·临床研究·

大脑淋巴瘤病的临床及MRI特点分析

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摘　要：【目的】大脑淋巴瘤病(LC)是中枢神经系统淋巴瘤(PCNSL)的特殊类型，目前报道较少，预后较其它类型的PCNSL差，早期诊断对判断预后十分重要。本文报道经脑立体定向活检明确病理的大脑淋巴瘤病3例，以提高临床医师对大脑淋巴瘤病的认识。【方法】回顾性分析2017年1月-2020年7月间，中山大学附属第三医院岭南医院确诊为大脑淋巴瘤病3例患者的临床表现、影像学、神经病理特征。【结果】3例患者分别为44、61和64岁男性，出现进展性认知下降、视物模糊、下肢乏力等神经功能障碍表现，脑部核磁共振(MRI)发现双侧大脑弥漫性脑白质病变，表现为长T1长T2信号影，T2液体衰减反转恢复序列(T2-FLAIR)呈高信号，弥散加权序列(DWI)不均匀稍高，增强扫描强化不明显，经立体定向穿刺脑组织活检取材，镜下可见弥漫性B细胞浸润，CD20(+)，结合影像学特征，均确诊为B细胞来源的大脑淋巴瘤病。【结论】大脑淋巴瘤病为中枢神经系统淋巴瘤的特殊类型，影像诊断困难，极易误诊，对于双侧大脑半球弥漫性病变、同时累及深部脑白质和灰质结构、无强化或小斑片状强化为影像学表现的患者，注意与此病相鉴别，尽早病灶活检，明确病理诊断，对患者的早期诊断及预后具有重要意义。

关键词：中枢神经系统淋巴瘤；大脑淋巴瘤病；立体定向手术；脑活检
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Clinical and MRI Characteristics of Lymphomatosis Cerebri

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Abstract:【Objective】Lymphomatosis cerebri (LC) is a very rare variant of central nervous system lymphoma (PCNSL). However, there are few reports at present and LC has worse prognosis than other types of PCNSL. Hence, this study reports 3 cases of LC whose pathologic features had been clarified through stereotactic brain biopsy, to better characterize LC in order to improve early diagnosis and treatment.【Methods】From January 2017 to July 2020, the clinical manifestations, imaging and neuropathology of 3 patients diagnosed with LC in Lingnan Hospital of the Third Affiliated Hospital of Sun Yat-sen University were retrospectively analyzed.【Results】The 3 patients were 44-year-old, 61-year-old, and 64-year-old males with neurological dysfunction such as progressive cognitive decline, blurred vision, and lower limb weakness. Magnetic resonance imaging (MRI) revealed diffuse white matter lesions in the bilateral brain, which were manifested as long T1 and long T2 signal and demonstrated increased signal intensity on T2-fluid attenuated inversion recovery

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(T2-FLAIR) sequences and slightly higher in diffusion weighted imaging (DWI). Stereotactic brain biopsy specimen showed diffuse B cells infiltration, CD20 (+), consistent with LC.【Conclusions】LC is a rare variant of central nervous system lymphoma that usually has no specific clinical performance, so the doctor can easily succumb to misdiagnosis and missed diagnosis. MRI evidence of bilateral hemispheric involvement should be alerts for this diagnosis. Brain biopsy should be early performed to clarify the pathology, which is of great significance for early diagnosis and prognosis.

Key words: primary central nervous system lymphomas; lymphomatosis cerebri; stereotactic surgery; brain biopsy

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原发性中枢神经系统淋巴瘤(primary central nervous system lymphomas,PCNSL)是少见的仅限于中枢神经系统的结外非霍奇金淋巴瘤,占所有原发性脑肿瘤的2%~3%[1-2]。其中大脑淋巴瘤病(lymphomatosis cerebri, LC)是PCNSL的更加罕见类型,其临床症状及影像学表现与典型的PCNSL存在明显差异,且无特征性表现,容易误诊为其他类型脑白质病变,临床诊断困难,造成治疗延误。笔者总结我院3例大脑淋巴瘤病病例结合文献复习,分析其临床及MRI特点,以提高对该病的认识。

