·论著·

伴单克隆免疫球蛋白边缘带淋巴瘤三例报告及文献复习

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【摘要】 **目的** 探讨伴单克隆免疫球蛋白(McIg)边缘带淋巴瘤(MZL)患者的临床特征和治疗方法。**方法** 收集2007年1月至2014年12月3例伴McIg的MZL患者资料,结合文献报道的36例患者资料进行回顾性分析。**结果** 39例患者中男女比例为1.05∶1,年龄(65.1±12.3)岁。黏膜相关淋巴组织淋巴瘤(MALTL)28例(71.8%),结内MZL 9例(23.1%),脾MZL 2例(5.1%)。早期患者9例(23.1%),晚期患者30例(76.9%)。首发症状以皮肤紫癜、周围神经病等非占位性表现常见(65.5%,19/29)。13例(33.3%,13/39)伴自身免疫现象,以干燥综合征最多见。MALTL以非胃肠道型为主(60.7%,17/28)。伴有的McIg以IgM型最多见(82.0%,32/39),余依次为IgA、κ-轻链、IgG和双克隆型。血浆McIgM水平为(25.55±21.31)g/L,晚期患者明显高于早期患者[(29.85±20.60)g/L对(3.23±2.95)g/L,*P*=0.008]。30例患者接受2~8个疗程化疗,完全缓解(CR)率56.0%,总反应率92.0%;中位随访10个月,3年无疾病进展生存率和总生存率分别为44.7%和76.5%。含和不含利妥昔单抗化疗组患者的总反应率为100.0%和78.6%,CR率为63.6%和50.0%,但差异均无统计学意义(*P*值均>0.05)。McIgM型患者CR率明显高于非McIgM型者(*P*=0.026);治疗后血浆McIgM水平较治疗前明显下降(*P*=0.002)。**结论** 伴McIg的MZL好发于60岁以上老年人,诊断时分期较晚,易伴发自身免疫现象,可能是MZL的一种独特亚型。非胃肠道型MALTL更易伴发McIg,多见McIgM型,其他免疫球蛋白型少见。MZL患者接受含利妥昔单抗的治疗方案可能疗效会更好。

【关键词】 淋巴瘤,B细胞,边缘带; 自身免疫; 抗肿瘤联合化疗方案; 单克隆免疫球蛋白; 单克隆抗体,CD20

Marginal zone lymphoma with monoclonal immunoglobulin: three cases report and literatures review

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【**Abstract**】 **Objective** To investigate the clinical features and treatment in patients of marginal zone lymphoma (MZL) with monoclonal immunoglobulin (McIg). **Methods** The clinical data of MZL patients with McIg, including 3 cases diagnosed and treated in Beijing Anzhen Hospital from Jan 2007 to Dec 2014 were retrospectively studied, meanwhile 36 patients searched from literatures were reviewed. **Results** Of a total of 39 patients, the ratio of male and female was 1.05∶1 with an average age of 65.1±12.3 years old. 28 cases (71.8%) were with mucosa associated lymphoid tissue lymphomas (MALTL), 9 cases (23.1%) with nodal marginal zone lymphoma, and 2 cases (5.1%) with splenic marginal zone lymphoma. Nine cases (23.1%) were in the early stage, 30 cases (76.9%) in the advanced stage. The common initial symptom was non-mass lesions (65.5%), such as skin purpura, peripheral neuropathy; 13 patients (33.3%) were accompanied by autoimmune phenomenon, and most were with Sjogren's syndrome. Among MALTL patients, the common primary lesion was in non-gastrointestinal tract (17 cases, 60.7%). Most of patients with McIg were one with McIgM (82.0%); the others with McIgA, Mcκ-light chain, McIgG and double McIg. The level of plasma McIgM was (25.55±21.31) g/L, which was higher in advanced stage patients than in early stage ones [(29.85±20.60) g/L *vs* (3.23±2.95) g/L, *P*=0.008]. The complete remission (CR) rate was 56.0% and the overall response rate (ORR) 92.0%,

