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以中枢神经系统浸润为首发症状的套细胞淋巴瘤 1 例并文献复习*

侯军¹ 胡晓静¹ 韩颖¹ 孟秀琴¹ 施菊妹¹

[关键词] 中枢神经系统浸润; 套细胞淋巴瘤; 诊断

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Mantle cell lymphoma with central nervous system infiltration as the initial symptom: a case report and review of literatures

Summary A case of 56 years old male mantle cell lymphoma (MCL) patient with central nervous system infiltration as the initial symptom was reported. He had a progressive limbs numbness and weakness firstly and then appeared chest segmental tension. Electromyography showed the neurogenic damage in double arms. Cerebrospinal fluid infiltration was confirmed by a large number of white blood cells ($10.0 \times 10^6/L$) and high concentration of protein (1007 mg/L). Flow cytometry analysis of cerebrospinal fluid revealed 6.7 percent of abnormal cells, positive for CD5 and negative for CD10 expression at the same time. PET-CT demonstrated that there had a mild increased intake of FDG in cervical and thoracic spine without obvious destruction in vertebral body. Routine blood test showed that the number of white blood cells was $21.89 \times 10^9/L$ with 31 percent of abnormal cells. Furthermore, the laboratory results showed 5 percent of blast lymphocytic cells in bone marrow and 38.3 percent of monoclonal mature small B lymphocytic cells with CD5-positive and CD10-negative expression in peripheral blood. FISH showed IGH/CCND1(+) fusion gene. At last, this patient was diagnosed with MCL.

Key words central nervous system infiltration; mantle cell lymphoma; diagnosis

1 病例资料

患者,男,56岁,既往体健,无神经系统疾病史。

2012年11月起无明显诱因突发左侧肢体麻木、无力,伴前胸部节段性紧绷感、麻木感,且症状进行性加重,并出现右侧肢体和足底麻木,伴腹胀、暖气,无口角流涎,无头晕、头痛、胸闷、胸痛、腹痛、呕血及黑便。有盗汗,半年体重下降10 kg。入我院神

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¹ 同济大学附属第十人民医院血液科(上海,200072)

通信作者:施菊妹, E-mail: shijumei@hotmail.com

经内科,查血常规:白细胞计数 $21.89 \times 10^9/L$,血红蛋白 $128 g/L$,血小板计数 $188 \times 10^9/L$,中性粒细胞 23.0% ,淋巴细胞 38% ,单核细胞 7% ,异常细胞 31% ;C反应蛋白 $9.7 mg/L$ 。经会诊转入血液科。查血清乳酸脱氢酶 $129 g/L$,肝肾功能正常。骨穿提示:淋巴细胞占 37% ,形态偏小,成熟细胞为主,幼淋占 0.5% 。淋巴细胞增殖性疾病,慢性淋巴细胞性白血病可能。染色体:46,XY[16]。椎体磁共振成像增强示颈2~7椎体水平、胸1~10椎体水平脊髓病变,结合病史,考虑白血病脊髓浸润可能性大,胸3、4、8、9椎体异常信号影,白血病骨髓改变。肌电图示双上肢神经源性损害,累及C5、6、7、8前角,左侧明显。腰穿:脑脊液无色透明,潘氏试验阴性,白细胞 $10.0 \times 10^6/L$,蛋白 $1007 mg/L$,葡萄糖 $4.3 mmol/L$ 。脑脊液免疫:蛋白定量白蛋白(Alb) $55.10 mg/dl$,QAib(脑脊液/血清蛋白) 15.31 ,IgG $6.50 mg/dl$,QIgG 7.56 ,生成指数 0.49 ;鞘内合成率 $0.59 mg/dl$ 。提示血脑屏障明显破坏,但未见伴鞘内IgG合成增加的证据,白血病脊髓浸润可能。脑脊液流式分析可见 6.7% 的异常细胞,免疫表型CD5(+),CD19(+),CD20(部分+),CD10(-),CD23(-),FMC7(-),胞膜免疫球蛋白Kappa轻链限制性表达,提示为单克隆B淋巴细胞。浅表淋巴结B超提示左锁骨上、双侧腋窝、腹股沟淋巴结肿大。PET-CT提示颈、胸段脊髓条带状脱氧葡萄糖(FDG)轻度摄取增高,椎体骨质未见明显异常;脾大伴FDG轻度摄取增高;全身多发淋巴结轻度肿大伴FDG轻度摄取增高;脑FDG代谢未见异常。FISH结果未归。

因患者症状进行性加重,给予地塞米松 $20 mg d1 \sim 5$ + 替尼泊苷 $100 mg d1 \sim 5$ + 阿糖胞苷 $1 g d1 \sim 5$ 治疗,麻木症状减轻,但很快又出现。复查骨穿提示原淋+幼淋占 5% ,外周血流式见约 38.3% 的CD5(+),CD10(-)成熟单克隆小B淋巴细胞。此时FISH结果回报IGH/CCND1(+),检测到t(11;14)易位形成的IGH/CCND1融合基因。据上述结果明确诊断为套细胞淋巴瘤(mantle cell lymphoma, MCL) IV期B,中枢神经浸润。先后给予美罗华+Hyper-CVAD/甲氨蝶呤+阿糖胞苷、R-CHOP+替尼泊苷等方案化疗,并口服反应停 $75 \sim 100 mg/d$,同时给予鞘内注射地塞米松+阿糖胞苷。目前已化疗7个疗程,患者麻木感和紧绷感完全消失,血常规和脑脊液指标正常,处于随访中。

