS-ITP 病理生理学机制尚未完全阐明,可能是多种机制共同作用的结果,但已提出了几种机制包括抗磷脂介导的血小板活化和消耗、ITP 样自身抗体导致血小板破坏以及血栓性微血管病^[26]。值得重视的是,APS 患者可同时出现血栓形成和血小板减少,提示血小板是参与疾病调节的重要因素^[18]。一些受体被认为通过辅因子-抗体复合物介导血小板活化,如 Toll 样受体、ApoER2、GPIb-V-IX 和 Fc γ RIIA^[27,28]。在 APS 中发现 Fc γ RIIA 通过免疫复合物激活的血小板,这与 SLE 研究一致^[29,30]。免疫复合物对血小板的持续低度激活会导致更高的血小板代谢,最终导致血栓形成并伴血小板减少症^[31]。

二、临床特点

SLE 是 CTD-ITP 最常见疾病,近 40 年国际学会 SLE 的分类标准及疾病活动度均包含血小板减少^[32]。SLE 中血小板减少发生率 20% ~ 40%,多达 16% 的患者以此为首发表现,在诊断前数月甚至 10 年就可出现,重度细胞减少率为 3% ~ 10%^[7,33,34]。对 ITP 患者中 SLE 的发生率及其之间的潜在关系,有报道在 ITP 组和对照组中 SLE 发生率分别为 62.0/10 万人年和 2.10/10 万人年,累积发生率高于对照组 ($P < 0.0001$)^[35]。一项最新 Meta 研究也支持抗核抗体 (antinuclear antibody, ANA) 阳性的 ITP 患者中 SLE 发生率显著提高^[36]。因此,早期筛选出自身免疫性 ITP 患者并密切监测其转归对早期 SLE 诊断及治疗具有重要意义。国内外研究均证实血小板减少是 SLE 具有较高疾病活动性、终末器官损伤可能性和死亡率的一个预测因子^[37,38]。

与 SLE 患者类似,pSS 血液系统受累最常见的是全血细胞减少^[39],一项对 1 927 名干燥综合征国际合作联盟登记的受试者研究中,886 名 pSS 患者血小板减少的发生率为 5% ~ 13%,可以出现在病程中的任何时间^[40]。我中心研究 CTD 疾病中 pSS 继发血小板减少仅次于 SLE,高达 18.8%^[7];在 pSS 患者中,与无 ITP 的 pSS 患者相比,pSS-ITP 患者更年轻,疾病活动性更高^[41]。也有报道 SS 发生率高于 SLE,分别为 53.4% 和 40.5%^[42]。

APS 是一种以血管血栓栓塞或产科并发症为特征的疾病,伴有持续的血清学抗磷脂抗体^[43,44]。APS-ITP 作为常见的“非标准”临床表现,发生率高达 20% ~ 50%^[31,45]。大多数 APS-ITP 为轻度且无大出血,小部分患者可能出现严重的血小板减少症,

进而导致大出血,故即使血小板减少症没有进入APS定义标准,但被广泛视为“高风险”APS的警告信号^[31],因此应进行全面评估。同时,ITP常与严重的APS表型有关,例如动静脉血栓形成风险增加。当妊娠APS-ITP诊断一旦成立,出血及血栓风险极高,大大增加了不良妊娠及死亡风险。

我中心探索ITP与CTD-ITP的临床差异,SLE-ITP组较原发性ITP组存在较高的ANA阳性率及低补体血症,在原发性ITP患者中有一部分患者有一些免疫学特征^[7],如ANA阳性,但不符合任何CTD的诊断,将之归类为自身免疫性ITP。与其他原发性ITP患者相比,自身免疫性ITP患者的C3水平下降率明显升高,说明补体系统在自身免疫性ITP患者的发病机制中起着重要作用。

三、治疗进展

目前CTD-ITP治疗尚无明确循证指南,临床上多参照原发性ITP方案进行治疗,即阻止血小板过度破坏和促血小板生成。治疗上除了传统的激素、免疫抑制剂以外,生物制剂和促血小板生成药物的使用让更多患者获益。

1. 一线治疗:糖皮质激素类药物(glucocorticosteroids,CS)是ITP的一线治疗药物和基石。若患者起病危急,为重症或难治性甚至危及生命,则需予以大剂量激素冲击治疗或大剂量地塞米松。大剂量激素慎用高龄、糖尿病、高血压、青光眼等患者,必要时可给予抗病毒药,预防疱疹、乙肝等病毒再激活。研究显示大剂量地塞米松7d内的早期反应率显著高于常规剂量,不良反应发生率低,尤其适用于需快速提升血小板水平患者^[46],但对于CTD-ITP患者CS的使用剂量及减停时间,需要区别于原发性ITP,不仅需要评估患者血小板减少程度、出血风险,更需要结合CTD其他受累器官情况及权衡药物副作用的风险及获益。考虑CTD为系统性慢性疾病,建议不盲目过度追求血小板一定要达到正常,不应按照原发性ITP治疗指南,血小板计数正常后立即撤减激素。

静脉免疫球蛋白(intravenous immune globulin,IVIg)是治疗ITP的一线用药,对70%~80%的ITP有效,且反应时间优于CS。静脉免疫球蛋白可竞争性抑制抗原呈递细胞与T细胞结合,通过阻断活化的Fc γ 受体后上调抑制性受体Fc γ RIIb,中和病理性自身抗体和致病性细胞因子,发挥调节免疫平衡的作用^[47]。故常用于ITP合并大出血、紧急侵入性手术准备、难治性ITP、妊娠或分娩前^[1]。目前研究表