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respectively in 30 patients treated by chemotherapy. At a median follow-up of 10 months, the 3-year progression free survival and the 3-year overall survival were 44.7% and 76.5%, respectively. The rates of ORR and CR in the patients received rituximab-included regimen were seemly better than those without rituximab one (100.0% *vs* 78.6%, 63.6% *vs* 50.0%; *P*>0.05), but no statistic differences were found. The CR rate in patients with McIgM was significantly higher than that with non-McIgM (*P*=0.026). The plasma McIgM level decreased after chemotherapy (*P*=0.002). **Conclusion** The MZL with McIg, perhaps a kind of unique subtype, usually occurred in 60 years or older patients. It was often diagnosed in patients of advanced stage and susceptible to autoimmune phenomenon. MALTL in non-gastrointestinal tract was more prone to find McIg. In MZL patients with McIg, McIgM was more common and other McIg rare. Rituximab-included regimen produced a better therapeutic response.

【Key words】 Lymphoma, B-cell, marginal zone; Autoimmunity; Antineoplastic combined chemotherapy protocols; Monoclonal immunoglobulin; Rituximab

单克隆免疫球蛋白(monoclonal immunoglobulin, McIg)是由单克隆浆细胞或B淋巴细胞增殖产生的一种异常免疫球蛋白,临床上以血清或尿中出现大量McIg或其片段为特征,多见于恶性浆细胞与B淋巴细胞肿瘤患者。最近研究发现分泌McIg的B细胞淋巴瘤可能为一类特殊的亚型[1-2]。边缘带淋巴瘤(marginal zone lymphoma, MZL)属于B细胞非霍奇金淋巴瘤(B cell non-Hodgkin lymphoma, B-NHL),临床上伴McIg的MZL(McIg-MZL)并不常见,在本文中我们报道3例McIg-MZL患者资料,并结合文献对McIg-MZL患者的临床特征进行综合分析。

病例与方法

1. 病例:我院2007年1月至2014年12月收治McIg-MZL患者3例。男2例、女1例,年龄56~75岁,均经组织活检病理诊断。黏膜相关淋巴组织淋巴瘤(mucosa associated lymphoid tissue lymphoma, MALTL)1例、结内MZL(nodal MZL, NMZL)2例。根据Ann Arbor临床分期,Ⅲ期2例、Ⅳ期1例。血浆免疫固定电泳法证实存在McIg,IgM-κ型2例,IgM-λ型1例,血浆IgM 18.0~30.5 g/L。

以MZL、McIg中英文为关键词,检索PubMed.cn、Medline、万方数据库,2001至2014年McIg-MZL相关文献27篇,报道患者36例。

将上述39例患者的临床资料纳入分析。根据Ann Arbor临床分期,将患者分为早期(Ⅰ~Ⅱ期)、晚期(Ⅲ~Ⅳ期)。疗效评价:按照WHO淋巴瘤疗效评价标准进行疗效判断,总有效率(ORR)为完全缓解(CR)与部分缓解(PR)率之和。远期疗效以总生存(OS)率和无疾病进展生存(PFS)进行评价。

2. 统计学处理:采用SPSS17.0软件进行统计学分析,计数资料采用Fisher's确切概率法,计量资料采用*t*检验,采用Kaplan-Meier法及Log-rank检验进行生存分析。*P*<0.05为差异有统计学意义。

结　果

1. 一般资料:我院收治的3例患者分别以右眼肿痛、咽喉肿痛、腹部包块为首发症状。除1例确诊后出院失访,另2例患者接受CHOP(环磷酰胺、多柔比星、长春新碱、泼尼松)方案化疗4~6个疗程,分别获得PR、CR;血浆McIg水平下降17.6%、65.6%;随访6个月、6年,McIg持续存在,其中1例患者淋巴瘤本病一直处于稳定期,持续伴原发免疫性血小板减少症(primary immune thrombocytopenia, ITP),小剂量激素治疗可维持较高血小板水平。以上3例患者及文献报道的36例患者资料见表1。

