doi: 10.13241/j.cnki.pmb.2019.22.027

胃癌组织中 HER2、PD-L1 的表达与临床病理特征的相关性 *

赵玲娜 赵海滨△ 王 倩 李巧转 殷婷婷

(联勤保障部队第 904 医院 病理科 江苏 无锡 214000)

摘要 目的:检测胃癌组织中人表皮生长因子受体 2(HER2)、程序性死亡因子 1 配体(PD-L1)的表达,并分析其与胃癌患者临床病理特征的相关性。**方法:**采用分层整群抽样回顾性分析的方法抽取我院 2016 年 1 月至 2018 年 12 月经手术病理诊断为胃癌的 100 例原发性胃癌患者,全部患者术后均经病理组织切片免疫组化染色检测其 HER2、PD-L1 表达,对比不同性别、年龄、肿瘤大小、肿瘤部位、分化程度、病理类型等临床病理特征胃癌患者 HER2、PD-L1 的表达,分析二者与胃癌患者临床病理特征的相关性。**结果:** 100 例胃癌患者中男女比例为 2.8:1,年龄>60 岁占比高,肿瘤大小多超过 4 cm,WHO 分型以分化不良与分化较好为主,肿瘤部位主要位于胃下 2/3,浸润深度多为 T4,TNM 分期集中在Ⅰ~Ⅲ期,多伴淋巴结转移,几乎无远处转移,多存在脉管侵犯,部分有神经侵犯。100 例胃癌患者胃癌组织 HER2 表达阴性、弱阳性、强阳性检出率分别为 42.00%、31.00%、27.00%;PD-L1 阴性、阳性检出率分别为 57.00%、43.00%。胃癌组织 HER2 阳性表达、PD-L1 阳性表达均高于癌旁正常胃组织,差异有统计学意义(P<0.05)。胃癌组织中 HER2 表达与疾病分化程度呈负相关(r<0,P<0.05),PD-L1 的表达与肿瘤分化程度、浸润深度、与远处转移均呈显著正相关(r>0,P<0.05)。**结论:**HER2 的阳性表达可能提示胃癌患者较低的恶性程度,PD-L1 的高表达可能提示胃癌患者存在远处转移、浸润深度深、恶性程度高。HER2 和 PD-L1 有望成为胃癌患者诊断参考指标及药物干预的靶点。

关键词:胃癌;HER2 表达;PD-L1 表达;临床病例特征;相关性

中图分类号:R735.2 **文献标识码:**A **文章编号:**1673-6273(2019)22-4324-06

Correlation of HER2 and PD-L1 Expression in the Gastric Cancer Tissues with the Clinicopathological Features*

ZHAO Ling-na, ZHAO Hai-bin△, WANG Qian, LI Qiao-zhuan, YIN Ting-ting

(Department of Pathology, 904 Hospital of Joint Logistics Support Force, Wuxi, Jiangsu, 214000, China)

ABSTRACT Objective: To detect the expression of human epidermal growth factor receptor 2 (HER2) and programmed cell death ligand 1 (PD-L1) in gastric cancer tissues, and to analyze the correlation between HER2, PD-L1 expression and the clinicopathological features. **Methods:** The stratified cluster sampling retrospective analysis method was adopted. 100 patients with primary gastric cancer who underwent surgical pathological diagnosis of gastric cancer from January 2016 to December 2018 were enrolled. The HER2 and PD-L1 expression of all the patients were detected by immunohistochemical staining of pathological tissue sections after surgery. The expression of HER2 and PD-L1 in gastric cancer patients with different gender, age, tumor size, tumor location, differentiation degree, pathological type was compared. The correlation between HER2, PD-L1 expression and the clinicopathological features in gastric cancer patients was analyzed. **Results:** The ratio of male to female in 100 patients with gastric cancer was 2.8:1, the proportion of aged >60 was high, and the tumor size was more than 4 cm, the WHO classification was mainly poorly differentiated and well differentiated, the tumor site was mainly located in the 2/3 of the stomach, the depth of infiltration was mostly T4, the TNM stage was concentrated in stage I~III, with lymph node metastasis, almost no distant metastasis, and there were many vascular invasions, and some of them had nerve invasion; The detection rate of negative, weakly positive and strongly positive expression of HER2 in gastric cancer tissues of 100 patients were 42.00%, 31.00% and 27.00%, respectively; The PD-L1 negative and positive detection rates were 57.00% and 43.00%, respectively; Pearson correlation analysis showed that the expression of HER2 in gastric cancer tissues had negative correlation with the degree of disease differentiation (r<0, P<0.05); The positive expression of HER2 and PD-L1 in gastric cancer tissues was higher than that in adjacent normal gastric mucosa (P<0.05); The HER2 expression in gastric cancer tissues had negative correlation with the degree of disease differentiation (r<0, P<0.05), the PD-L1 expression had positive correlation with the tumor differentiation degree, depth of infiltration and distant metastasis (r>0, P<0.05). **Conclusion:** The positive expression of HER2 may suggest a lower degree of malignancy in gastric cancer patients. The high expression of PD-L1 may indicate that the gastric cancer patients have distant metastasis, deep infiltration depth and high degree of malignancy. HER2 and PD-L1 are expected to be the diagnosis reference index and the target of drug intervention for gastric cancer patients.