1　材料与方法

1.1　病例资料

搜集2017年1月至2020年7月在中山大学附属第三医院岭南医院经脑立体定向活检和影像证实的大脑淋巴瘤病患者共3例,均为男性患者,发病年龄分别为44、61和66岁。本组患者临床表现不一,首发症状包括睡眠增多、肢体乏力、视物模糊、认知障碍。外院核磁共振(magnetic resonance imaging, MRI)均提示存在双侧大脑白质弥漫性异常信号;3例患者于外院分别诊断为葡萄膜炎、脑白质病、自身免疫性脑炎,行激素冲击治疗后症状短时间内好转,后症状加重,激素疗效差,为进一步确诊,转我院立体定向穿刺活检。本组3例患者均为汉族人,分别为公务员、工人、个体经营者,既往无免疫性疾病及特殊慢性疾病史,无毒物及放射性物质接触史,发病起至确诊时间为2~9月。研究经患者知情同意,获得中山大学附属第三医院伦理委员会批准(中大附三医伦[2021]02-138-01)。

1.2　方　法

3例患者入院后行头颅MRI平扫和增强、弥散加权序列(diffusion weighted imaging, DWI)及磁共振波谱(MRI spectroscopy, MRS)分析,脑立体定向穿刺活检取材,行组织病理学及免疫组织化学检测,经两位不同单位神经病理学专家判读病理结果。

2　结　果

2.1　临床表现

本组患者临床表现不一,首发症状包括睡眠增多、肢体乏力、视物模糊、认知障碍。未出现明显的头痛、呕吐等颅高压症状,亦无癫痫发作表现。本文参考文献中其它类型PCNSL的病例资料,对比LC在临床、MRI、病理特征的差异(表1)。

2.2　MRI表现

均未见明显占位性病变,可见双侧大脑半球异常信号,同时侵犯幕上及幕下,主要涉及大脑半球深部及侧脑室周围白质,大部分同时累及基底节区、胼胝体、丘脑、小脑、脑干等部位。本组患者的MRI检查表现基本一致:平扫可见斑片状异常信号影,边界不清,T1WI呈等或稍低信号,T2WI及T2液体衰减反转恢复序列(T2-fluid attenuated inversion recovery, T2-FLAIR)呈高信号,DWI部分病变呈不均匀高信号,增强扫描强化不明显,其中一例患者可见局部病灶强化,另一例患者局部呈斑片状强化。3例患者均同时行MRS检查,显示病灶区域呈Cho峰增高,NAA峰呈略下降或下降,Cho/NAA比值升高,Cr/NAA比值升高(图1)。

2.3　病理表现

本组患者送检组织HE染色镜下见神经组织结构基本完整,可见弥漫性浸润的异型性淋巴细胞,细胞核仁明显,核分裂像易见;其中两例患者可见肿瘤细胞围绕神经元呈"卫星样"生长及围绕血管生长的"血管袖套样"表现,免疫组化可见神经细胞相关标记物GFAP、Syn、Neu-N为阳性,淋巴瘤细胞的B细胞标记物CD20、Bcl-2 、Bcl-6为阳性,细胞

表1 LC和其他类型PCNSL的主要临床特点、MRI及病理学特征

Table 1 Clinical presentation, MRI characteristics and pathological features of LC versus other types of PCNSL

Items	LC	Other types of PCNSL
Symptoms	Cognitive decline, dementia, gait instability, headache, seizures	Limb movement disorders, increased intracranial pressure, cognitive decline
Lesion locations	Lesions showed diffuse infiltration in bilateral cerebral hemispheres. These areas might include subcortical white matter, basal ganglia, brainstem, corpus callosum, thalamus, cerebellum, and spinal cord. MRI showed diffuse hyperintense lesions in bilateral cerebral hemispheres in T2WI and T2 FLAIR sequence. Patchy gadolinium enhancement lesion might present in enhanced T1WI images. ^{1}H-MRS showed elevated Cho level or Cho/Cr ratio and decreased NAA level or Cho/NAA ratio in the abnormal areas on T2- FLAIR images.	Most often a single lesion, multi-lesions were rare. Most lesions occurred in supratentorial space. Hypo-intense signal on T1WI and hyper-intense signal on T2WI and DWI images, usually revealed a homogenously enhancing mass with peritumoral edema and cystic degeneration.
Pathological features	Undamaged nerve tissue, scattered small round lymphocytes diffusely infiltrate in parenchyma without mass formation, focal perivascular distribution as "vascular sleevelet" could be seen; lymphocytes were strongly stained with CD20, most often B-cell lymphoma.	Tumor cells were similar to centroblasts with diffuse growth and characteristic as perivascular distribution, and lymphocytes were CD20 positive, most often B-cell lymphoma.