明GP I b-IX抗体阴性ITP患者对IVIg疗效相对较差,且IVIg价格较高,故建议有条件者可行血小板糖蛋白特异性自身抗体检测,有助于对其疗效进行预判^[48]。IgA缺乏和肾功能不全患者应慎用。

2. 二线治疗:免疫抑制剂是治疗CTD-ITP的基本二线药物,包括羟氯喹、环孢素、吗替麦考酚酯、硫唑嘌呤、环磷酰胺等。此类药物通过抑制T、B淋巴细胞过度活化,抑制自身抗体对血小板的破坏。CTD-ITP免疫抑制剂的使用策略既要联合又要个性化定制,因为CS联合免疫抑制剂的使用,依据受累脏器及其损伤程度确定治疗方案,不仅可控制基础疾病,提高并维持CTD-ITP疗效,同时更有助于CS减量,减少激素副作用,提高安全性。需要注意免疫抑制剂本身的骨髓抑制作用,密切监测病情及治疗过程中患者血小板变化,及时调整用量或改用另一种免疫抑制剂。

除了传统的激素和免疫抑制剂以外,生物疗法如利妥昔单抗和促血小板生成药物:重组人血小板生成素(rhTPO)、非肽类TPO类似物(艾曲泊帕)和TPO拟肽(罗米司汀)已逐渐被广泛用于ITP的治疗。利妥昔单抗对年轻女性和病程小于1年者疗效较好,病程较长的患者疗效相对较差^[49,50],其反应率可能与ITP患者病程及既往治疗种类相关。脾切除与否不影响ITP患者对利妥昔单抗的治疗反应^[51]。利妥昔单抗治疗后特别是联合大剂量激素使用者可予小剂量IVIg预防感染。利妥昔单抗禁用于活动性乙型肝炎患者。ITP患者使用促血小板生成药物反应率满意,持续应用时可维持6~8年的长期疗效^[1],但停药后多数患者复发,故CTD-ITP患者使用该类药物需联合其他一、二线药物巩固疗效。不同的血小板生成药物其分子结构、作用靶点不同,因此,对于一种促血小板生成药物无效或不耐受患者,更换其类型或采用序贯疗法可能使患者获益^[52]。这两类药物在CTD-ITP特别是SLE-ITP及SS-ITP患者中同样取得较好的治疗效果^[53]。

近年来随着新药的涌现及诊断治疗的规范化,脾切除术率明显下降,虽然对难治性ITP有效率明确,但因其相关感染、术后出血、血栓等并发症,使其手术的必要性及时机充满争议性。

另一种新的ITP药物福坦替尼(Fostamatinib)是一种脾酪氨酸激酶(SYK)抑制剂,通过阻断巨噬细胞吞噬血小板。慢性ITP患者中应答率为43%,稳定响应率为18%,如果较早使用福坦替尼,该比率可能会更高^[54,55]。已报道的不良事件分别包括

28%的受试者出现轻中度高血压和31%的受试者出现轻中度腹泻。

较多针对ITP的治疗还处于临床开发的晚期阶段,包括抗新生儿Fc受体(抗FcRn)、BTK抑制剂和补体抑制剂。新生儿Fc受体能保护IgG和白蛋白在细胞内“不被降解”,并将其释放回血液循环中。靶向FcRn的抑制剂通过去除对IgG的保护作用治疗由自身抗体导致的自身免疫性疾病。目前该类药物主要有洛利昔珠单抗(Rozanolixizumab)和艾加莫德(Efgartigimod),两者耐受性良好,在原发性ITP患者中反应率分别为50%和38%,尽管IgG水平下降,但感染风险不会显著增加^[56,57]。BTK抑制剂(BTKi)可以通过与BTK上的Cys-481位点共价结合,阻止BTK的活化,从而抑制B细胞的发生、发展,是ITP治疗的潜在靶点。BTKi已开发用于慢性淋巴细胞白血病等^[58]。利扎鲁替尼(Rilzabrutinib)是一种可逆的口服BTKi,可通过双重作用机制增加ITP患者的血小板数量,减少巨噬细胞(Fc γ 受体)介导的血小板破坏以及减少致病性自身抗体的产生。最新一项复发/难治ITP患者的全球I/II期临床研究表明^[59],40%患者可到达主要终点:定义为至少连续两次血小板计数 $\geq 50 \times 10^9/L$ 。所有剂量组的不良反应均为1级或2级,常见的不良反应为腹泻、恶心等消化道症状。然而,BTKIs可抑制血小板聚集而导致出血。舒替利单抗(Sutimlimab)是一种人源化单克隆抗C1s IgG4抗体,选择性抑制经典途径。一项慢性/难治性ITP研究中,共有12例患者接受了治疗,其中42%患者获得持久的血小板计数提高,三分之一的患者在两天或更短的时间内血小板计数就得到提升,未发现与治疗相关的不良事件^[60]。

因CTD-ITP本身发病机制复杂性且表现形式多样性,决定了其治疗策略并非单一药物的使用,不同经典药物联用的治疗策略也为ITP提供新思路,如羟氯喹和泼尼松联合使用对较多ITP患者有效。Arnal等^[61]报道了11例单纯CS失败的患者中羟氯喹联用泼尼松的长期结果,其中64%获得了持久的应答。Khellaf等^[62]研究了羟氯喹对不能确诊为SLE但ANA阳性的ITP及SLE-ITP患者的影响,其中羟氯喹与泼尼松联合使用的总应答率为60%,SLE患者的总应答率高于仅ANA阳性的患者(83% vs. 50%)。

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