* 基金项目:国家自然科学基金项目(81000964)

作者简介:赵玲娜(1982-),女,本科,主治医师,主要研究方向:肿瘤病理临床,E-mail: zhaolingnaa@163.com

△ 通讯作者:赵海滨(1969-),男,本科,副主任医师,主要研究方向:肿瘤病理,E-mail: zhoumnp@163.com

(收稿日期:2019-03-07 接受日期:2019-03-30)

Key words: Gastric cancer; HER2 expression; PD-L1 expression; Clinicopathological features; Correlation
Chinese Library Classification(CLC): R735.2 Document code: A
Article ID: 1673-6273(2019)22-4324-06

前言

胃癌是消化道常见的恶性肿瘤,对于疾病分期在Ⅱ期的患者,即便是获得理想的治疗,其 5 年内生存率仍较低[1,2]。目前,评价胃癌恶性程度多以疾病的侵袭性与转移性为主,在胃癌组织侵袭与转移期间,新生血管生成作用关键[3]。人表皮生长因子受体 2(Human Epidermal Growth Factor Receptor2,HER2)是酪氨酸激酶受体中的一员,有酪氨酸激酶活性,能够抗细胞凋亡并调控细胞增殖。此外,该因子还可上调血管内皮生长因子或血管通透因子表达加速新生血管生成,加速肿瘤侵袭与转移[4-6]。程序性死亡因子 1 配体 (programmed cell death li-gand 1, PD-L1) 是免疫系统内抑制性通路, 在调节生理性免疫应答幅度、时间及免疫耐受维持方面意义重大[7,8]。HER2 及 PD-L1 虽已被用于黑色素瘤与肺癌的研究,但其在胃癌中的作用并不明确。本研究主要探讨了胃癌组织 HER2、PD-L1 表达及其与临床病理特征的相关性,作如下报道。

1 资料与方法

1.1 研究对象

采用分层整群抽样回顾性分析的方法, 抽取我院 2016 年 1 月至 2018 年 12 月经手术病理诊断为胃癌的 100 例原发性胃癌患者,全部患者均经术后经病理诊断证实或术前经胃镜活检证实为胃癌者,均属于原发性胃癌者,均为首发接受手术治疗者,术前均未接受任何放射治疗、化疗及生物治疗等操作,经手术患者肿瘤组织完整切除,术后肿瘤组织均接受免疫组织化学染色,其中包括 HER2、PD-L1 结果,且结果完整,全部患者临床资料完整。排除合并全身其他器官或系统良性或恶性肿瘤者、临床病例资料有缺失者、切除术未将肿瘤完全切除者、胃癌类型属于绒癌、肝样腺癌等少见类型者。

100 例胃癌患者中男女比例为 2.8:1,年龄＞60 岁占比高,肿瘤大小多超过 4 cm,WHO 分型以分化不良与分化较好为主,肿瘤部位主要位于胃下 2/3,浸润深度多为 T4,TNM 分期集中在Ⅰ~Ⅲ期,多伴淋巴结转移,几乎无远处转移,多存在脉管侵犯,部分有神经侵犯。详见表 1。