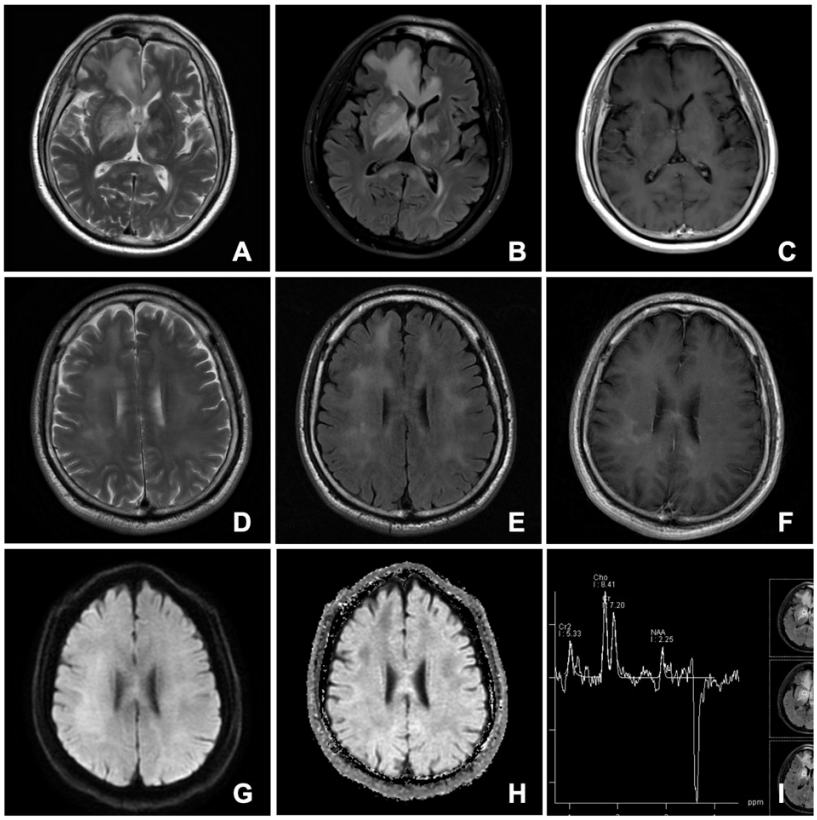
增殖相关标记物Ki-67均显示阳性率大于80%，3例活检组织的病理特征与文献报道的LC病理学特征相符(图2)。本组病例经免疫组织化学及组织病理学诊断证实为弥漫大B细胞淋巴瘤，结合影像学最终诊断为LC。

3 讨 论

PCNSL是可累及脑、软脑膜、脊髓和眼的结外非霍奇金淋巴瘤，近年随着影像学及脑组织活检诊断技术的提高，PCNSL诊断率逐渐增加。LC是PCNSL中的罕见类型，MRI表现为广泛的灰白质病变且无明显肿块，组织病理学显示病变中存在淋巴瘤细胞弥漫性浸润。该病于1999年由Bakshi等[1]首次提出，认为淋巴瘤细胞弥漫性浸润脑组织，但不形成局限性肿块，因此命名为"大脑淋巴瘤病(LC)"，目前该病的英文文献中报道50余例。数十年前由于缺乏先进的神经影像学诊断技术，国际上发表的大脑淋巴瘤病是通过尸体解剖偶然发现；而相较于国内，在国人对于尸解的伦理和传统观念的影响下，通过尸解发现大脑淋巴瘤病是比较难的。现代影像技术的发展，使得诸多中枢神经系统病变可根据MRI特征加以诊断，国内刘效辉等[2]于2016年首次报道了该病，但是由于大脑淋巴瘤病的症状学和影像学特征均不典型，国内外极少的活检病例报导，导致临床上对本病普遍性认识不足。本文总结了LC与其它类型PCNSL的临床特点、MRI及病理学特征差异，见表1[3-4]。

系统回顾1996年1月至2021年3月期间PubMed的文献，收集所有病理证实的中枢淋巴瘤和MRI表现为弥漫性异常病变的PCNSL相关的英文文献。从20篇文章[5-24]和本病例报告中确定了58例。患者年龄28～85岁(平均58.6岁)。最常见的临床表现是认知改变或痴呆(51.7%)。MRI检查表现为双侧大脑半球弥漫性T2WI或T2FLAIR异常信号占50例(86.2%)，首次MRI增强扫描病灶呈轻微强化23例(39.7%)，病灶无强化33例(58%)，其中44例(77.1%)经脑活检确诊，12例(21%)经尸检确诊。58例大脑淋巴瘤病中，B细胞淋巴瘤54例(93.1%)，T细胞淋巴瘤4例(6.8%)。

