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·临床研究·

检测肿瘤标志物Pro GRP、NSE、CYFRA21-1、CEA 对胸腔积液鉴别诊断价值的研究

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【摘要】 背景与目的 恶性胸腔积液多由肺癌引起,肿瘤标志物检测对其鉴别诊断有一定临床价值。本研究的目的是探讨血清及胸腔积液胃泌素前体释放肽片断 31-98(Pro GRP)、神经元烯醇化酶(NSE)、细胞角蛋白 19(CYFRA21-1)和癌胚抗原(CEA)单项或联合检测对肺癌所致恶性胸腔积液鉴别诊断与组织学分型的临床价值。方法 将肺癌所致的恶性胸腔积液患者按原发肿瘤类型分为小细胞肺癌(SCLC)组、肺腺癌组及肺鳞癌组,同时以良性胸腔积液组、健康对照组作为对照。评估胸腔积液 Pro GRP、NSE、CYFRA21-1 和 CEA 单项及联合检测对各组恶性胸腔积液的诊断价值。结果 血清及胸腔积液 Pro GRP、NSE、CYFRA21-1、CEA 在各恶性胸腔积液组的水平均明显高于对照组($P < 0.01$)。SCLC 组检测胸腔积液 Pro GRP 的 Youden 指数和诊断准确性最高;肺腺癌和肺鳞癌组则以胸腔积液 CEA + CYFRA21-1 联合检测(按平行试验)的 Youden 指数及诊断准确性最高。结论 胸腔积液肿瘤标志物系列(Pro GRP、NSE、CYFRA21-1、CEA)检查对恶性胸腔积液的鉴别诊断与组织学分型有很大的临床价值。胸腔积液 Pro GRP 为 SCLC 所致恶性胸腔积液的最佳肿瘤标志物;胸腔积液 CEA + CYFRA21-1 联合检测(按平行试验)为肺腺癌、肺鳞癌所致恶性胸腔积液较好的辅助诊断指标。

【关键词】 肺肿瘤 胸腔积液 Pro GRP NSE CYFRA21-1 CEA 肿瘤标志物

【中图分类号】 R730.4;R561.4

Study on the value of tumor markers Pro GRP, CYFRA21-1, NSE and CEA in the differential diagnosis of pleural effusion

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【Abstract】 **Background and objective** Malignant pleural effusion is usually caused by lung cancer, and tumor markers may be helpful to its differential diagnosis. The aim of this study is to explore the clinical value of serum and pleural effusion pro-gastrin-releasing peptide (Pro GRP), neuron specific enolase (NSE), cytokeratin fragment 19 (CYFRA21-1) and carcinoembryonic antigen (CEA) in differential diagnosis and histological typing of malignant pleural effusion caused by lung cancer. **Methods** According to histological type of primary tumor, 99 patients with malignant pleural effusion caused by lung cancer were divided into small cell lung cancer (SCLC) group, adenocarcinoma group and squamous cell carcinoma group, with 37 patients with benign pleural effusion and 35 healthy persons as controls. Diagnostic value of serum and pleural effusion Pro GRP, NSE, CYFRA21-1 and CEA was evaluated for each group. **Results** The levels of Pro GRP, NSE, CYFRA21-1 and CEA in serum and pleural effusion of all the malignant groups were significantly higher than those in the control groups ($P < 0.01$). In the SCLC group, detection of pleural effusion Pro GRP showed the highest Youden index and accuracy. In the adenocarcinoma group and squamous cell carcinoma group, combined detection of pleural effusion CEA + CYFRA21-1 (on parallel test) showed the highest Youden index and accuracy. **Conclusion** Detection of pleural effusion tumor markers Pro GRP, CYFRA21-1, NSE and CEA is of great clinical value in differential diagnosis and histological typing of malignant pleural effusion. Pleural effusion Pro GRP is the optimal tumor marker for malignant pleural effusion caused by SCLC. Pleural effusion CEA + CYFRA21-1 (on parallel test) is a good auxiliary diagnosis index for malignant pleural effusion caused by adenocarcinoma and squamous cell carcinoma of the lung.