1.2 方法

1.2.1 **一般资料** 仔细阅览患者病历资料,详细记录其一般情况,包括姓名、性别、年龄、体重、肿瘤大小、病理分型(参照世界卫生组织 2010 年制定的胃癌病理组织学分型标准判定)[9]、疾病分期 (参照国际抗癌联盟与美国癌症联合会 2010 年共同制定的 TNM 分期篇判定)[10]、肿瘤部位、浸润深度、淋巴结转移、远处转移、脉管侵犯、神经侵犯等情况。

1.2.2 **病理 / 正常组织 HER2、PD-L1 表达检测** 全部因子均采用免疫组织化学染色法检测。

1.2.2.1 HER2 (1)仪器与试剂:该因子免疫组织化学染色采用二步法,并严格参照操作步骤进行操作,所用 HER2 单克隆抗体及其相关试剂均由北京中杉金桥有限公司提供。(2)结果判读:免疫组化结果的判读均由病理科 2 名高年资医师利用双盲法独立判读,参照《胃癌 HER2 检测指南(2011 版)》[11]中相关规定判定结果。在 400 倍显微镜下抽取 5 个视野,参照显色强度与阳性细胞率决定得分,① 阳性细胞率:＜5%为 0 分,5%~25%为 1 分,26%~50%为 2 分,51%~75%为 3 分,＞75%为 4 分;② 显色强度:0 分为未显色,1 分为淡黄色,2 分为棕黄色,3 分为棕褐色。阳性细胞率得分与显色强度得分乘积结果在 0~1 分别为阴性,2~4 分为弱阳性,≥ 5 分为强阳性。

1.2.2.2 PD-L1 (1) 仪器与试剂:兔抗 PD-L1 (SP142) 抗体 (RAB-0724, 0.2 mL)二抗,Max Vision TM 型即用快速免疫组织化学染色检测试剂盒与 DBA 显色试剂盒, 上述仪器与试剂均由福州迈新生物技术开发有限公司提供。(2)操作步骤:将病理组织切片放置在 60℃烤箱内 120 min 以上, 经 10 min/ 次的二甲苯脱蜡 3 次,使用梯度乙醇水化,经 5 min/ 次的蒸馏水冲洗 1 次。后将切片放置在塑料染色架上,并置入装有柠檬酸组织抗原缓冲液(0.01 mol/L pH6.0)容器内,微波加热至沸腾,20 min 左右将容器取出使其在室温下自然冷却。由缓冲液内将玻片取出并经 2 次蒸馏水冲洗后,使用 PBS 冲洗,3 min/ 次,共进行 3 次。将过氧化物酶阻断剂滴加在每张组织切片上,在室温下孵育约 10 min 左右,经 3 次 PBS 冲洗后除去 PBS,滴加配置完成的抗体于切片上,置入 4℃容器内过夜,次日取出复温,经 3 次 PBS 冲洗后滴加试剂, 室温下孵育约 15 min, 经 3 次 PBS 冲洗。将 PBS 除去,滴加显色剂显色。在光学显微镜下显色 3-5 min 使用自来水冲洗,冲洗 10 min 将残留显色剂清除,苏木精复染细胞核 60 s,自来水冲洗,经梯度乙醇脱水后使用二甲苯透明 10 min,后使用吹风机吹干后封片。(3)结果判读:结果的判读需结合染色强度及阳性细胞数进行:① 染色强度:0 分:无着色,1 分:淡黄色,2 分:棕黄色,3 分:棕褐色。② 阳性细胞数:在低倍显微镜下仔细观察切片, 随机抽取 5 个× 400 倍的高倍视野,每视野细胞计数为 100 个,阳性细胞率 = 阳性细胞数 / 观察细胞数× 100%。阳性分级:1 分:细胞率≤ 10%,2 分:11%~50%,3 分:＞50%。若染色强度与阳性细胞率所得分值相乘＞3 分,则判定为阳性。

1.3 统计学方法

应用 SPSS20.0 统计学软件处理数据, 以百分比表示计数资料,组间比较采用 x^2 检验,相关性采用双变量 Pearson 相关性分析,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 胃癌组织与癌旁正常胃组织 HER2、PD-L1 的表达