LC患者的临床表现多样，无特征性表现，最常见的临床表现为认知下降或痴呆、步态不稳[15]，其次为类似其它脑肿瘤的临床表现，如头痛、癫痫发作等，该病的临床表现与肿瘤本身的生物学行为相关，即淋巴瘤细胞弥漫性浸润，不形成明显的占位效应。



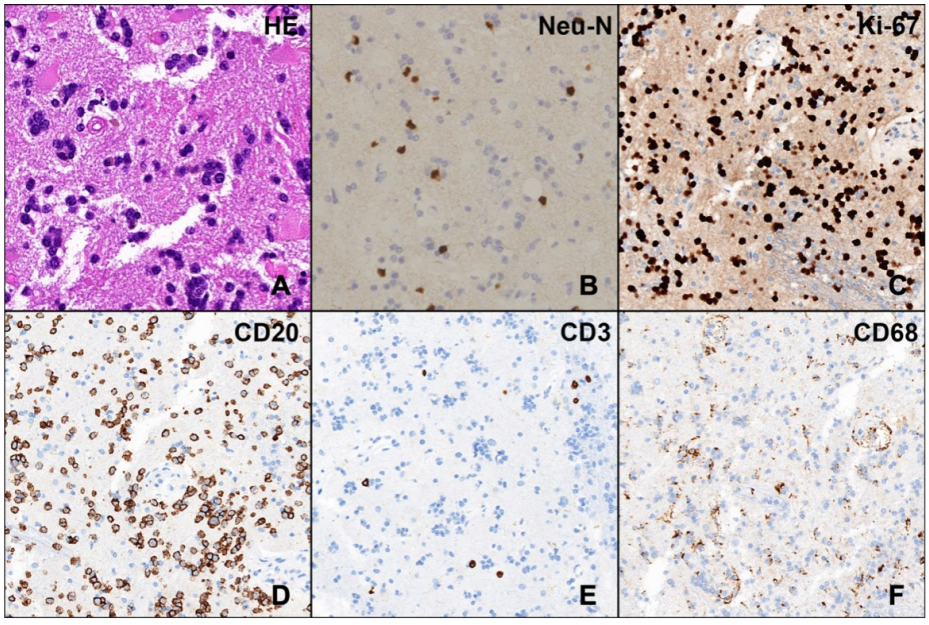
(A, B) Case 1, MRI showed diffuse hyperintense lesions in bilateral cerebral hemispheres in T2WI and T2 FLAIR sequence. (C) Those lesions were not accentuated in gadolinium-enhanced T1WI images. (I) ^{1}H-MRS showed elevated Cho level as well as decreased NAA level in the abnormal areas on T2- FLAIR images; (D, E) Case 2, MRI showed diffuse hyperintense lesions in the bilateral cerebral hemispheres in T2WI and T2 FLAIR images (F) Patchy gadolinium enhancement lesion was presented in enhanced T1WI images. (G) DWI sequence from case 2 showed lesions with slightly elevated or elevated signal. (H) ADC map showed low signal in the lesion confirming that it was restricted diffusion in the right frontal lobe and lateral ventricle and showed high signal in the rest of the lesions.

图1　三例大脑淋巴瘤病患者的MRI表现

Fig. 1　The MRI feature of three cases of LC

据统计，近90%的LC患者会出现双侧大脑半球弥漫性浸润，近一半的患者可出现幕上及幕下浸润，受累区域可包括皮质下白质、基底节区、脑干、胼胝体、丘脑、小脑及脊髓，病变可沿着皮质脊髓束向上或者向下扩散[8, 25-26]；影像检查中MRI扫描对该病有较高诊断价值，其中T2WI及T2-FLAIR弥漫性高信号是该病最常见的表现，而MRI增强扫描中异常信号区域通常无明显增强表现，但部分病例存在针尖样或线样强化，若出现该特征，在影像诊断中应考虑LC的可能[12]；绝大多数病变在弥散成像上表现为DWI高信号及ADC图高信号，一定程度上反映了肿瘤细胞密度分布的不均一性，本组病例中1例患者出现局部DWI高信号和ADC图低信号；LC通常表现为弥漫性脑白质病变，经常难以与其它脑白质病变相鉴别，而^{1}H-MRS检查有助于鉴别脑白质病变的肿瘤性与非肿瘤性的病变，在LC患者中，^{1}H-MRS检查常常出现Cho峰或Cho/Cr升高，NAA峰下降及Cho/NAA比值升高，另外当Lip峰出现时，还可以鉴别淋巴瘤与GBM或转移瘤[27]。本组病例中，^{1}H-MRS检查均出现NAA峰轻度或显著下降及Cho/NAA比值升高，这种表现与肿瘤细胞快速增殖有关，类似于高增殖活性的肿瘤如胶质瘤母细胞瘤及转移瘤，在弥漫性脑白质病中对于诊断LC存在一定的价值。有学者强调采用多模态策略包括多模态磁共振、脑脊液细胞学、流式细胞术和PET-CT，有助于LC的诊断[9]。

