

继发性中枢神经系统淋巴瘤的诊疗进展

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摘 要

继发性中枢神经系统淋巴瘤(secondary central nervous system lymphoma, SCNSL)是一种起源于其他部位随后侵入中枢神经系统(central nervous system, CNS)的淋巴瘤亚型, 其治疗方法有限, 预后较差, 早期诊断和干预至关重要。在本文中, 我们综述了与SCNSL相关的常见临床表现、影像学特征、鉴别诊断、治疗及预后, 以期对相关研究和临床实践提供参考。

关键词

中枢神经系统, 淋巴瘤, 弥漫大B细胞淋巴瘤, 磁共振成像

Advances in the Diagnosis and Treatment of Secondary Central Nervous System Lymphoma

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Abstract

Secondary central nervous system lymphoma (SCNSL) is a lymphoma subtype originating extraneurally and subsequently infiltrating the central nervous system (CNS). Treatment options are limited, and the prognosis is generally poor, making early diagnosis and intervention crucial. In this paper, we discussed the common clinical manifestations, imaging features, differential diagnoses, treatment,

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and prognosis associated with SCNSL, in order to provide a reference for related research and clinical practice.

Keywords

Central Nervous System, Lymphoma, Diffuse Large B-Cell Lymphoma, Magnetic Resonance Imaging

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1. 引言

淋巴瘤是起源于淋巴结和淋巴组织的恶性肿瘤，通常表现为淋巴结进行性无痛肿大，伴有发热、盗汗和体重减轻等症状。它包括霍奇金淋巴瘤(Hodgkin's lymphoma, HL)和非霍奇金淋巴瘤(non-Hodgkin's lymphoma, NHL)，前者通常预后更好。虽然淋巴瘤的确切病因和发病机制尚不清楚，但据推测，感染、免疫、物理和化学原因以及遗传等因素均可导致淋巴瘤的发生。在 NHL 中，弥漫性大 B 细胞淋巴瘤(diffuse large B-cell lymphoma, DLBCL)是最常见的亚型[1]。R-CHOP 方案(利妥昔单抗 + 环磷酰胺 + 阿霉素 + 长春新碱 + 泼尼松)可使 60%以上的患者得到缓解。然而，若 R-CHOP 治疗无效，那么尽管后续治疗可能达到部分缓解，这些患者的预后仍然很差[2]。

中枢神经系统淋巴瘤(central nervous system lymphoma, CNSL)包括原发性和继发性，由 Kakulas 等人[3]于 1962 年正式报告。原发性中枢神经淋巴瘤(primary central nervous system lymphoma, PCNSL)是一种罕见的淋巴结外非霍奇金淋巴瘤，通常局限于大脑、脊髓、软脑膜、眼睛和脑脊液，没有全身扩散的证据。继发性中枢神经淋巴瘤(secondary central nervous system lymphoma, SCNSL)是指无论在系统性淋巴瘤的初次诊断时还是在复发的情况下，存在中枢神经系统(central nervous system, CNS)受累。临床上，中枢神经淋巴瘤的症状多种多样，包括局灶性神经功能障碍、颅内压升高症状、精神和情绪改变、认知功能障碍和癫痫发作。最常见的 SCNSL 亚型是 DLBCL。与未受 CNS 累及的患者相比，受 CNS 累及的 DLBCL 患者的总体生存率(overall survival, OS)较低[4]。一项大型国际回顾性队列研究[5]显示 SCNSL 预后不良。目前，现有的预防方法已被证明效果不佳，需要进一步探索新的治疗方法，包括靶向通路抑制剂和细胞疗法等[6]。

2. SCNSL 的临床特征

SCNSL 是 CNSL 的一种罕见且具有侵袭性的亚型，其特征是淋巴瘤从颅外部位扩散到脑、脑膜、脊髓和眼睛。它约占所有 CNSL 的 10%~25%，中位 OS 为 3.9 个月至 1.5 年[7]。SCNSL 患者多为中老年发病，发病率男性略高于女性。临床上，SCNSL 的表现根据淋巴瘤在中枢神经系统中的位置和范围而不同，可出现认知障碍、共济失调、乏力、感觉障碍、癫痫等神经系统症状，也可出现与颅内压增高相关的症状，如头痛、恶心、呕吐、精神状态改变等。影像学检查，比如计算机断层扫描(computed tomography, CT)或磁共振成像(magnetic resonance imaging, MRI)通常会发现大脑或脊髓内有多处病变，这些病变可能表现为增强的肿块，周围伴有水肿。DLBCL 是最常见的病理类型，要获得明确的诊断通常需要通过脑组织活检或对脑脊液进行病理学分析。

