·论著·

八例HIV阴性的浆母细胞淋巴瘤患者临床特征及转归

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【摘要】 **目的**　提高对人免疫缺陷病毒(HIV)阴性浆母细胞淋巴瘤的认识。**方法**　回顾性分析北京协和医院1997年1月至2015年5月确诊的8例HIV阴性浆母细胞淋巴瘤患者的临床资料,分析其临床特征及转归。**结果**　8例HIV阴性浆母细胞淋巴瘤中男3例,女5例,中位年龄60(43~80)岁,其中4例存在导致免疫功能低下的疾病或状态。8例患者均有结外受累,2例Ann Arbor分期为Ⅰ~Ⅱ期,6例为Ⅳ期,其中5例有骨髓受累。所有患者均弥漫表达CD38和CD138,B细胞标志包括PAX-5及Bcl-6少见。5例患者进行EBV-DNA检测,均为阴性。接受化疗并规律随访的7例患者中位随访36(11~57)个月,中位无进展生存时间为15(6~52)个月,中位总生存时间为36(2~52)个月;其中4例采用了硼替佐米联合化疗,3例有效,但疗效难以维持,分别于治疗后2、9、21个月疾病进展。2例Ⅰ~Ⅱ期患者均治疗有效,未出现疾病进展,持续存活;5例Ⅳ期患者化疗后虽然有效,但疗效难以维持,中位总生存时间仅12(6~52)个月,中位无进展生存时间仅10(2~21)个月。**结论**　该组HIV阴性浆母细胞淋巴瘤患者以中老年为主,临床呈现高侵袭性,均出现结外(尤其是骨髓)受累,其免疫表型与浆细胞瘤较为接近,分期较晚的患者预后不良。

【关键词】 浆母细胞淋巴瘤;　临床特征;　治疗结果

Clinical characteristics and survival analysis of eight cases HIV-negative plasmablastic lymphoma

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【**Abstract**】 **Objective**　To deepen the knowledge of HIV-negative plasmablastic lymphoma (PBL). **Methods**　Medical records from 8 HIV-negative PBL patients diagnosed in Peking Union Medical College Hospital from January 1997 to May 2015 were collected, and the clinical features and prognosis of these patients were analyzed. **Results**　All of these 8 patients were diagnosed as HIV-negative PBL, 3 of 8 patients were males, and others were female. The median age was 60 (43−80) year. Among these patients, 4 cases had underlying immunosuppressive state. These patients all had extra-nodular involvement, and 6 cases of them were at stage Ⅳ according to Ann Arbor Staging, 5 patients had bone marrow involvement. CD38 and CD138 were diffusely positive for all patients, while the positive rate of B cell marker including PAX-5 and Bcl-6 were relative low. 5 of 8 patients had been detected for EBV-DNA, and all of them were negative. The median follow-up for the 7 patients receiving chemotherapy and regular follow-ups was 36 (11−57) months, the median progression-free survival (PFS) was 15 (6−52) months, and the median overall survival was 36 (2−52) months. Among these patients, 4 cases had received chemotherapy combined with Bortezomib, showing 3 cases of effective, but it seems to be difficult to keep the long term efficacy, and disease progression occurred in 2, 9, and 21 months after treatment. 2 patients at stage Ⅰ−Ⅱ were treated effectively, without disease progression and survival, 5 patients at stage Ⅳ acquired the efficacy unsustainably, with a median PFS of 10 (2−21) months and a median overall survival of 12 (6−52) months. **Conclusion**　HIV-negative PBL is relatively prevalent in elderly patients, and presenting with high invasiveness in clinical, extremely prone to extra-nodular involvement, especially the bone marrow. The immunophenotype of PBL is more resemble to that of plasmacytoma. Patients who were in late stage at diagnosis show poor prognosis.

【**Key words**】 Plasmablastic lymphoma;　Clinical characteristics;　Treatment outcome

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浆母细胞淋巴瘤(plasmablastic lymphoma, PBL)是一种罕见的后生发中心活化B细胞来源的弥漫大B细胞淋巴瘤,WHO 2016淋巴瘤分类标准将其定义为获得性免疫缺陷综合征相关的淋巴瘤(acquired immunodeficiency syndrome- related lymphoma, ARL)[1],与人免疫缺陷病毒(human immunodeficiency virus,HIV)和EBV的感染密切相关。近年来,HIV阴性PBL的报道也逐渐增多[2-5]。PBL侵袭性强,复发率和病死率较高,预后差,目前缺乏有效的治疗方法[6-7]。本文我们对我院确诊的8例HIV阴性PBL患者的临床特征、治疗及转归进行回顾性分析,以提高对该病的认识。