100 例胃癌患者胃癌组织 HER2 阳性表达、PD-L1 阳性表达均高于癌旁正常胃组织,见表 2、图 1-2。

2.2 HER2、PD-L1 表达与胃癌临床病理特征的相关性分析

如表 3 所示,分化程度越好的胃癌患者 HER2 阳性表达越高,差异有统计学意义($P<0.05$)。远处转移胃癌患者 PD-L1 阳性表达高于无远处转移者($P<0.05$)。胃癌组织 PD-L1 表达与肿

表 1 100 例胃癌患者临床资料分布情况

Table 1 The distribution of clinical data of 100 patients with gastric cancer

Items	-	Cases	Constituent ratio (%)
Gender	Male	76	76.00
	Female	24	24.00
Age (Years old)	≤ 60	40	40.00
	＞60	60	60.00
Size of tumor (cm)	≤ 4	40	40.00
	＞4	60	60.00
WHO classification	Well differentiation	35	35.00
	Poor differentiation	46	46.00
	Worse differentiation	19	19.00
Location of tumor	Upper 1/3 gastric cancer	17	17.00
	Lower 2/3 gastric cancer	83	83.00
Depth of infiltration	T1	16	16.00
	T2	12	12.00
	T3	11	11.00
	T4	61	61.00
TNM stage	Stage Ⅰ	21	21.00
	Stage Ⅱ	18	18.00
	Stage Ⅲ	54	54.00
	Stage Ⅳ	7	7.00
Lymph node metastasis	Have	71	71.00
	Without	29	29.00
Distant metastasis	Have	6	6.00
	Without	94	94.00
Vascular invasion	Have	67	67.00
	Without	33	33.00
Nerve invasion	Have	43	43.00
	Without	57	57.00

表 2 胃癌组织与癌旁正常胃组织 HER2、PD-L1 表达比较【例(%)】

Table 2 Comparison on expression of HER2 and PD-L1 between gastric cancer tissues and adjacent normal gastric mucosa[n(%)]

Tissues	HER2			PD-L1	
	Negative	Weakly positive	Strongly positive	Negative	Positive
Gastric cancer tissues (n=100)	42(42.00)	31(31.00)	27(27.00)	57(57.00)	43(43.00)
Adjacent normal gastric mucosa (n=100)	100(100.00)	0	0	100(100.00)	0
x^2	81.690			54.778	
P	＜0.001			＜0.001	

瘤分化程度、浸润深度、远处转移均呈正相关(r=0.391、0.413、0.206，P＜0.05)，见表 4。

3 讨论

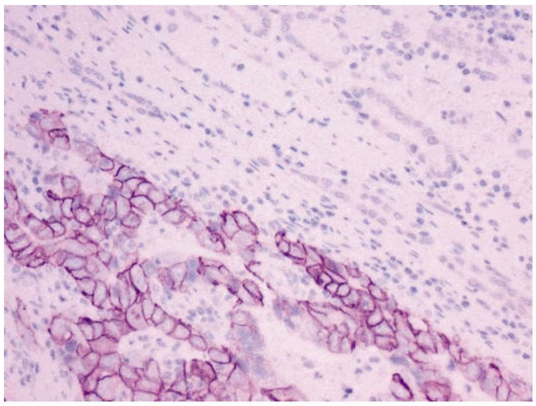

图 1 胃癌组织中 HER2 的免疫组化染色

Fig. 1 Immumohistochemical staining of HER2 in gastric cancer tissues

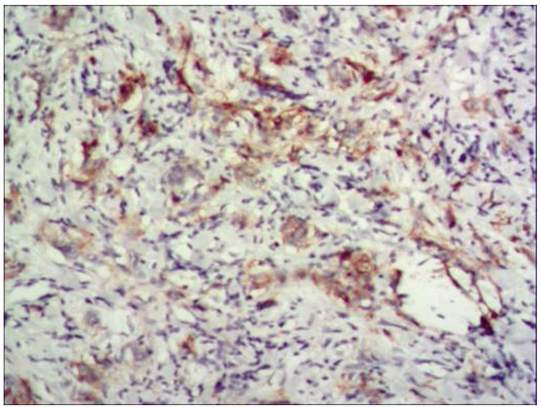

图 2 胃癌组织中 PD-L1 的免疫组化染色

Fig. 2 Immumohistochemical staining of PD-L1 in gastric cancer tissues

表 3 胃癌组织 HER2 表达与临床病理特征相关性(例)