39例患者中,男20例,女19例,中位年龄66(35~83)岁,其中>60岁者25例(64.1%)。NMZL 9例(23.1%),MALTL 28例(71.8%),脾MZL(splenic MZL, SMZL)2例(5.1%);早期者9例(23.1%),晚期者30例(76.9%)。早、晚期患者性别、年龄差异均无统计学意义(*P*值均>0.05)。

2. 首发症状:39例患者中有29例有首发症状记录,其中10例(34.5%)表现为局部占位(眼附属器、唾液腺、结肠、胰腺、肾脏以及咽部、颈部、腹腔淋巴结)。19例(65.5%)表现为非占位性症状。

3. 自身免疫现象:13例(33.3%)患者伴自身免疫现象,其中干燥综合征5例,自身免疫性溶血性贫血、冷球蛋白血症各3例,类风湿性关节炎2例,ITP、Evan's综合征、皮肌炎、系统性血管炎各1例;4例患者同时有2种自身免疫性疾病。自身免疫现象与M蛋白类型、McIg定量、临床分期、治疗有效率未发现相关性(*P*>0.05)。

4. 原发病灶部位:9例NMZL患者中,原发淋巴结7例,唾液腺、皮肤各1例。28例MALTL患者中,

11例(39.3%)原发于胃肠道,17例(60.7%)为非胃肠道。2例SMZL患者原发脾脏(表1)。

5. McIg类型与定量:39例患者中,IgM型32例(82.0%),IgA型3例(7.7%),κ-轻链型2例(5.1%),

表1 39例伴单克隆免疫球蛋白边缘带淋巴瘤患者的临床资料统计

例号	性别	年龄(岁)	首发症状	原发部位	诊断	分期	McIg类型	McIg定量(g/L)		自身免疫现象	治疗方案	随访时间(月)	疗效
								治疗前	治疗后				
1	男	75	右眼肿痛	眼附属器	MALTL	ⅣA	IgM-λ	28.40	23.40	无	CHOP	6	PR
2	女	70	咽喉肿痛	咽喉淋巴结	NMZL	ⅢB	IgM-κ	18.00	–	无	不详	不详	不详
3	男	56	腹部包块	腹腔淋巴结	NMZL	ⅢA	IgM-κ	30.50	10.50	ITP	CHOP	72	CR
4[3]	男	80	发热	胃	MALTL	ⅢB	IgM-κ	28.70	19.60	无	R	2	PR
5[4]	女	72	右肾肿块	肾脏	MALTL	ⅠA	IgM-κ	5.69	1.45	无	Clb +P	8	CR
6[5]	男	72	胰尾肿块	胃	MALTL	ⅡA	κ	2.03	2.03	无	不详	不详	不详
7[6]	男	70	不详	肺	MALTL	ⅡA	IgA-κ	16.60	0	无	R-CHOP	不详	PR
8[6]	男	51	不详	胃	MALTL	ⅠA	IgA-λ	3.80	0	无	R-CHOP	不详	PR
9[7]	女	59	乏力	脾脏	SMZL	ⅣA	κ	40.70	–	Evan's综合征	不详	不详	不详
10[8]	女	81	下颌包块	唾液腺	NMZL	ⅣA	IgM-λ	17.35	–	无	VAD	10	CR
11[9]	男	66	呼吸困难	回肠	MALTL	ⅣA	IgM-λ	21.00	–	无	R-CAVP	3	CR
12[10]	男	76	右眼不适	眼附属器	MALTL	ⅣA	IgM-κ	11.00	0	无	放疗	不详	存活
13[11]	男	78	不详	小肠	MALTL	ⅣA	IgM-κ	8.20	–	CG	保守治疗	7	死亡
14[12]	女	54	腹胀	横结肠	MALTL	ⅣA	IgM-κ	29.74	–	无	R-CHOP	12	CR
15[13]	男	77	肾功能衰竭	肾脏	MALTL	ⅣA	IgM-κ	46.40	29.70	无	手术+ Clb	32→40	PR→死亡
16[14]	女	35	不详	胃	MALTL	ⅣB	IgM-λ	11.20	–	无	R-CHOP	8→17	CR
