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血清 PIVKA- II、Calretinin 及 DJ-1 蛋白在卵巢癌中的表达 及与病情严重程度的相关性 *

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摘要 目的:探讨血清异常凝血酶原(PIVKA- II)、钙网膜蛋白(Calretinin)及 DJ-1 蛋白在卵巢癌中的表达及与病情严重程度的相关性。**方法:**选择 2019 年 3 月至 2020 年 3 月我院接诊的 100 例卵巢癌患者为本研究对象,设为病例组,并选择我院同期体检的健康对照组 90 例,分析两组血清 PIVKA- II、Calretinin 及 DJ-1 蛋白水平的表达,及其与卵巢癌患者病情严重程度的相关性。**结果:**病例组血清 PIVKA- II、Calretinin 及 DJ-1 蛋白水平显著高于对照组,差异显著 ($P<0.05$);I-II 期组患者血清 PIVKA- II、Calretinin 及 DJ-1 蛋白水平显著低于 III 期、IV 期患者,III 期患者血清 PIVKA- II、Calretinin 及 DJ-1 蛋白水平显著高于 IV 期患者,差异显著($P<0.05$);相关性分析结果中显示,血清 PIVKA- II、Calretinin 及 DJ-1 蛋白和病理分期之间呈正相关($P<0.05$)。**结论:**在卵巢癌患者中血清 PIVKA- II、Calretinin 及 DJ-1 蛋白与病情严重程度之间存在着密切关系,可作为卵巢癌的潜在标记物。

关键词:异常凝血酶原;钙网膜蛋白;DJ-1 蛋白;卵巢癌;病情严重程度;相关性

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Analysis of the Expression of Serum Pivka- II, Calretinin and DJ-1 Proteins in Ovarian Cancer and Their Correlation with the Severity of the Disease*

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ABSTRACT Objective: To study Analysis of the Expression of serum Abnormal prothrombin (PIVKA - II), Calretinin (Calretinin) and DJ-1 proteins in ovarian cancer and their correlation with the severity of the disease. **Methods:** 100 patients with ovarian cancer admitted by our hospital from March 2019 to March 2020 were selected as the study subjects, and 90 healthy control patients who underwent physical examination in our hospital during the same period were selected to analyze the expression of serum Pivka- II, Calretinin and DJ-1 protein in the two groups, and their correlation with the severity of ovarian cancer patients. **Results:** Serum Pivka- II, Calretinin and DJ-1 protein levels in case group were significantly higher than those in control group ($P<0.05$). Serum Pivka- II, Calretinin and DJ-1 protein levels in stage I to II group were significantly lower than those in stage III and IV patients, and serum Pivka-a-in, Calretinin and DJ-1 protein levels in stage III patients were significantly higher than those in stage IV patients, with significant differences ($P<0.05$). Correlation analysis results showed that serum Pivka- II, Calretinin and DJ-1 proteins were positively correlated with pathological stages ($P<0.05$). **Conclusion:** Serum Pivka- II, Calretinin and DJ-1 protein are closely related to the severity of the disease in patients with ovarian cancer, which can be used as a potential marker for ovarian cancer.

Key words: Abnormal prothrombin; Calciomentum protein; DJ - 1 protein; Ovarian cancer; Severity of illness; The correlation

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前言

卵巢癌是临床常见的恶性肿瘤,早期无明显症状,多数患者确诊时已是中晚期,治疗后患者 5 年生存率仅 20%~30%,死亡率居妇科生殖系统肿瘤首位,严重影响患者预后^[1,2]。因此,寻找卵巢癌早期诊断指标是卵巢癌研究的重点。PIVKA- II 是一种维生素 K 缺乏诱导蛋白,是一种诊断肝细胞癌的肿瘤标志物;Calretinin 是一种细胞内钙结合蛋白,其特征具有恶性行为,是已被证实的间皮组织标志物,在胰腺癌胸水中高表达,对

胰腺癌患者胸水中癌细胞的诊断具有较高的价值^[3-5]。近年来随着基因组学和代谢组学等技术的应用,与卵巢癌相关的新肿瘤标志物被发现^[6]。DJ-1 蛋白由 PARK7 基因编码,具有促进细胞转化和抑制细胞凋亡等功能,在多种肿瘤中表示异常,与肿瘤的发生、转移密切相关^[7,8]。血清 PIVKA- II、Calretinin 及 DJ-1 蛋白均被证实与多种恶性肿瘤关系密切,但与卵巢癌的关系目前缺乏相关报道^[9]。因此,本研究旨在探讨血清 PIVKA- II、Calretinin 及 DJ-1 蛋白在卵巢癌中的表达,并分析其与病情严重程度的相关性。