【Key words】 Lung neoplasms Pleural effusion Pro GRP NSE CYFRA21-1 CEA Tumor marker

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我们对 2001 年 1 月至 2005 年 1 月住院的 136 例胸腔积液患者进行血清和胸腔积液胃泌素前体释放肽片断 31-98 (pro-gastrin-releasing peptide, Pro GRP)、神经元烯醇化酶(neuron specific enolase, NSE)、细胞角蛋白 19 (cytokeratin fragment 19, CYFRA21-1) 和癌胚抗原(carcinoembryonic antigen, CEA)测定,旨在进一步探讨 Pro GRP、NSE、CYFRA21-1 和 CEA 单项及联合检测对肺癌所致恶性胸腔积液鉴别诊断与组织学分型的临床价值,以期在胸腔积液鉴别诊断中,寻找一种无创、简便且有较高临床价值的诊断方法。

1　资料与方法

1.1　研究对象　我们将 136 例良恶性胸腔积液患者分为以下 4 组:小细胞肺癌(small cell lung cancer, SCLC)组(SCLC 所致的恶性胸腔积液患者组) 31 例,男 17 例,女 14 例,年龄 27～78 岁,平均年龄 53.8 岁;肺腺癌组(肺腺癌所致的恶性胸腔积液患者组) 35 例,男 16 例,女 19 例,年龄 30～81 岁,平均年龄 59.1 岁;肺鳞癌组(肺鳞癌所致的恶性胸腔积液患者组) 33 例,男 17 例,女 16 例,年龄 35～83 岁,平均年龄 57.6 岁;良性胸腔积液组 37 例,男 19 例,女 18 例,年龄 26～85 岁,平均年龄 60.6 岁,其中结核性胸膜炎 26 例、类肺炎性胸腔积液 8 例、系统性红斑狼疮 2 例、类风湿性关节炎 1 例。肺癌所致的恶性胸腔积液患者均经胸腔积液细胞学检查和(或)闭式经皮胸膜活检术获得病理组织学和(或)细胞学依据而确诊。良性胸腔积液组均根据影像学检查、胸腔积液常规及细菌学检查、闭式经皮胸膜活检术、抗结核试验性治疗的结果以及临床相关资料的综合分析确定诊断。同时选取身体健康的正常人 35 例作为健康对照组。

1.2　试剂与方法　Pro GRP 测定采用日本先瑞生命株式会社生产的 Pro GRP 定量检测试剂盒,NSE、CYFRA21-1和 CEA 测定采用新湾生物科技有限公司生产的酶联免疫定量检测试剂盒,均采用酶联免疫吸附实验进行定量测定。收集治疗前同期抽取的胸腔积液患者空腹静脉血及入院后第 1 次的胸腔积液标本各 6 mL 进行 Pro GRP、NSE、CYFRA21-1 和 CEA 测定,同时用改良的 Cope 胸膜活检针行闭式经皮胸膜活检术检查、胸腔积液细胞学检查、胸腔积液细菌学检查及其它临床相关检查。并对每一位健康对照组的受检者抽取空腹静脉血标本 6 mL 进行 Pro GRP、NSE、CYFRA21-1和 CEA 测定。

1.3　统计学处理　采用 SAS 软件行统计学处理,计量资料数据用 $\bar{x}\pm s$ 表示,采用方差分析,$P<0.05$ 为有统计学意义。

2　结果

2.1　胸腔积液 Pro GRP、NSE、CYFRA21-1、CEA 在各组的检测结果见表 1。血清 Pro GRP、NSE、CYFRA21-1、CEA 在各组的检测结果见表 2。

表 1　胸腔积液 Pro GRP、NSE、CYFRA21-1 及 CEA 在各组的检测结果 ($\bar{x}\pm s$)

Tab 1　Detection of pleural effusion Pro GRP, NSE, CYFRA21-1 and CEA in each group ($\bar{x}\pm s$)