17[15]	男	64	皮肤紫癜	皮肤	NMZL	ⅣA	IgM-κ	50.74	5.44	AIHA	手术+BD	3	PD
18[16]	女	75	周围神经病	唾液腺	MALTL	ⅣA	IgM-λ	36.00	10.00	RA、DM	R-CP	6	CR
19[17]	女	56	肾功能不全	胸腺	MALTL	ⅡA	IgM-κ	0.12	–	SS、CG	RD	6	CR
20[18]	男	59	发热	淋巴结	NMZL	ⅣB	IgM-κ	25.40	–	AIHA	FCD	2	死亡
21[18]	女	77	乏力	淋巴结	NMZL	ⅣA	IgM-κ	32.50	16.25	AIHA	R-CHOP	2	PR
22[19]	男	59	黑便	胃	MALTL	ⅢA	IgM-κ	53.00	0	无	Clb	3→53	PR
23[20]	女	69	皮肤紫癜	皮肤	MALTL	ⅡA	IgM-κ	–	–	CG、SV	Flu	6	CR
24[21]	女	72	踝关节肿胀	脾脏	SMZL	ⅣA	IgM-κ	11.60	2.71	无	R	12	CR
25[22]	女	82	咳嗽	肺	MALTL	ⅣA	IgM-λ	21.45	–	无	手术	10	存活
26[23]	男	83	颈部左侧包块	颈部淋巴结	NMZL	ⅣA	IgA-κ	36.25	–	无	CHOP	48	PR
27[24]	女	65	腹痛	小肠	MALTL	ⅠA	IgM-κ	0.48	–	无	保守治疗	10	死亡
28[25]	女	61	腹痛	腹腔淋巴结	NMZL	ⅣA	IgM-κ	7.33	3.90	无	CHOP	8	PR
29[26]	女	62	皮肤紫癜	腮腺	MALTL	ⅣA	IgM-κ	1.50	0	SS	CHOP	23	CR
30[26]	女	37	周围神经病	淋巴结	NMZL	ⅡB	IgM-κ	3.20	0	SS	CHOP	15	CR
31[26]	女	54	周围神经病	腮腺	MALTL	ⅣB	IgM-κ	4.00	0	SS	CHOP	10	CR
32[27]	男	68	腹痛	胃	MALTL	ⅠA	IgM-κ	6.64	–	无	Hp根除	12	存活
33[28]	男	59	右下颌肿大	唾液腺	MALTL	ⅣA	IgG-λ	87.42	26.10	无	COP+R	17→72	PR→死亡
34[29]	男	50	不详	鼻咽	MALTL	ⅠA	IgM-κ	88.00	–	无	CVP	11	存活
35[29]	男	40	不详	眼附属器	MALTL	ⅣA	IgM-κ	66.00	–	无	CP+Flu	9	存活
36[29]	女	60	不详	腮腺	MALTL	ⅣA	IgM-κ	32.00	–	SS、RA	CVP	8	存活
37[29]	女	61	不详	肺	MALTL	ⅠA	IgM-κ	45.00	–	无	CVP+ Flu	2	存活
38[29]	男	74	不详	眼附属器	MALTL	ⅠA	IgM-κ IgA-κ	12.00 13.00	–	无	不详	不详	不详
39[29]	男	79	不详	胃	MALTL	ⅣA	IgM-κ	51.00	–	无	CAVP	4	存活

注:MALTL:黏膜相关淋巴组织淋巴瘤;SMZL:脾边缘带淋巴瘤;NMZL:结内边缘带淋巴瘤;ITP:原发免疫性血小板减少症;CG:冷球蛋白血症;AIHA:自身免疫性溶血性贫血;RA:类风湿性关节炎;DM:皮肌炎;SS:干燥综合征;SV:系统性血管炎;CHOP:环磷酰胺+多柔比星+长春新碱+泼尼松;R:利妥昔单抗;Clb:苯丁酸氮芥;P:泼尼松;VAD:长春新碱+阿霉素+地塞米松;CAVP:环磷酰胺+阿霉素+长春新碱+泼尼松;BD:硼替佐米+地塞米松;CP:环磷酰胺+泼尼松;RD:利妥昔单抗+地塞米松;FCD:氟达拉滨+环磷酰胺+地塞米松; Flu:氟达拉滨;Hp:幽门螺杆菌;COP:环磷酰胺+长春新碱+泼尼松;CVP:环磷酰胺+长春新碱+泼尼松;PR:部分缓解;CR:完全缓解;PD:疾病进展;–:未测

