

本文引用:朱春霞,孟勇,王秀虹.血清人附睾分泌蛋白4、糖类抗原125和脂联素在子宫内膜癌淋巴结转移诊断中的价值[J].新乡医学院学报,2016,33(5):403-405,410. DOI:10.7683/xyxyxb.2016.05.016.

【临床研究】

血清人附睾分泌蛋白4、糖类抗原125和脂联素在子宫内膜癌淋巴结转移诊断中的价值

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摘要: **目的** 血清人附睾分泌蛋白4(HE4)、糖类抗原125(CA125)及脂联素在子宫内膜癌淋巴结转移诊断中的价值。**方法** 选择2011年12月至2014年6月在咸宁市中心医院接受治疗的子宫内膜癌患者82例,其中伴淋巴结转移47例(观察组),无淋巴结转移35例(对照组)。对2组患者血清HE4、CA125及脂联素水平进行比较,并分析血清HE4、CA125及脂联素在子宫内膜癌淋巴结转移诊断中的价值。**结果** 观察组患者血清HE4和CA125水平显著高于对照组($P < 0.05$),血清脂联素水平显著低于对照组($P < 0.05$)。受试者工作特征曲线分析显示,以血清HE4水平为 $170.6 \text{ pmol} \cdot \text{L}^{-1}$ 作为临界值,其对子宫内膜癌伴淋巴结转移诊断的敏感度为47.27%,特异度为77.78%;以血清CA125水平为 $40.69 \text{ kU} \cdot \text{L}^{-1}$ 作为临界值,其对子宫内膜癌伴淋巴结转移诊断的敏感度为23.40%,特异度为91.43%;以血清脂联素水平为 $7.13 \text{ mg} \cdot \text{L}^{-1}$ 作为临界值,其对子宫内膜癌伴淋巴结转移诊断的敏感度为44.68%,特异度为81.35%;血清HE4、CA125和脂联素联合检测对子宫内膜癌伴淋巴结转移诊断的敏感度为65.47%,特异度为89.02%。血清HE4与脂联素对子宫内膜癌伴淋巴结转移诊断的敏感度和特异度比较差异均无统计学意义($P > 0.05$);血清HE4和脂联素对子宫内膜癌伴淋巴结转移诊断的敏感度高于CA125($P < 0.05$),特异度低于CA125($P < 0.05$);血清HE4、CA125和脂联素联合检测对子宫内膜癌伴淋巴结转移诊断的敏感度均高于单独检测血清HE4、CA125及脂联素($P < 0.05$)。血清HE4、CA125和脂联素联合检测对子宫内膜癌伴淋巴结转移诊断的特异度高于单独检测血清HE4和脂联素($P < 0.05$),但三者联合检测与单独检测CA125对子宫内膜癌伴淋巴结转移诊断的特异度比较差异无统计学意义($P > 0.05$)。**结论** 血清HE4、CA125和脂联素可作为诊断子宫内膜癌伴淋巴结转移的肿瘤标志物,三者联合检测对诊断子宫内膜癌淋巴结转移具有较高价值。

关键词: 子宫内膜癌;淋巴结转移;人附睾分泌蛋白4;糖类抗原125;脂联素

中图分类号: R737.33 **文献标志码:** A **文章编号:** 1004-7239(2016)05-0403-04

Value of serum human epididymis protein 4, carbohydrate antigen 125 and adiponectin in the diagnosis of lymphatic metastasis in patients with endometrial carcinoma

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Abstract: **Objective** To investigate the value of serum human epididymis protein 4 (HE4), carbohydrate antigen 125 (CA125) and adiponectin in the diagnosis of lymphatic metastasis in patients with endometrial carcinoma. **Methods** A total of 82 cases of endometrial cancer were selected in Xianning Central Hospital From December 2011 to June 2014, including 47 patients with lymphatic metastasis (observation group), 35 patients without lymphatic metastasis (control group). The levels of serum HE4, CA125 and adiponectin were compared between the two groups, and the value of serum HE4, CA125 and adiponectin in the diagnosis of lymphatic metastasis in patients with endometrial carcinoma. **Results** The levels of serum HE4 and CA125 in observation group were significantly higher than those in control group ($P < 0.05$), but the level of serum adiponectin in observation group was significantly lower than that in control group ($P < 0.05$). Receiver operating characteristic curve analysis showed that the sensitivity and specificity of serum HE4 in diagnosing lymphatic metastasis in patients with endometrial carcinoma was 47.27% and 77.78% respectively when $170.6 \text{ pmol} \cdot \text{L}^{-1}$ was selected as the critical value of serum HE4. The sensitivity and specificity of serum CA125 in diagnosing lymphatic metastasis in patients with endometrial carcinoma was 23.40% and 91.43% respectively when $40.69 \text{ kU} \cdot \text{L}^{-1}$ was selected as the critical value of serum CA125. The sensitivity