3. SCNSL 的鉴别诊断

SCNSL 需要与其他疾病相鉴别, 包括 PCNSL、高级别胶质瘤(high-grade gliomas, HGG)、脑转移瘤和脑膜瘤等肿瘤性疾病, 以及脱髓鞘假瘤(demyelinating pseudotumors, DPT)、脑脓肿、中风和脑结核瘤等非肿瘤性疾病。

3.1. 与其他肿瘤疾病的鉴别

3.1.1. PCNSL

PCNSL 是一种罕见的淋巴结外 NHL, 局限于中枢神经系统, 通常累及脑室周围区域、基底神经节或胼胝体。PCNSL 的发病率为 0.47/100,000 人年, 占淋巴结外淋巴瘤的 4%~6%, 占新诊断的 CNS 肿瘤的 4%。它在男性中比在女性中更常见[8], 在免疫功能低下和免疫功能正常的患者中均有发生。由于 PCNSL 和 SCNSL 的临床特征和神经影像学表现非常相似, 仅通过 CT 或 MRI 来区分 PCNSL 和 SCNSL 具有很大的挑战性[9]。从症状上看, 这两种疾病都可能表现出非特异性表现, 包括局灶性神经功能障碍、颅内压升高(例如头痛、恶心、呕吐)、精神和情绪变化、认知能力下降和癫痫发作等。在影像学上, PCNSL 病变在免疫功能正常的患者的 CT 扫描中通常呈现等密度。病变在 MRI 上通常为 T1 加权相(T1-weighted images, T1WI)和 T2 加权相(T2-weighted images, T2WI)呈现等或低密度, 在扩散加权成像(diffusion-weighted imaging, DWI)上显示高信号强度伴周围水肿。此外, PCNSL 病变在增强 MRI 上通常表现出均匀的增强, 具有明确的边界[10]。在免疫功能低下的患者中, 例如患有艾滋病或正在接受免疫抑制治疗的患者, 病变通常表现为多灶性, 伴有不均匀的周边增强和广泛的血管源性脑水肿[11]。一般而言, 此类病变在脑 CT 上表现为等低信号, 在 T1WI 上表现为等至低信号, 在 T2WI 上表现为等高信号。坏死性病变可能在 T2WI 上呈现中心高信号, 90%的患者可出现周围水肿。总体而言, PCNSL 的影像学特征可能因患者的免疫状态而异[10]。

SCNSL 在 T1 和 T2 加权成像上表现出与免疫功能正常的 PCNSL 相似的特征[12], 既往研究称约三分之二的 SCNSL 病例表现出软脑膜侵犯, 三分之一表现出脑实质侵犯[12][13]。然而, 最近的研究表明, 脑实质受累可能更为普遍[5][9][14]。虽然 SCNSL 病变在增强 MRI 上也可能表现出均匀增强, 但与 PCNSL 相比, 它们也可能表现出边界不太清晰的异质增强模式。总体而言, MRI 在区分 PCNSL 和 SCNSL 方面并不敏感。有趣的是, PCNSL 病变和 SCNSL 病变在 PET 成像上通常都表现出代谢活性增加[15]。然而, PCNSL 病变通常局限于中枢神经系统, 而 SCNSL 则可能涉及颅外部位, 这凸显了 PET 在区分 PCNSL 与 SCNSL 方面的关键作用。

综上所述, 临床表现和 CT/MRI 不足以区分 PCNSL 与 SCNSL。可能需要 PET 成像、睾丸超声、骨髓活检、腰椎穿刺、玻璃体和/或视网膜细胞学检查以及立体定位脑活检等辅助技术才能准确识别[16][17]。

3.1.2. HGG

在增强 MRI 上, 可以观察到 SCNSL 和 HGG 之间的明显区别。SCNSL 病变通常显示均匀增强, 而 HGG 通常表现为包含坏死和更多皮质受累的区域[18]。此外, 灌注加权成像(perfusion-weighted imaging, PWI)和磁共振波谱(magnetic resonance spectroscopy, MRS)是可靠的鉴别工具[18]。相对脑血容量(relative cerebral blood volume, rCBV)值升高表明存在 HGG [19]而不是淋巴瘤[20], 因为胶质瘤通常表现出与恶性肿瘤相关的丰富新生血管[21]。此外, 胆碱(choline, Cho)化合物峰值的显著增加进一步支持 HGG 的诊断[21]。