IgM-κ和IgA-κ双克隆型、IgG-λ型各1例(2.6%)。McIgM型患者最多见,其血浆McIgM水平为0.12~88.00 g/L,平均(25.55±21.31)g/L;晚期患者血浆McIgM水平明显高于早期患者[(29.85±20.60)g/L对(3.23±2.95)g/L],差异有统计学意义(P=0.008)。

6. 治疗及生存分析:30例患者接受化疗,有明确疗效者25例。平均化疗4(2~8)个疗程,CR率56.0%(14/25),PR率36.0%(9/25),ORR 92.0%;中位随访10(2~72)个月,中位PFS、OS时间分别为32、72个月,3年PFS、OS率分别为44.7%、76.5%(图1)。其中含利妥昔单抗化疗组11例,ORR 100.0%(11/11),CR率63.6%(7/11);不含利妥昔单抗化疗组14例,ORR 78.6%(11/14),CR率50.0%(7/14);两组患者ORR、CR、PFS、OS率差异均无统计学意义(P值均>0.05)。此外幽门螺杆菌(helicobacter pylori, Hp)根除、手术、放疗各1例,至随访结束患者均存活;2例保守治疗随访7、10个月后死于淋巴瘤扩散。4例患者治疗不详。

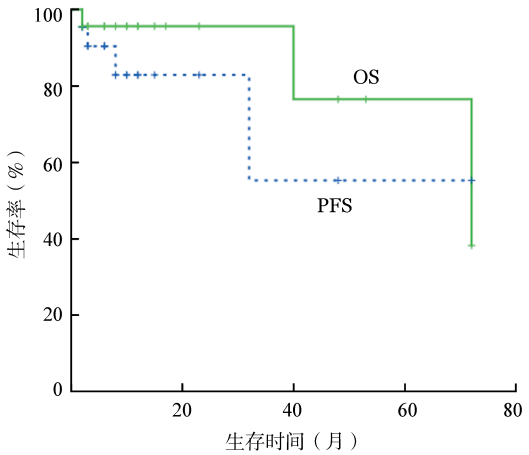

图1　30例伴单克隆免疫球蛋白边缘带淋巴瘤患者总生存(OS)和无疾病进展生存(PFS)曲线

有明确疗效的25例患者中21例为McIgM型,其ORR为95.2%(20/21),CR率为66.7%(14/21);4例非McIgM型患者中3例获PR;两组患者的CR率差异有统计学意义(P=0.026),ORR差异无统计学意义(P>0.05)。15例患者治疗后血浆McIgM水平较治疗前明显下降[(23.37±18.18)g/L对(8.20±9.76)g/L],差异有统计学意义(P=0.002)。

讨　论

McIg(M蛋白)是淋巴细胞或浆细胞增殖性疾病的重要标志。临床上McIg-MZL极为少见。Economopoulos等[30]分析255例B-NHL患者资料,伴McIg分泌者比例为17.3%,以淋巴浆细胞淋巴瘤/华氏巨球蛋白血症(LPL/WM)、滤泡性淋巴瘤最常见,18例MZL患者均为阴性。Lin等[31]分析382例McIgM型淋巴瘤患者,MZL患者占7.1%。

本组资料表明,McIg-MZL好发于60岁以上老年人,男女无明显差异。MALTL最多见(71.8%),NMZL次之,SMZL少见。但McIg-MALTL,原发病灶以眼附属器、肺、唾液腺等非胃肠道更为多见(60.7%),胃肠道仅占39.3%,与不伴McIg的MALTL(胃肠道约占50.0%)略有不同。