病例与方法

1. 病例资料:以1997年1月至2015年5月我院诊断的共9例PBL患者为研究对象,诊断标准参照2008年WHO血液系统和淋巴组织肿瘤的分类标准,所有诊断均经过病理科医师二次审核,其中1例因最终病理复审诊断为浆细胞瘤而排除,其余8例符合PBL的诊断。收集患者的临床及随访资料,包括诊断时的年龄、性别、既往史、受累部位、Ann Arbor分期、血清HIV抗体检测、血清EBV DNA检测、治疗方案、疗效、随访时间、存活时间等。

2. 疗效判断标准及生存定义:治疗后的疗效评估增强CT的判断标准根据2014年Cheson的修订标准[8],PET-CT的疗效评价依据2007年Cheson的修订标准[9],包括完全缓解(CR)、部分缓解(PR)、稳定(SD)和进展(PD)。总体生存(OS)期定义为确诊至死亡或末次随访的时间,无进展生存(PFS)期定义为确诊至疾病进展或末次随访的时间。

结　果

1. 临床特征:见表1。8例PBL患者中男3例,女5例,中位年龄60(43~80)岁,均无HIV感染。Ann Arbor分期:Ⅰ期、Ⅱ期各1例,Ⅳ期6例。国际预后指数(IPI)评分为0~2分3例,3~5分5例。8例患者中4例无导致免疫抑制的疾病或状态(如糖尿病、慢性感染、结缔组织病、服用激素或免疫抑制剂、器官移植术后、高龄等);4例存在导致免疫抑制的疾病或状态:例2为高龄(76岁),例5为高龄(80岁)、乳腺癌术后规律化疗、类风湿性关节炎服用免疫抑制剂,例7曾患结核性脑膜炎,例8为HBV携带者。所有患者均出现结外受累,其中5例为单纯结外受累而无结内器官受累,6例Ⅳ期的患者中5例出现骨髓受累;8例患者的受累部位包括骨髓(5例)、淋巴结(3例)、软组织(2例)、硬膜外(2例)、子宫(2例)、胸膜(2例)、鼻咽部(1例)、皮肤(1例)、口腔(1例)、直肠(1例)、横纹肌(1例)。8例患者中5例进行了EBV-DNA检测,均阴性。所有患者均未测定HHV-8。

2. 组织病理及免疫组化特征:8例患者的病理标本均采用HE染色,并进行免疫组化染色分析,可见浆母细胞淋巴瘤的典型形态及免疫表型特点,见图1。具体免疫表型见表2。本组患者瘤细胞弥漫表达浆细胞标志物主要为CD38和CD138,其次为MUM-1;B细胞标志物CD20、CD79α、PAX-5及Bcl-6相对少见,3例患者表达CD3。Ki-67中位数为72%(40%~99%)。5例患者进行了EBV编码的小RNA原位杂交(EBER)检测,均为阴性。

3. 遗传学特征:本组患者中有2例骨髓受累的患者采用FISH进行了骨髓染色体核型检测。例2

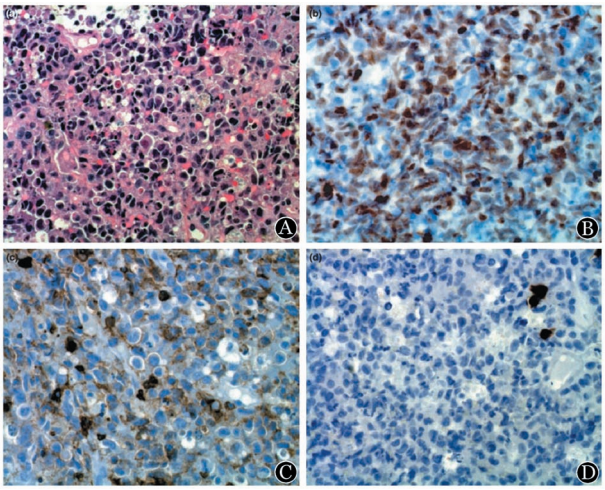
表1 8例人免疫缺陷病毒阴性浆母细胞淋巴瘤患者临床特征

例号	年龄(岁)	性别	Ann Arbor分期	IPI评分	结外受累		EBV DNA检测	导致免疫抑制的因素
					受累部位	是否骨髓受累		
1	51	女	ⅡA	1	鼻咽部	否	N/A	无
2	76	男	ⅣA	4	右下颌软组织	是	阴性	高龄
3	50	男	ⅣB	4	皮肤、心膈角软组织、口腔	是	阴性	无
4	59	女	ⅣA	1	硬膜外	是	阴性	无
5	80	女	ⅣA	4	胸膜(胸腔积液)	否	阴性	乳腺癌术后化疗、类风湿关节炎口服免疫抑制剂、高龄
6	61	女	ⅠA	1	子宫	N/A	阴性	无
7	60	男	ⅣA	5	硬膜外、横纹肌、胸膜(胸腔积液)	是	N/A	结核性脑膜炎病史
8	43	女	ⅣB	3	子宫、直肠	是	N/A	携带HBV