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1 资料与方法

1.1 一般资料

选择2019年3月至2020年3月我院接诊的100例卵巢癌患者设为病例组,年龄33~62岁,平均(45.56±4.62)岁,体重43~72kg,平均(51.31±1.31)kg,肿瘤类型:粘液性腺癌58例,浆液性腺癌42例,病理分期:I~II期38例,III期42例,IV期20例。选择同期在我院进行检查的90例人群为对照组,年龄30~60岁,平均年龄(45.42±4.67)岁,体重44~70kg,平均(51.19±1.26)kg。两组基线资料无明显差异,可比较。

参照《卵巢癌诊疗规范》^[10]:伴有下腹不适、腹胀、食欲下降等症状;影像检查确诊。

纳入标准:(1)符合上述诊断标准;(2)临床资料完整;(3)研究前未接受过放化疗治疗;(4)知情同意。排除标准:(1)合并其他肿瘤者;(2)患有意识障碍、精神障碍者;(3)合并恶性肿瘤者;(4)存在血小板疾病者;(5)妊娠者;(6)依从性较差者;(7)

生存期<3月者。

1.2 方法

纳入研究前均进行病理分期;采集空腹静脉血5mL,提取上层血清后,置于零下20℃的冷冻箱内存储以备检测,采用酶联免疫吸附法测定PIVKA-II、Calretinin及DJ-1蛋白,试剂盒购于英国Abcam公司。

1.3 统计学分析

以spss19.0软件包处理,计量资料用均数±标准差($\bar{x} \pm s$)表示,t检验,多组比较采用方差分析,相关性分析使用Spearman相关系数,计数资料以率表示, χ^2 检验, $P < 0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组血清PIVKA-II、Calretinin及DJ-1蛋白水平比较

病例组血清PIVKA-II、Calretinin及DJ-1蛋白水平显著高于对照组,差异显著($P < 0.05$)见表1。

表1 两组血清PIVKA-II、Calretinin及DJ-1蛋白水平比较($\bar{x} \pm s$)

Table 1 Comparison of serum Pivka-II, Calretinin and DJ-1 protein levels between the two groups($\bar{x} \pm s$)

Groups	n	PIVKA-II (U/L)	Calretinin(ng/mL)	DJ-1(μ g/L)
Case group	100	35.91±8.78	0.46±0.17	11.86±4.52
Control group	90	18.62±4.34	0.17±0.05	4.21±0.89
t value		16.912	15.584	15.779
P value		0.000	0.000	0.000

2.2 不同分期血清PIVKA-II、Calretinin及DJ-1蛋白水平比较

I~II期组患者血清PIVKA-II、Calretinin及DJ-1蛋白水平显著低于III期、IV期患者,III期患者血清PIVKA-II、Calre-

tinin及DJ-1蛋白水平显著高于IV期患者,差异显著($P < 0.05$),见表2。

表2 不同分期血清PIVKA-II、Calretinin及DJ-1蛋白水平比较($\bar{x} \pm s$)

Table 2 Comparison of serum Pivka-II, Calretinin and DJ-1 protein levels in different stages($\bar{x} \pm s$)

Installment	n	PIVKA-2(U/L)	Calretinin(ng/mL)	DJ-1(μ g/L)
I~II period	38	28.59±8.54	0.32±0.18	8.56±4.24
III period	42	34.98±8.81	0.45±0.19	11.89±4.53
IV period	20	51.77±8.95	0.75±0.25	18.07±4.68
F value		46.538	30.494	29.895
P value		0.000	0.000	0.000

2.3 血清PIVKA-II、Calretinin及DJ-1蛋白水平与病情严重程度的相关性分析

将病理分期作为因变量,将血清PIVKA-II、Calretinin及

DJ-1蛋白分别作为自变量,在相关性分析结果中显示,血清PIVKA-II、Calretinin及DJ-1蛋白和病理分期之间呈正相关($P < 0.05$),见表3。

表3 血清PIVKA-II、Calretinin及DJ-1蛋白水平与病情严重程度的相关性分析

Table 3 Correlation analysis of serum Pivka-II, Calretinin and DJ-1 protein levels with the severity of the disease

Items	The pathological staging	
	r value	P value
PIVKA-II	0.568	0.000
Calretinin	0.713	0.000
DJ-1	0.652	0.000

3 讨论

卵巢癌是女性生殖系统三大恶性肿瘤之一,由于卵巢位于盆腔的深部,临床症状通常表现不明显,多数患者以腹痛、腹部肿块就诊,此时病情多已进展到晚期,错过手术最佳时期,导致治疗效果不佳^[11-13]。卵巢癌发病率较高,有研究显示,美国是卵巢癌高发国家,仅北美地区 2013 年新发病例即高达 2 万例,其中死亡病例为 1.4 万例^[14,15]。据调查显示,2015 年全球约有 15 万人死于卵巢癌,严重影响患者预后^[16]。卵巢癌早期临床症状不明显,早期诊断依据精确性较,成为死亡率高的主要原因,因此寻找一种准确性高的血清学指标对疾病进行早期诊断,对降低患者死亡率具有重要意义^[17]。