Table 3 Correlation of the expression of HER2 with the clinicopathological features of in the gastric cancer tissues (Cases)

Items	-	Cases	HER2			x^2/Z	*P*
			Negative	Weakly positive	Strongly positive		
Gender	Male	76	32	22	22	0.876	0.645
	Female	24	10	9	5		
Age (Years old)	≤ 60	40	16	16	8	3.015	0.221
	＞60	60	26	15	19		
Size of tumor (cm)	≤ 4	40	16	13	11	0.118	0.943
	＞4	60	26	18	16		
WHO classification	Well differentiation	35	6	17	12	-2.462	0.014
	Poor differentiation	46	23	12	11		
	Worse differentiation	19	13	2	4		
Location of tumor	Upper 1/3 gastric cancer	17	10	2	5	4.365	0.113
	Lower 2/3 gastric cancer	83	32	29	22		
Depth of infiltration	T1	16	5	5	6	-1.510	0.113
	T2	12	6	5	1		
	T3	11	6	3	2		
	T4	61	25	18	18		
TNM stage	Stage Ⅰ	21	9	5	7	0.857	0.878
	Stage Ⅱ	18	6	9	3		
	Stage Ⅲ	54	24	15	15		
	Stage Ⅳ	7	3	2	2		
Lymph node metastasis	Have	71	29	21	21	0.840	0.657
	Without	29	13	10	6		
Distant metastasis	Have	6	2	2	2	0.222	0.895
	Without	94	40	29	25		
Vascular invasion	Have	67	28	20	19	0.227	0.893
	Without	33	14	11	8		
Nerve invasion	Have	43	19	15	9	1.482	0.447
	Without	57	23	16	18		

表 4 胃癌组织 PD-L1 表达与临床病理特征相关性

Table 4 Correlation of the expression of PD-L1 with the clinicopathological features of in the gastric cancer tissues

Items	-	Cases	PD-L1		x^2/Z	*P*
			Negative	Positive		
Gender	Male	76	43	33	0.023	0.880
	Female	24	14	10		
Age (Years old)	≤ 60	40	21	19	0.551	0.458
	＞60	60	36	24		
Size of tumor (cm)	≤ 4	40	22	18	0.109	0.742
	＞4	60	35	25		
WHO classification	Well differentiation	35	31	4	-3.607	＜0.001
	Poor differentiation	46	18	28		
	Worse differentiation	19	8	11		
Location of tumor	Upper 1/3 gastric cancer	17	13	4	3.168	0.075
	Lower 2/3 gastric cancer	83	44	39		
Depth of infiltration	T1	16	16	0	23.735	＜0.001
	T2	12	8	4		
	T3	11	7	4		
	T4	61	26	35		
TNM stage	Stage Ⅰ	21	12	9	-0.658	0.510
	Stage Ⅱ	18	8	10		
	Stage Ⅲ	54	32	22		
	Stage Ⅳ	7	5	2		
Lymph node metastasis	Have	71	37	34	2.386	0.122
	Without	29	20	9		
Distant metastasis	Have	6	1	5	4.237	0.040
	Without	94	56	38		
Vascular invasion	Have	67	35	33	2.651	0.104
	Without	33	22	10		
Nerve invasion	Have	43	22	21	1.049	0.306
	Without	57	35	22		