研究发现伴McIg的B-NHL,IgG占50%,IgM占41%,IgA占9%;惰性淋巴瘤以IgM为主,侵袭性淋巴瘤则以IgG常见[30]。Wöhrer等[32]报道McIg-MALTL患者中IgM占63%,IgG占31%,IgA占5%。本组患者与Wöhrer报道类似,IgM最多见(82.0%),但略有差异,McIg类型更为丰富,IgA(7.7%)、κ-轻链型(5.1%),IgG和双克隆型(各2.6%)。

本组76.9%的患者诊断时处于晚期,且McIg水平较早期患者增高8.8倍,与Economopoulos等[30]和Asatiani等[33]报道一致,前者发现伴McIg的B-NHL患者诊断时77%达晚期,后者发现伴McIg的结外侵犯MZL患者均达Ⅳ期,而不伴McIg者仅42%达Ⅳ期,推测McIg水平高,疾病进展快、临床分期晚。

已有研究发现自身免疫疾病是淋巴瘤发生的危险因素,但伴自身免疫现象对淋巴瘤患者预后的影响研究较少,其对NHL分层和生存率的影响文献报道不一[34-35]。本组33.3%患者出现自身免疫现象,明显高于Wang等[36]报道的5.8%;但与McIg类型及疗效无关。Jacson等[37]报道248例唾液腺MALTL患者资料,自身免疫现象发生率高达41%。

最近有作者提出分泌McIg的淋巴瘤可能是淋巴瘤的一种特殊亚型。Cox等[1]研究分泌McIgM弥漫大B细胞淋巴瘤(DLBCL),发现其起源于分化成熟的活化B细胞,对R-CHOP方案治疗反应差,因而提出分泌McIgM为临床预后差的重要标志;与90%的LPL/WM患者、6.5%~17%非选择性DLBCL患者存在MYD88基因L265P突变不同,McIgM-DLBCL患者该突变为阴性,推测可能存在其他与McIgM相关的分子通路。Martinez-Lopez等[2]研究发现15%的SMZL患者存在MYD88基因L265P突变,并与McIgM分泌密切相关;但NMZL和MALTL患者均未发现该突变,因此MZL与MYD88基因L265P突

变的相关性及其意义值得进一步研究。

分泌McIg对淋巴瘤治疗及预后的影响文献报告不一。Buske等[38]发现分泌McIgM与LPL患者的治疗反应无相关性;但在伴与不伴WM的LPL患者中,R-CHOP方案治疗者的ORR均明显优于CHOP方案治疗者。本组MZL患者多数应用CHOP±R方案,有较高的ORR(92.0%),含利妥昔单抗化疗组ORR及CR率优于不含利妥昔单抗化疗组(100.0%对78.6%,63.6%对50.0%),但差异无统计学意义。McIgM型MZL患者CR率明显高于非McIgM型,提示McIgM型患者对化疗反应较好;随着淋巴瘤的治疗McIg水平也随之下降。目前McIg-MZL多为个案报道,尚无针对其治疗的随机对照研究,多数仍然按照最新NCCN推荐的指南方案治疗,早期胃肠道MALTL患者的治疗,Hp阳性者首选根除Hp,阴性者首选放疗;非胃肠道者首选放疗或手术。晚期MALTL患者首选苯达莫司汀+R/R-CHOP。SMZL患者选择切脾或利妥昔单抗治疗。对难治/复发患者,已有报道借鉴WM治疗,包含硼替佐米、氟达拉滨、来那度胺的方案能提高患者ORR、改善长期生存[39-41];年轻、早期复发、NMZL患者建议大剂量化疗+自体干细胞移植,部分患者能获得长期生存[42]。

综上,McIg-MZL在临床上并不常见,好发于老年人,以非胃肠道MALTL、McIgM型最多见,易伴发自身免疫现象,诊断时分期较晚,可能是MZL的一种独特亚型。患者接受含利妥昔单抗的治疗方案可能疗效会更好。相信随着分子生物学的深入研究及更多临床试验的开展,McIg-MZL的发病机制及有效的治疗手段也会获得进一步的发展。

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