DOI:10.7683/xyxyxb.2016.05.016

收稿日期:2015-06-28

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and specificity of serum adiponectin in diagnosing lymphatic metastasis in patients with endometrial carcinoma was 44.68% and 81.35% respectively when $7.13 \text{ mg} \cdot \text{L}^{-1}$ was selected as the critical value of serum adiponectin. The sensitivity and specificity of the combined detection of serum HE4, CA125 and adiponectin in diagnosing lymphatic metastasis in patients with endometrial carcinoma was 65.47% and 89.02% respectively. There was no significant difference in the sensitivity and specificity between serum HE4 and adiponectin in diagnosing lymphatic metastasis in patients with endometrial carcinoma ($P > 0.05$). The sensitivity of serum HE4 and adiponectin in diagnosing lymphatic metastasis in patients with endometrial carcinoma was higher than that of serum CA125 ($P < 0.05$), but the specificity of serum HE4 and adiponectin was lower than that of serum CA125 ($P < 0.05$). The sensitivity of combined detection of serum HE4, CA125 and adiponectin in diagnosing lymphatic metastasis in patients with endometrial carcinoma was higher than that of any one of serum HE4, CA125 and adiponectin ($P < 0.05$). The specificity of combined detection of serum HE4, CA125 and adiponectin in diagnosing lymphatic metastasis in patients with endometrial carcinoma was higher than that of any one of serum HE4 and adiponectin ($P < 0.05$). But there was no significant difference in the specificity between the combined detection of the three indexes and CA125 in diagnosing lymphatic metastasis in patients with endometrial carcinoma ($P > 0.05$). **Conclusions** Serum HE4, CA125 and adiponectin can be used as tumor markers for diagnosing lymphatic metastasis in patients with endometrial carcinoma. Combined detection of the three indexes has a high value in diagnosing lymphatic metastasis.

Key words: endometrial cancer; lymphatic metastasis; human epididymis protein 4; carbohydrate antigen 125; adiponectin

子宫内膜癌是一种起源于子宫内膜上皮细胞的恶性肿瘤,是女性生殖系统最常见的恶性肿瘤之一,发病人群多为绝经后或围绝经期女性^[1]。由于子宫内膜癌的病灶局限,且子宫内膜外肌层较厚,癌细胞发生转移较晚,患者5 a生存率为60%~70%。近年来,子宫内膜癌发病率呈现逐年上升趋势,严重危害患者的身体健康和生活质量。研究发现,妇科恶性肿瘤患者血清人附睾分泌蛋白4(human epididymis protein 4, HE4)水平显著升高,是一种新的肿瘤标志物^[2-3]。血清脂联素水平降低与子宫内膜癌的发生、转移有一定关系^[4]。糖类抗原125(carbohydrate antigen 125, CA125)是从上皮性卵巢癌抗原检测出可被单克隆抗体OC125结合的一种糖蛋白,常用于上皮性卵巢肿瘤的检测。本研究旨在探讨血清HE4、CA125及脂联素在子宫内膜癌淋巴结转移诊断中的价值。

1 资料与方法

1.1 一般资料 选择2011年12月至2014年6月在咸宁市中心医院接受治疗的子宫内膜癌患者82例,年龄49~81岁,平均 (43.5 ± 12.4) 岁;根据国际妇产科协会(federation international of gynecology and obstetrics, FIGO)制定的手术-病理分期标准^[5]: I期13例, II期22例, III期36例, IV期11例;所有病理经术后病理检查确诊,82例患者根据是否伴有淋巴结转移分为观察组(伴淋巴结转移)和对照组(无淋巴结转移)。观察组47例,年龄47~76岁,平均 (54.72 ± 10.36) 岁;绝经28例,未绝经19例;有肿瘤家族史11例,无肿瘤家族史36例。对照组35例,年龄49~81岁,平均 (52.44 ± 8.91) 岁;绝经21

例,未绝经14例;有肿瘤家族史7例,无肿瘤家族史28例。2组患者的年龄、绝经情况、肿瘤家族史比较差异均无统计学意义($P > 0.05$)。

1.2 血清HE4、CA125及脂联素水平检测 采集患者清晨空腹肘静脉血5 mL, $3\ 000 \text{ r} \cdot \text{min}^{-1}$ 离心3 min,取其上清液置 $-20 \text{ }^{\circ}\text{C}$ 冰箱保存待测。采用酶联免疫吸附试验测定血清HE4、CA125和脂联素水平,试剂盒购自北京金辉智诚医学科技有限公司。