注:IPI:国际预后指数;N/A:不适用

同时存在del(1q21)、del(13q14)、del(17p13.1)和del(14q32);例7存在del(14q32)和1q21信号扩增。上述2例患者未见Myc基因的重排或扩增。

4. 治疗及转归:除例7采用HyperCVAD(环磷酰胺、表柔比星、长春地辛、地塞米松)联合依托泊苷方案化疗1个疗程后失访,无法评价疗效及生存;其余7例均规律随访,中位随访时间36(11~57)个月。其中6例患者均以CHOP(环磷酰胺、表柔比星、长春地辛、泼尼松)方案或类CHOP方案联合或不联合其他药物作为一线化疗方案。2例(28.6%)患者接受预防性鞘注,例1为ⅡA期,累及鼻咽部,例4为ⅣA期,累及硬膜外,随访过程中所有患者均未出现中枢神经系统侵犯。



A:HE染色,低倍;细胞大、圆形或卵圆形、胞质丰富、偏心核、类似未成熟浆细胞。B:MUM-1免疫组化染色,低倍。C:抗CD45-RB免疫组化染色,低倍。D:抗CD79α免疫组化染色,低倍

图1　人免疫缺陷病毒阴性浆母细胞淋巴瘤患者组织病理及免疫组化特征

7例规律随访的患者中1例达到完全缓解(CR),5例达部分缓解(PR),1例疾病稳定(SD)。随访中5例患者疾病进展。中位PFS期为21(2~52)个月,中位OS期为36(6~52)个月。4例采用硼替佐米联合化疗的患者中3例PR,但是疗效均难以维持,分别于治疗后2、8、21个月疾病进展,于治疗后6、11、40个月死于原发病。规律随访的7例患者中Ⅰ~Ⅱ期2例,均治疗有效,1例CR,1例PR,未出现疾病进展,持续存活;其余5例患者均为Ⅳ期,化疗后虽然有效,但疗效难以维持,中位随访12(11~57)个月,中位OS时间仅12(6~52)个月,中位DFS时间仅10(2~21)个月(表3)。

表2　8例人免疫缺陷病毒阴性浆母细胞淋巴瘤患者免疫表型

例号	CD38	CD138	MUM-1	CD20	CD79α	CD56	Ki-67	Bcl-6	CD3	PAX-5	EBER
1	+	N/A	+	散在+	+	散在+	40%	−	部分+	−	N/A
2	−	+	+	部分+	+	N/A	60%	N/A	−	N/A	−
3	+	部分+	−	−	N/A	−	50%	−	−	N/A	−
4	N/A	+	+	−	N/A	N/A	84%	N/A	弱+	弱+	−
5	+	+	+	−	−	N/A	90%	−	−	−	−
6	散在+	+	−	散在+	散在+	−	99%	−	−	+/−	−
7	+	+	N/A	−	−	−	85%	N/A	−	−	N/A
8	+	+	N/A	+/−	N/A	N/A	60%	N/A	散在+	N/A	N/A

注:EBER:EBV编码的小RNA原位杂交;N/A:不适用

表3　8例人免疫缺陷病毒阴性浆母细胞淋巴瘤患者治疗及转归

例号	治疗方案	疗效	随访时间(月)	总生存时间(月)	无进展生存时间(月)	转归
1	CHOP×4+TBI	部分缓解	36	36	36	存活
2	B+CHOP×1	部分缓解后进展	11	6	2	死亡
3	BD+CHO×6	部分缓解后进展	11	11	8	死亡
4	B+CHOP×2、CHP×4	部分缓解后进展	40	40	21	存活
5	CHOP/CHP×9、MINE×5	部分缓解后进展	57	52	15	死亡
6	手术切除+化疗[a]	完全缓解	52	52	52	存活
7	手术切除+E-hyperCVAD×1	失访	1[b]	N/A	N/A	N/A
8	CHOP×1+PAD×5	疾病稳定后进展	12	12	10	死亡

注:CHOP:环磷酰胺、表柔比星、长春地辛、泼尼松;B:硼替佐米;D:地塞米松;MINE:环磷酰胺、米托蒽醌、依托泊苷;E-hyperCVAD:依托泊苷、环磷酰胺、长春地辛、表柔比星、地塞米松;PAD:硼替佐米、表柔比星、地塞米松。[a]化疗方案不详;[b]为入院治疗时间;N/A:不适用