血清 PIVKA-II 是肝脏合成的无凝血活性的异常凝血酶原,与患者肝脏维生素 K 代谢异常有关,在原发性肝癌血清中阳性率高,被认为是原发性肝癌的诊断标志物,有研究显示,PIVKA-II 在肝脏肿瘤生长过程中起自体生长因子的作用,在早期肝脏肿瘤中具有良好的反应^[18,19]。Aleksandra K^[20]等研究证实,血清 PIVKA-II 在肝细胞癌中表达较高,且与 AFP 联合检测有助于提高肝癌诊断的准确率,后来被发现其在直肠癌、胰腺癌等都出现升高现象。本研究结果显示,血清 PIVKA-II 在卵巢癌中高于健康人,且 I-II 期组患者血清 PIVKA-II 水平显著低于 III 期、IV 期患者,III 期患者血清 PIVKA-II 水平显著高于 IV 期患者,进一步相关性分析发现,血清 PIVKA-II 和病理分期之间呈正相关,提示,血清 PIVKA-II 在卵巢癌中表达较高,且可随着疾病的严重程度而升高,Manchanda R^[21]等研究也显示,卵巢癌患者血清 PIVKA-II 水平高于良性肿瘤,特异性高达 90%,在卵巢癌中有一定的预测价值。但目前卵巢癌与血清 PIVKA-II 的相关报道较少,是否可作为卵巢癌的检测指标还需进一步深入研究。

Calretinin 属于 EF- 手性蛋白大家族的一员,主要表达在中枢神经系统及恶性间皮组织细胞中,在体外可促进肿瘤细胞迁移,参与人间皮瘤细胞系上皮到间充质转化的过程^[22,23]。有研究显示,在脂肪细胞或卵巢基质中观察到了 Calretinin 表达,Calretinin 蛋白在多种上皮和非上皮性肿瘤中表达异常^[24,25]。有研究发现,卵巢癌患者血清 Calretinin 高于健康人,且术后也低于术前^[26]。本研究结果显示,血清 Calretinin 在卵巢癌中高于健康人,且 I-II 期组患者血清 Calretinin 水平显著低于 III 期、IV 期患者,III 期患者血清 Calretinin 水平显著高于 IV 期患者,进一步相关性分析发现,血清 Calretinin 和病理分期之间呈正相关,提示,血清 Calretinin 在卵巢癌中表达较高,且与疾病的严重程度密切相关,可作为卵巢癌疗效监测和预后预测的指标。分析其原因可能是因为卵巢表面无腹膜覆盖,组织胚胎学起源于腹膜间皮,卵巢本身起源于泌尿生殖嵴的中胚层,而 Calretinin 表达在生发上皮,在增殖期表达于内膜基质细胞中,分泌期在功能层弥漫表达,因此在卵巢癌中表达异常。

DJ-1 基因是一种新的丝裂原依赖性癌基因,对蛋白激酶介导细胞形成肿瘤有促进作用,DJ-1 蛋白单体在人体肾脏、肌肉组织等组织中广泛表达,且其二聚体形式在细胞的转录、氧化应激等活动中发挥重要作用^[27,28]。有研究显示,DJ-1 在子宫内膜癌组织中表达较高,与子宫内膜癌发生密切相关^[29]。国外研

究也显示,DJ-1 在非小细胞肺癌中异常表达,在肺癌发生远处转移时更高,可作为评估肺癌预后的肿瘤标志物^[30]。Lei Z^[31]等研究显示,眼葡萄膜恶性黑色素瘤能分泌 DJ-1 蛋白,且可在眼葡萄膜恶性黑色素瘤患者中被检测出,早期检测 DJ-1 蛋白有望作为临床评估卵巢癌病情严重程度重要标志物。本研究结果显示,DJ-1 蛋白在卵巢癌中高于健康人,且 I-II 期组患者血清 DJ-1 水平显著低于 III 期、IV 期患者,III 期患者血清 DJ-1 水平显著高于 IV 期患者,进一步相关性分析发现,血清 DJ-1 和病理分期之间呈正相关,结果提示,DJ-1 蛋白在卵巢癌中呈高表达,且随着疾病的严重程度而升高,与疾病的发生关系密切,可作为预测卵巢癌的标准物。Jones H M^[32]等研究也显示,DJ-1 与卵巢癌分期及淋巴结转移等临床病理特征密切相关,参与了卵巢癌的发生、侵袭转移过程,与本研究结果相似。

综上所述,血清 PIVKA-II、Calretinin 及 DJ-1 蛋白在卵巢癌中表达较高,且与病情严重程度之间存在着密切关系,可作为卵巢癌的潜在标记物。

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