3.1.3. 脑转移瘤

区分 SCNSL 和脑转移瘤需要考虑临床病史、影像学特征、组织病理学和全身评估。SCNSL 通常发

生在已知的全身淋巴瘤背景下,在MRI上表现为均质增强的肿块,而脑转移瘤源自身体其他部位的原发性癌症(如肺癌、乳腺癌、胃癌、皮肤癌或结肠癌),通常表现为位于灰白质和血管边界区的多发性病变,边缘增强,有明显的血管性水肿[22]。MRS中的转移通常显示Cho/肌酐(creatinine, Cr)水平升高和N-乙酰天冬氨酸(N-acetyl-aspartate, NAA)水平降低。此外,可能观察到脂质(lipids, Lip)和乳酸(lactate, Lac)峰,这分别归因于坏死和无氧呼吸[23]。组织病理学检查和分子检测有助于明确诊断,并进行系统评估以在疑似脑转移病例中识别潜在的原发性恶性肿瘤。

3.1.4. 脑膜瘤

脑膜瘤是最常见的非恶性脑肿瘤。通常,病变在CT扫描中呈现等密度或略高密度。此外,CT成像可以有效检测骨侵犯[24]。在MRI上,脑膜瘤在T1WI上呈现等低信号,在T2WI上呈现等略高信号。一般而言,它们表现出特征性的硬脑膜位置,与硬脑膜以宽基相连,增强后呈明显均匀强化。脑膜瘤在必要时可行手术切除,但CNSL很少采用根治性手术切除。

3.2. 与其他非肿瘤疾病的区别

3.2.1. DPT

脱髓鞘假瘤又称为肿瘤样脱髓鞘疾病,是一种影响中枢神经系统的炎症性疾病,会导致神经纤维脱髓鞘[25]。由于SCNSL和DPT的临床表现和影像学表现存在重叠,因此很难区分它们。DPT病变通常位于幕上区域,主要位于额叶和顶叶,通常表现为直径大于2厘米的单个肿块[25]。CT上,DPT表现为边界清晰的低密度病变。MRI上,DPT病变孤立,T1WI上呈相对低信号,T2WI、FLAIR和DWI上呈高信号[25][26]。此外,DPT病变可能表现出不同的增强模式,包括独特的“开环”模式,以及结节性、环状增强或弥漫性增强[18][26]。糖皮质激素是治疗DPT的首选药物[27]。重要的是,DPT和NHL都对类固醇敏感,这可能导致两种疾病的区分不准确[25][26]。

3.2.2. 脑脓肿

脑脓肿常表现为全身感染症状,如发热和白细胞增多,以及非特异性中枢神经系统症状,如头痛、局灶性神经功能障碍和精神状态改变[28]。MRI上,脓腔在T1WI上呈低信号,在T2WI上呈高信号。此外,脓肿壁在T1WI和T2WI上均呈等信号。通常,周围的水肿在T1WI上呈稍低信号,在T2WI上呈稍高信号[29]。DWI常显示中心脓肿扩散受限,信号强度高。随后的对比增强显示仅在脓肿壁中出现明显的环状增强。在脑脊液分析中,脑脓肿通常表现为白细胞计数升高,主要是中性粒细胞,以及病原体培养阳性[28]。相反,SCNSL可能出现淋巴细胞增多或与淋巴瘤一致的非典型细胞[30]。

3.2.3. 脑卒中

中风通常发生在具有高血压、糖尿病、吸烟和心房颤动等风险因素的个体中,而SCNSL通常与免疫抑制有关,包括HIV感染、器官移植或免疫抑制治疗等情况。缺血性中风通常表现为与受影响的大脑区域相对应的神经功能缺损突然发作,例如虚弱、麻木或言语困难。在CT上,缺血性中风表现为低密度。在MRI上,它在T1WI和表观扩散系数(ADC)上显示为低信号,在T2WI和DWI上显示为高信号,并且负责血管可能出现狭窄或阻塞。重要的是,与SCNSL相比,缺血性中风病变通常不会增强。一种罕见的缺血性中风形式源于脑静脉或窦阻塞,称为静脉梗塞。CT扫描可能显示阻塞静脉和/或窦内的高密度阴影,显示诸如索带征或空三角征等特征。MRI可能显示闭塞静脉和/或窦内没有流空信号[31]。数字减影血管造影(Digital subtraction angiography, DSA)可以显示受影响的静脉或窦结构中相应的充盈缺损,是诊断静脉窦病变的金标准。对于出血性中风,CT比MRI更敏感。在CT上,出血性中风表现为脑实质或蛛

网膜下腔内的高密度。总体而言,钆增强是区分淋巴瘤和中风的显著特征[32]。当识别变得困难时,可能需要进行 PET 和活检等额外检查。

3.2.4. 脑结核瘤

脑结核瘤是结核分枝杆菌感染引起的中枢神经系统肉芽肿性病变,通常是全身性结核病的后遗症。它表现出典型的结核病症状,例如低热、盗汗和疲劳[33]。颅内结核可分为脑膜结核和脑实质结核。结核球是脑实质结核中最常见的形式,其特征是单个或多个病变,通常位于灰白质交界处[34]。在 MRI 上,脑结核瘤在 T1WI 上显示为低信号,在 T2WI 上显示为不均匀信号,常表现为钙化[35]。确诊依靠于脑脊液培养或脑活检中结核分枝杆菌的检测[33]。