Group	Pro GRP (ng/L)	NSE (μg/L)	CYFRA21-1 (μg/L)	CEA (μg/L)
SCLC group	1339.10 ±789.22 △	50.06 ±33.81 △	14.94 ±20.34 *	30.39 ±33.27 *
Adenocarcinoma group	26.42 ±10.60 *	16.67 ±18.68 *	23.70 ±22.13 *	41.04 ±24.33 △
Squamous cell carcinoma group	25.24 ±8.85 *	17.97 ±14.30 *	43.21 ±31.09 △	33.48 ±34.93 *
Benign group	16.55 ±10.51	8.39 ±5.48	2.90 ±2.70	7.56 ±5.17

*: Compared with the benign group, $P<0.01$; △: Compared with the other groups, $P<0.01$

表 2　血清 Pro GRP、NSE、CYFRA21-1 及 CEA 在各组的检测结果 ($\bar{x}\pm s$)

Tab 2　Detection of serum Pro GRP, NSE, CYFRA21-1 and CEA in each group ($\bar{x}\pm s$)

Group	Pro GRP (ng/L)	NSE (μg/L)	CYFRA21-1 (μg/L)	CEA (μg/L)
SCLC group	925.90 ±700.52 △	31.26 ±22.77 △	9.77 ±12.77 *	18.45 ±20.41 *
Adenocarcinoma group	25.30 ±8.74 *	13.87 ±10.17 *	16.50 ±16.24 *	30.66 ±24.34 △
Squamous cell carcinoma group	24.76 ±8.80 *	14.45 ±13.73 *	30.42 ±26.79 △	20.55 ±21.57 *
Benign group	16.72 ±11.12	8.72 ±6.50	3.03 ±2.21	5.75 ±5.66
Normal control group	15.97 ±8.81	7.41 ±3.51	2.41 ±0.92	5.66 ±4.12

*: Compared with the benign group and normal control group, $P<0.01$; △: Compared with the other groups, $P<0.01$

2.2　以胸腔积液中 Pro GRP > 46 ng/L、NSE > 15 μg/L、CYFRA21-1 > 4.0 μg/L、CEA > 10 μg/L 为诊断恶性胸腔积液的阳性判定标准(参照试剂盒说明书标定的临界值设定),比较四种指标诊断各组恶性胸腔积液

的敏感度、特异度、阳性预测值、阴性预测值、Youden 指数、诊断准确性及 Kappa 值。对各组诊断价值较大的单项及联合检测结果分别见表 3～5，其他诊断价值较小的检测结果未列入表中。

表 3 SCLC 组胸腔积液 ProGRP、NSE、CYFRA21-1、CEA 检测结果

Tab 3 Detection of pleural effusion ProGRP, NSE, CYFRA21-1 and CEA in the SCLC group

Item	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Youden index	Accuracy	Kappa value
ProGRP	0.9032	1.0000	1.0000	0.9231	0.9032	0.9552	0.909 33
NSE	0.8065	0.8889	0.8621	0.8421	0.6953	0.8507	0.698 47
CYFRA21-1	0.5161	0.9167	0.8421	0.6875	0.4328	0.7313	0.269 75
ProGRP + NSE *	0.8065	1.0000	1.0000	0.8571	0.8065	0.9104	0.817 43
ProGRP + NSE △	0.9355	0.8649	0.8529	0.9412	0.8003	0.8971	0.794 118
ProGRP + CYFRA21-1 △	0.8710	0.8378	0.8182	0.8857	0.7088	0.8529	0.705 117
ProGRP + NSE + CYFRA21-1 △	0.9355	0.8056	0.8056	0.9355	0.7410	0.8657	0.732 83

*: Sequence test; △: Parallel test

表 4 肺腺癌组胸腔积液 ProGRP、NSE、CYFRA21-1、CEA 检测结果

Tab 4 Detection of pleural effusion ProGRP, NSE, CYFRA21-1 and CEA in the adenocarcinoma group

Item	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Youden index	Accuracy	Kappa value
CEA	0.7143	0.9189	0.8929	0.7727	0.6332	0.8194	0.636 646
CYFRA21-1	0.6000	0.8649	0.8077	0.6957	0.4649	0.7361	0.468 118
CEA + CYFRA21-1 *	0.6857	0.9730	0.9600	0.7660	0.6587	0.8333	0.663 813
CEA + CYFRA21-1 △	0.9429	0.7838	0.8049	0.9355	0.7266	0.8611	0.723 29
CEA + NSE + CYFRA21-1 △	0.8857	0.7568	0.7750	0.8750	0.6425	0.8194	0.640 00