1.3 统计学处理 应用SPSS 19.0软件进行数据分析,计量资料以均数 \pm 标准差($\bar{x} \pm s$)表示,两两比较采用 t 检验,计数资料比较采用 χ^2 检验, $P < 0.05$ 为差异有统计学意义。应用受试者工作特征(receiver operating characteristic, ROC)曲线评价血清HE4、CA125和脂联素对子宫内膜癌伴淋巴结转移诊断的敏感度和特异度。

2 结果

2.1 2组患者血清HE4、CA125及脂联素水平比较

结果见表1。观察组患者血清HE4和CA125水平显著高于对照组($P < 0.05$),血清脂联素水平显著低于对照组($P < 0.05$)。

表1 2组患者血清HE4、CA125和脂联素水平比较

Tab.1 Comparison of the levels of serum HE4, CA125 and adiponectin between the two groups ($\bar{x} \pm s$)

组别	<i>n</i>	HE4/($\text{pmol} \cdot \text{L}^{-1}$)	CA125/($\text{kU} \cdot \text{L}^{-1}$)	脂联素/($\text{mg} \cdot \text{L}^{-1}$)
对照组	35	161.02 \pm 16.45	39.83 \pm 7.36	12.08 \pm 1.71
观察组	47	254.61 \pm 30.73 ^a	46.74 \pm 13.72 ^a	5.87 \pm 0.96 ^a

注:与对照组比较^a $P < 0.05$ 。

2.2 血清HE4、CA125和脂联素检测对子宫内膜癌伴淋巴结转移的诊断价值比较 结果见图1。ROC曲线分析显示以血清HE4水平为 $170.6 \text{ pmol} \cdot \text{L}^{-1}$

作为临界值,其对子宫内膜癌伴淋巴结转移诊断的敏感度为47.27%,特异度为77.78%;以血清CA125水平为 $40.69 \text{ kU} \cdot \text{L}^{-1}$ 作为临界值,其对子宫内膜癌伴淋巴结转移诊断的敏感度为23.40%,特异度为91.43%;以血清脂联素水平为 $7.13 \text{ mg} \cdot \text{L}^{-1}$ 作为临界值,其对子宫内膜癌伴淋巴结转移诊断的敏感度为44.68%,特异度为81.35%;血清HE4、CA125和脂联素联合检测对子宫内膜癌伴淋巴结转移诊断的敏感度为65.47%,特异度为89.02%。血清HE4与脂联素对子宫内膜癌伴淋巴结转移诊断的敏感度和特异度比较差异均无统计学意义($\chi^2 = 0.098, 0.341; P > 0.05$);血清HE4和脂联素对子宫内膜癌伴淋巴结转移诊断的敏感度高于CA125($\chi^2 = 10.670, 8.786; P < 0.05$),特异度低于CA125($\chi^2 = 5.711, 4.096, P < 0.05$);血清HE4、CA125和脂联素联合检测对子宫内膜癌伴淋巴结转移诊断的敏感度均高于单独检测血清HE4($\chi^2 = 5.558, P < 0.05$)、CA125($\chi^2 = 30.240, P < 0.05$)及脂联素($\chi^2 = 7.135, P < 0.05$)。血清HE4、CA125和脂联素联合检测对子宫内膜癌伴淋巴结转移诊断的特异度高于单独检测血清HE4($\chi^2 = 4.307, P < 0.05$)和脂联素($\chi^2 = 5.875, P < 0.05$),但三者联合检测与单独检测CA125对子宫内膜癌伴淋巴结转移诊断的特异度比较差异无统计学意义($\chi^2 = 0.277, P > 0.05$)。

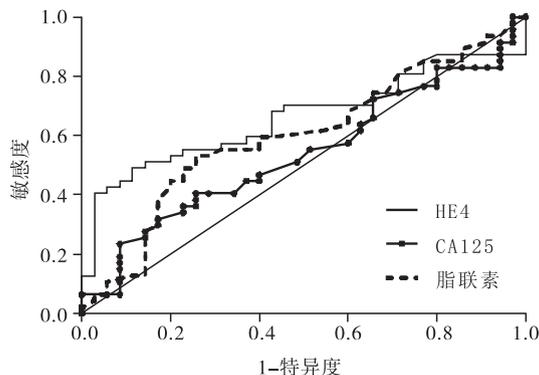


图1 血清HE4、CA125和脂联素诊断子宫内膜癌伴淋巴结转移的ROC曲线

Fig.1 ROC curve of serum HE4, CA125 and adiponectin in diagnosing lymphatic metastasis in patients with endometrial carcinoma