2 讨论

MCL最常见的临床表现是淋巴结肿大,多数同时伴有淋巴结外受累,以骨髓、脾脏及胃肠道多见,中枢神经系统淋巴瘤(central nervous system lymphoma, CNSL)少见,文献报道其发病率变化较大,为 $4\% \sim 26\%$ ^[1]。大部分患者为疾病晚期的一

种结外复发表现,如Ferrer等^[2]报道82例MCL患者,11例存在中枢浸润,其中仅1例为原发病变(占 1.2%),其余均为转移灶。CNSL的临床表现主要涉及神志改变、头痛及颅神经麻痹等,也可能无明显症状^[2]。本例患者以肢体及胸部节段性麻木感为初发症状,无颅内压增高的表现,PET-CT也提示颅内FDG代谢未见异常,而脊髓中有异常信号。此时,除影像学依据外,通过腰穿行流式和免疫等检测获取确诊证据非常必要。

目前公认高乳酸脱氢酶、高国际预后指数、Ki-67高表达以及病理形态为母细胞样者为CNSL易发的高危因素。Gill等^[3]对300余例MCL患者分析发现,非母细胞样MCL患者初诊时即存在CNSL或早期发生独立的CNSL者仅约占 1% ,而在已发生CNSL的MCL患者中 $20\% \sim 50\%$ 初诊时即为母细胞样或复发时转化为该型。此外,有研究报道CNSL患者中存在罕见的cyclinD1阴性亚型,此类患者高表达cyclinD2、D3或cyclinE^[4-5]。

CNSL通常在MCL初诊后1~2年出现,一旦确诊,病情进展迅速,很快出现全身复发,大部分患者1年内死亡(中位4个月)^[2,6]。像本例患者以脊髓症状首发的病例少见。MCL患者是否应常规行腰穿检查尚存争议,但已具有高危因素或有神经系统症状的MCL患者应进行该检查。CNSL通常在疾病晚期出现,短期随访时容易忽略。因此,对于具有上述CNSL高危因素的患者需在治疗早期即开始CNSL防治。常规预防手段为应用含大剂量甲氨蝶呤的化疗方案以及鞘内注射甲氨蝶呤/阿糖胞苷。Gill等^[6]报道10例MCL患者接受CNSL预防治疗后,无一例出现CNSL复发,而未接受预防措施的52例患者中有4例发生CNSL。但也有报道大剂量甲氨蝶呤治疗并无生存优势,因此现有措施能否真正减少CNSL的发生仍未明确。

目前针对年龄小于65岁的MCL患者首选利妥昔单抗+Hyper-CVAD/MA方案,但利妥昔单抗是大分子蛋白,难以有效渗透入血脑屏障,因此对CNSL的局部预防作用有限。近期小分子蛋白酶体抑制剂硼替佐米已被批准用于复发的MCL治疗,硼替佐米+利妥昔单抗+细胞毒药物的II期临床试验完全缓解率达 59% ,中位无进展生存26个月,但对CNSL的防治效果尚待评估^[7]。化疗、免疫治疗联合自体造血干细胞移植可明显提高疗效,2012年临床资料显示中位总生存期大于10年,无事件生存期达7.4年,低危组更受益,这给存在CNSL高危因素的患者带来希望^[8]。

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索拉非尼治疗 FLT3-ITD 阳性的难治性急性髓系白血病 1 例

齐凌¹ 黄瑞滨¹

[关键词] 白血病, 髓系, 急性; 索拉非尼; FMS 样酪氨酸激酶 3

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Sorafenib in the treatment of refractory FLT3-ITD positive acute myeloid leukemia: a case report

Summary Clinical and laboratory characteristics of an acute myeloid leukemia patient with FLT3-ITD positive were reported. The application of sorafenib combined with chemotherapy made the patient get the opportunity of bone marrow transplantation. No obvious adverse reactions occurred in the patient taking sorafenib process, and it achieved clinical and molecular remission after bone marrow transplantation. It suggested that sorafenib was safe and effective in the treatment of refractory FLT3-ITD positive acute myeloid leukemia.

Key words acute myeloid leukemia; sorafenib; FMS-like tyrosine kinase 3

白血病是一组造血干、祖细胞发生恶性改变, 细胞失去进一步分化、成熟能力, 阻滞在不同造血阶段, 从而导致的一组异质性造血系统恶性肿瘤。其异质性主要表现在遗传学异常和分子生物学的改变。其中 FLT3 突变在急性髓系白血病(AML)中的发生频率高, 提示预后不良, 已被 NCCN 诊疗指南选作为 AML 危险度分层的指标之一^[1]。FMS 样酪氨酸激酶 3-内部串联重复序列(FLT3-ITD)在 AML 中的发生率国内外各研究报道相差较大(14.7%~32.0%)^[2-5]。近年来研究发现,

FLT3-ITD 突变的 AML 患者对常规化疗不敏感, 且长期无病生存率低、复发率高。近年来以 FLT3 为靶点, 抑制其信号通路的靶向抑制剂成为新的研究热点。索拉非尼(sorafenib)是一种小分子多激酶抑制剂, 最初作为 c-Raf 激酶抑制剂, 用于治疗肾癌、肝癌, 还可抑制 RAS/RAF/MEK/ERK 信号通路、FLT3、c-kit、血管内皮生长因子受体、血小板衍生的生长因子受体及成纤维细胞生长因子受体等^[1]。索拉非尼可以通过阻止 FLT3 的自身磷酸化, 并作用于其信号通路的下游, 诱导白血病细胞凋亡; 同时通过抑制 MAPK 通路中 ERK, 从而促使白血病细胞进一步分化为正常造血细胞^[6]。我

¹南昌大学第一附属医院(南昌, 330006)

通信作者: 黄瑞滨, E-mail: rbhuang69@163.com