HER2 是一种原癌基因，具有酪氨酸激酶活性，是表皮生长因子受体家族中的一员，但与该家族内其他成员不同的是，HER2 并不具备自身特异性的配体，该因子主要经与表皮生长因子家族其他成员而产生异源或同源二聚体，从而对磷脂酰肌醇 3 激酶等通路产生激活之效，使其发挥主要的生物学作用[12]。HER2 在健康人体内的表达多为非激活状态，只有在胚胎时期其才以较高表达存在[13]。但当机体受到外界有害因素，尤其是致癌等高危因素刺激后，该因子将被激活并形成大量的异源或同源二聚体，直接激活磷脂酰肌醇 3 激酶通路，进一步抗细胞凋亡、调控细胞增殖，同时加速新生血管的形成，从而加速肿瘤的发生与发展[14,15]。目前，HER2 因子的过度表达在肺癌、乳腺癌、卵巢癌等诸多恶性肿瘤疾病中已被检测并证实[16,17]。过度的 HER2 表达将加速肿瘤细胞的转移，触发信号下游蛋白磷酸化，进一步加速新生血管生成与细胞增殖[18]。

HER2 是否可以作为评估胃癌患者病情与预后的指标，目前仍有较大争议。Jorgensen JT[19]等在 1986 年 ~2011 年间展开了与胃癌 HER2 过度表达有关的研究，发现胃癌患者 HER2 呈高表达，且与患者较差的生存质量及较短的生存时间密切相关，表明 HER2 在用于胃癌预后评估判断方面有一定潜在价值。而在《胃癌相关标志物免疫组化指标选择专家共识(2014 年版)》[20]中也推荐了将 HER2 列入胃癌常规检查，这一结果肯定了 HER2 用于胃癌治疗与预后评估方面的价值。本研究结果显示胃癌组织中 HER2 高表达仅与肿瘤分化程度呈负相关，而在性别、年龄、肿瘤大小等其他病理特征相关资料中分布无差异，本研究虽未得出 HER2 在评估胃癌转移性与侵袭性方面的证据，但其高表达与分化程度间的负相关性可能提示着患者恶性

程度较低,提示 HER2 在胃癌组织中的表达有选择性,检测胃癌患者组织中 HER2 表达对指导患者分子靶向治疗可能有一定的临床参考价值。

近年来,恶性肿瘤疾病的治疗出现越来越多的新手段。其中,免疫检查点抑制剂的应用备受关注与重视,主要的 PD-1/PD-L1 免疫检查点能够抑制患者 T 细胞活化,增加肿瘤的免疫耐受性,故对这一信号通路实施阻断可诱导 T 细胞的活化并达到杀灭肿瘤细胞的效果,这一机制已成为目前恶性肿瘤治疗研究热点[21-23]。PD-L1 是重要的 B7 家族 T 细胞抑制性刺激分子,又称作 CD274 或 B7-H1,是一种Ⅰ型穿膜蛋白,能够在部分炎症介质的刺激下诱导多种细胞类型表达,因此诸多恶性肿瘤蛋白中均存在 PD-L1 高表达现象[24,25]。PD-L1 只有在细胞膜上表达时才能具备生物学活性,但其也可通过改变炎性介质表达并激活致癌基因达到生物学效应。现有的研究已证实恶性肿瘤组织中 PD-L1 高表达能够加速肿瘤细胞的转移与浸润,保护肿瘤细胞不受 T 淋巴细胞的攻击,躲过机体免疫监视系统[26,27]。由此可见,在恶性肿瘤细胞组织中,PD-L1 高表达作用并不会直接诱使细胞凋亡,但将减少 T 细胞增殖与存活,达到促肿瘤病情进展与恶化的作用。此外,PD-L1 还能够结合 B 细胞上 PD-1,导致 PD-1 胞质区域的免疫受体中酪氨酸磷酸化,大量磷酸酶的募集将导致相关信号分子发生去磷酸化,从而抑制免疫传递信号,使得肿瘤躲过机体免疫监视及杀伤系统,从而加速患者病情恶化[28-30]。本研究结果显示胃癌组织中 PD-L1 过度表达,术前有转移、浸润深度深、分化程度高的患者阳性率更高,且 PD-L1 与胃癌患者远处转移、浸润深度、分化程度均呈正相关,提示 PD-L1 过度表达可作为胃癌患者术前有无远处转移、浸润深度、分化程度的评估指标。

综上所述,HER2 的阳性表达可能提示胃癌患者较低的恶性程度,PD-L1 的高表达可能提示胃癌患者存在远处转移、浸润深度深、恶性程度高。HER2 和 PD-L1 有望成为胃癌患者诊断参考指标及药物干预的靶点。

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