总之,SCNSL 的诊断仍然具有挑战性。目前正在进行许多研究,重点关注新型 PET 示踪剂[36]、独特的 MRI 造影剂[37]、创新的成像标记物[38]和集成 PET/MR 系统[39],这些研究对于改善早期诊断、治疗和预后发挥着关键作用。值得注意的是,CNSL 常常与其他脑部疾病相似,导致误诊和不慎使用类固醇。类固醇可能会影响成像和病理学结果,因此在确诊前应避免使用类固醇[17][18]。如果无法避免使用类固醇,应在 24 至 48 小时内立即进行活检[40]。目前,对活检或切除的肿瘤标本进行病理检查仍然是诊断的金标准。

4. SCNSL 的危险因素及预防

DLBCL 中继发中枢神经系统受累的发生率约为 5% [41],患者中位生存期为 2~5 个月[14]。中枢神经系统复发会导致毁灭性的后果,因此临床医生必须准确识别高危人群并制定有效的治疗和预防策略。多项研究已发现与 SCNSL 相关的多种风险因素,例如高国际预后指数(international prognostic index, IPI)评分、血清乳酸脱氢酶(lactate dehydrogenase, LDH)水平升高、淋巴瘤分期晚期、多个结外部位受累、特定的结外部位(例如肾脏、睾丸、子宫、乳腺)、BCL-2 和 MYC 双重扩增以及免疫球蛋白 M (IgM)副蛋白的存在[13][42]-[46]。

一些研究提出,利用脑脊液中的循环微小 RNA (miRNA)和循环肿瘤 DNA (ctDNA)可以监测和预防 SCNSL,尽管它们的临床应用仍然有限[47][48]。近年来,中枢神经系统国际预后指数(CNS-IPI)风险模型被广泛用于评估接受 R-CHOP 化疗的 DLBCL 患者中枢神经系统复发或进展的风险[44]。其可靠性和可重复性有助于及时干预并改善预后。尽管我们在识别高风险 SCNSL 患者方面取得了进展,但在制定安全有效的预防和治疗策略方面仍然存在很大差距[49]。常见的预防措施,例如鞘内注射(intrathecal injection, IT)甲氨蝶呤(methotrexate, MTX)和/或阿糖胞苷(Ara-C),由于血脑屏障渗透性差,效果有限。静脉注射高剂量甲氨蝶呤(HD-MTX)和其他策略在最近的大型回顾性研究中显示出不确定的预防效果[50][51]。

5. SCNSL 的治疗及预后

目前,SCNSL 尚无标准化治疗方法。通常,SCNSL 的当前选择主要包括基于 HD-MTX 和 R-CHOP 的化疗、基于全脑放射治疗的放疗、IT、自体造血干细胞移植(autologous hematopoietic stem cell transplantation, ASCT)以及嵌合抗原受体 T 细胞(chimeric antigen receptor T cell, CAR-T)、靶向通路抑制剂和免疫治疗等新兴治疗方式。能够穿过血脑屏障的新型药物如伊布替尼[52]和来那度胺[53]在 SCNSL 治疗中的应用越来越多。

先前的研究表明,SCNSL 患者的预后因素包括患者相关因素(例如年龄超过 60 岁、ECOG 评分 > 1 分)、疾病相关因素(例如脑实质和软脑膜受累、初始治疗期间 SCNSL 发展)以及治疗相关因素(例如足量的中枢系统 MTX 给药)。此外,表达模式(例如初始治疗或复发)和一线化疗(利妥昔单抗、MTX、阿糖胞苷和噻替哌)后的缓解情况可作为预后指标[5][54]。

6. 总结

目前, 由于临床表现多变、诊断程序复杂、鉴别诊断困难和预后不良, 诊断和治疗 SCNSL 面临巨大挑战。在早期筛查和微小病灶辨别上, SCNSL 的诊断有时需要通过更高灵敏度的早期诊断技术来提高对中枢神经系统微小病灶的检测灵敏度。外周血和脑脊液中 ctDNA 及 miRNA 的检测也正在成为一种可用于监测 SCNSL 的早期发生和复发的生物标志物诊断手段。基因检测指导的靶向治疗、免疫治疗、脑脊液屏障穿透药物的开发、精准的放射治疗等个性化治疗方案值得临床医生进一步探索。此外, 如何改善治疗副作用以及提高患者生活质量也需要得到更多关注。

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