3 讨论

子宫内膜癌是一种常见的妇科恶性肿瘤,其发病率仅次于卵巢癌和宫颈癌^[5],子宫内膜癌主要以子宫内膜腺体腺癌为主,腺体大量增生,并形成筛状结构,分化较差的腺癌腺体结构消失,最终发展为实

质性肿瘤,预后较差^[6]。子宫内膜癌早期症状不明显,多伴有持续性或间断性阴道出血,阴道排出血性液体或者浆液性分泌物,患者晚期肿瘤细胞发生浸润或压迫神经引起下腹疼痛等症状。子宫内膜癌的发病机制尚未完全清楚,大体可分为2种类型,一种为雌激素依赖型,此类患者长期受雌激素的刺激,子宫内膜异常增生,最终诱发癌变;另一种为非雌激素依赖型,多发生于老年妇女,恶性程度高,预后较差。子宫内膜癌患者的转移途径多为直接蔓延和淋巴转移,晚期以血液转移为主。原发癌细胞可以直接扩散到邻近器官与组织,淋巴转移途径主要有以下几种:(1)宫底肿瘤可经输卵管淋巴结转移至腹主动脉淋巴结;(2)子宫下段癌细胞经宫旁淋巴结扩散至髂前淋巴结;(3)宫角处癌细胞可转移至腹股沟深、浅淋巴结;(4)子宫后下方肿瘤由骶骨韧带旁淋巴结、直肠旁淋巴结扩散到骶前淋巴结^[7]。

以往临床常选择癌胚抗原、CA19-9及CA72-4等肿瘤标志物作为子宫内膜癌的诊断指标,但这些指标对子宫内膜癌的诊断不够灵敏,仅有约20%的患者血清中肿瘤标志物水平出现升高趋势^[8]。目前,临床诊断子宫内膜癌常使用CA125进行辅助检测,对于分期较差的子宫内膜癌患者CA125检出率高达60%以上,具有良好的诊断价值。HE4属于乳清酸性蛋白家族,是一种蛋白酶抑制剂。脂联素能抑制子宫内膜癌细胞的增殖分化,促进癌细胞凋亡,缓解病情的进展,是一种保护性细胞因子。近年来有研究报道,HE4和脂联素可用于子宫内膜癌的诊断,其中HE4是一种新型肿瘤标志物,在浆液性和子宫内膜样上皮卵巢癌患者呈高表达,对于子宫内膜癌敏感度为46%~67%,特异度达90%以上^[9]。脂联素是一种胰岛素增敏激素,可调节人体脂肪和糖类的代谢,降低内皮细胞中多种黏附分子的表达,与多种肿瘤的发生具有一定的相关性,可能是子宫内膜癌发生、发展的危险因素之一^[10]。

本研究结果显示,子宫内膜癌伴淋巴结转移患者血清中HE4、CA125水平显著高于无淋巴结转移患者,血清脂联素水平显著低于无淋巴结转移患者;提示血清HE4和CA125水平随着患者病程的发展逐渐升高,血清脂联素水平随着病情的加重逐渐降低。本研究结果显示,血清HE4和脂联素对子宫内膜癌伴淋巴结转移诊断的敏感度显著高于CA125,血清HE与脂联素对子宫内膜癌伴淋巴结转移诊断的敏感度比较差异无统计学意义,血清CA125对子宫内膜癌伴淋巴结转移诊断的特异度显著高于血清HE和脂联素,血清HE与脂联素对子宫内膜癌伴淋

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(本文编辑:徐自超 英文编辑:徐自超)

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巴结转移诊断的特异度比较差异无统计学意义;提示 CA125 在子宫内膜癌伴淋巴结转移诊断中可能发生漏诊病例;而 HE4、脂联素诊断敏感度高于 CA125,但是特异度显著低于 CA125,可能存在误诊。血清 HE、CA125 及脂联素联合检测对子宫内膜癌伴淋巴结转移诊断的敏感度均高于三者单独检测,提示血清 HE4、脂联素、CA125 联合检测对子宫内膜癌淋巴结转移具有较高的诊断价值。

综上所述,血清 HE4、CA125 和脂联素可作为诊断子宫内膜癌伴淋巴结转移的肿瘤标志物,血清 HE4、CA125 和脂联素联合检测对子宫内膜癌伴淋巴结转移具有较高的诊断价值。

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(本文编辑:徐自超 英文编辑:徐自超)