讨 论

PBL是一种罕见的弥漫大B细胞淋巴瘤(DLBCL)亚型。Castillo等[6]对570例PBL患者进行回顾性分析,其中HIV阴性者占28%。大部分HIV阴性PBL患者存在免疫抑制状态,如老年、化疗后、骨髓移植、慢性感染或长期应用免疫抑制剂等[10-15],本组中4例患者存在导致免疫抑制的疾病或状态,另外4例无明确的免疫抑制状态,而免疫健全的PBL也有报道[2-3,5]。PBL患者中男性约占75%,HIV阴性患者中女性比例更高,但仍以男性为主[6]。HIV阴性PBL患者诊断时的中位年龄为55岁,而HIV阳性PBL患者则为46岁[16]。

与HIV阳性PBL相比,HIV阴性PBL口外的结外器官受累更为多见,高达84%,骨髓受累比例约30%,且诊断时常为晚期[16],本组8例HIV阴性PBL均存在结外受累,且部位多样,包括硬膜外、子宫、胸膜、鼻咽部、皮肤等,5例骨髓受累。

PBL细胞常呈弥漫性增生,个大、圆或卵圆形、胞质丰富、核偏位、核仁单个或多个、呈“星空”样外观[17],免疫表型与浆细胞肿瘤相近[18],CD79a、IRF-4/MUM-1、CD38和CD138常阳性,而B细胞标志CD19、CD20、PAX-5常阴性,Ki-67常>90%[7]。本组7例PBL患者(1例未检测)的肿瘤细胞均弥漫表达浆细胞标志物CD38、CD138,其次为MUM-1,B细胞标志物PAX-5少见,与文献报道相似,而CD20表达率为50%,高于文献报道水平[6]。Ki-67中位数为72%(40%~99%),与既往报道相似[6]。EBER在HIV阴性PBL中阳性率较低,约为50%[6],本组患者中5例检测了EBER,均为阴性。Myc重排是PBL最常见的分子遗传学异常,约50%的患者存在Myc重排,且伴侣基因为IGH[19]。本组患者中仅2例进行了分子遗传学检测,均出现del(14q32),提示其可能有一定的诊断意义。

PBL重点需要与浆母细胞样浆细胞瘤、原发性渗出性淋巴瘤以及Burkitt淋巴瘤等鉴别。PBL的EBER常为阳性,Ki-67常较高,而浆母细胞样浆细胞瘤EBER为阴性,Ki-67常较低,常有单克隆M蛋白血症、高钙血症、溶骨性破坏等症状。比较基因组杂交技术,PBL在基因上与DLBCL更为接近[20],但DLBCL常CD20阳性,可鉴别。原发性渗出性淋巴瘤表型与PBL相似[7],但主要表现为胸腔或心包积液,而较少有淋巴结或脏器受累,且与HHV-8密切相关。典型Burkitt淋巴瘤CD20与Bcl-6均为阳性,也可与PBL鉴别[21]。

HIV阴性PBL患者预后差,总体生存期仅4个月[16]。免疫抑制状态为不良预后因素[12]。IPI评分可预测PBL患者预后[22-24],其中分期以及ECOG水平对预后的影响更为明确,而LDH水平、结外受累数目对预后影响较小,年龄是否影响预后尚存在争议[4,6,25]。EBV感染与预后是否相关尚不明确[16,25-26]。其他预后不良因素还包括Myc基因重排和高Ki-67指数[22]。从本组患者来看,Ⅰ~Ⅱ期患者预后较好,OS时间分别为52和36个月,而Ⅳ期患者预后较差,中位OS时间仅为12(6~52)个月。

目前尚没有PBL的标准疗法,NCCN指南推荐强化疗,包括剂量调整的EPOCH(依托泊苷、泼尼松、长春新碱、环磷酰胺、多柔比星)或HyperCVAD等方案[1]。然而高强度化疗对患者的生存改善有限[22,27]。自体造血干细胞移植(auto-HSCT)不论作为一线巩固还是挽救治疗,都明显改善PBL患者预后[28]。研究显示PBL患者诱导化疗CR后接受auto-HSCT,移植后2年复发率为30%,2年OS率为53%,中位随访30个月,11例患者至随访结束时仍无病存活[29]。本组患者均未行auto-HSCT,可能与其难以达到CR或患者状态较差有关。近年来,有硼替佐米治疗PBL的个案报道[30-32]。本组8例患者中4例接受硼替佐米联合化疗,3例有效,但疗效难以维持,分别于治疗后2、8、21个月疾病进展。此外,有报道利妥昔单抗在CD20阳性的PBL患者中有效[33],但多数PBL患者CD20阴性,因而限制了利妥昔单抗的应用。手术和放疗常作为姑息治疗[6]。

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