由于该病临床及影像学表现通常无特异性，需与许多疾病鉴别，如中枢神经系统感染性疾病、自身免疫性脑炎、脱髓鞘（包括多发性硬化和视神经脊髓炎）、弥漫型胶质瘤、中毒性或代谢性脑病



(A) Hematoxylin and eosin (H&E) staining showed fine structure of nerve tissue and scattered small round lymphocytes with diffuse infiltration of the parenchyma and perivascular distribution as "vascular sleevelet" (magnification ×400). (B) Cortical neurons were strongly stained with Neu-N, a neuron marker which was negative on small round tumor cells. Neurons were surrounded by lymphocytes, which resemble satellites and did not invade neurons (magnification×200). (C) Lymphoma cells that grow around neurons were significantly Ki-67 positive (magnification×200). (D) B lymphocytes were strongly stained with CD20 (magnification×200). (E) T lymphocyte marker CD3 was negative on Lymphoma cells (magnification ×200). (F) CD68 staining showed numerous microglial proliferation in the brain tissue (magnification ×200).

图2 大脑淋巴瘤病的组织病理学特征

Fig. 2 Pathology characteristic of LC

等[5, 28-29]。LC患者大多数在确诊前易被诊断为病毒性脑炎、自身免疫性脑炎及脱髓鞘病变等,因此,快速而准确的脑活检对于诊断该病具有重要意义。因为LC患者病变弥散,脑活检中,活检靶点设定是确诊的关键一环,除避开重要功能区和血管外,动态分析病灶影像学变化特点,尽可能根据病灶动态变化的特点,选择新近病灶为手术靶点,有助于提高病理确诊率。

LC大多为B细胞淋巴瘤,目前报道为T细胞淋巴瘤的病例较少。显微镜下淋巴瘤细胞浸润脑实质,分布稀疏,无肿块形成,表现为局灶性倾向血管周围分布。由于有更多的反应性小淋巴细胞和巨噬细胞,LC在组织学上需与血管炎及病毒性脑炎鉴别。另外,血管周围袖套征并非总存在于LC中,病毒性脑炎也可有此表现,因此,只有免疫组化评估提示了恶性淋巴细胞,才能作出正确诊断。然而,由于这种组织学形式较少见,及时准确诊断仍较困难,对于经验较少的病理学医生判读存在着挑战。因此本组病理诊断,通过两位不同中心的病理学专家确认,符合淋巴瘤的表现才得以确诊。

LC与其他类型PCNSL相比,预后明显差,这和疾病诊断困难及进展快速有着密切的关系。据统计,与其它原发脑肿瘤相比,LC的确诊常有较长的延迟时间,约4.5个月[30-31]。本组3例患者从发病至确诊时间分别为9、3和2月,早期活检明确诊断是影响患者预后的重要因素。常见的临床症状比如认知下降及人格变化容易被误诊为痴呆或抑郁症,除了文中所描述的临床症状外,亦有文献报导临床表现为帕金森综合症和多发性硬化病症状的LC患者[5, 16],非特异性临床综合征很容易被误诊为感染、中毒性代谢紊乱、脑小血管病变或炎性病变、神经退行性病变等疾病,有时需要繁杂的检查、鉴别以及过长的观察期而导致LC诊断困难,部分患者在治疗期间因疾病进展而死亡,最终尸检证实为LC。LC患者症状不典型、临床表现多样,临床诊断困难为目前该病的难点,目前国内外仅有病例报告总结大脑淋巴瘤病的临床及影像学特征及治疗预后情况。综合目前的资料,仍需更多的病例报告来展现该病的特点,并对怀疑LC的患者在进行严格评估后尽早行脑活检以明确诊断,以获得早期治疗。

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