*: Sequence test; △: Parallel test

表 5 肺鳞癌组胸腔积液 ProGRP、NSE、CYFRA21-1、CEA 检测结果

Tab 5 Detection of pleural effusion ProGRP, NSE, CYFRA21-1 and CEA in the squamous cell carcinoma group

Item	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Youden index	Accuracy	Kappa value
CYFRA21-1	0.8286	0.8919	0.8788	0.8462	0.7205	0.8611	0.721 578
CEA	0.5143	0.8378	0.7500	0.6458	0.3521	0.6806	0.355 14
CYFRA21-1 + CEA *	0.7143	0.9189	0.8929	0.7727	0.6332	0.8194	0.636 646
CYFRA21-1 + CEA △	0.9429	0.8649	0.8684	0.9412	0.8077	0.9028	0.805 855
NSE + CYFRA21-1 + CEA △	0.9429	0.7568	0.7857	0.9333	0.6996	0.8472	0.695 853

*: Sequence test; △: Parallel test

3 讨论

以往文献报道，NSE 是公认的对 SCLC 的首选肿瘤标志物，在肺癌鉴别诊断中起到了积极作用[1～4]。NSE 用于恶性胸腔积液的鉴别诊断亦屡有报道[5,6]。最近文献报道，ProGRP 作为 SCLC 又一个新的、良好的肿瘤标志物，其敏感性及特异性均优于 NSE[7～9]。但 ProGRP 在恶性胸腔积液鉴别诊断中的临床应用国内外报道较少[10]。

细胞角蛋白是细胞骨架蛋白之一，为细胞体中间丝，是非小细胞肺癌尤其是肺鳞癌的首选标志物[11～13]。CYFRA21-1在胸腔积液鉴别诊断中的临床应用亦陆续报道[14,15]。CEA 是 180 ku 的糖蛋白，目前认为它对肺癌尤其是肺腺癌的诊断意义较大[16]。CEA 用于胸腔积液的鉴别诊断亦有较多报道[17～20]。

本组资料表明，血清及胸腔积液 ProGRP、NSE、CYFRA21-1、CEA 在各组恶性胸腔积液中的水平均明显高于良性胸腔积液组（$P < 0.01$），说明血清及胸腔积液 ProGRP、NSE、CYFRA21-1、CEA 测定对良恶性胸腔积液的鉴别诊断有一定的临床价值。其中血清和胸腔积液 ProGRP 及 NSE、CYFRA21-1、CEA 水平分别以 SCLC、肺鳞癌、肺腺癌组最高，说明它们分别为 SCLC、肺鳞癌、肺腺癌所致恶性胸腔积液的首选肿瘤标志物，对肺癌原发灶的组织学分型有较大的临床意义。同时，在 SCLC 组，胸腔积液及血清 ProGRP 的浓度均值分别为 1339.10 ng/L 及 925.90 ng/L，分别

是临界值 46 ng/L 的 29.11 倍及 20.13 倍;而胸腔积液及血清 NSE 的浓度均值分别为 50.06 μg/L 及 31.26 μg/L,仅为临界值 15 μg/L 的 3.34 倍及 2.08 倍。提示血清及胸腔积液 Pro GRP 检测对 SCLC 所致恶性胸腔积液的鉴别诊断价值优于 NSE。

本组结果提示诊断 SCLC 所致恶性胸腔积液以胸腔积液 Pro GRP 单项检测价值最高,其次依次为胸腔积液 Pro GRP + NSE 联合检测(按序列试验)、胸腔积液 Pro GRP + NSE 联合检测(按平行试验)、胸腔积液 Pro GRP + NSE + CYFRA21-1 联合检测(按平行试验)、胸腔积液 Pro GRP + CYFRA21-1 联合检测(按平行试验)及胸腔积液 NSE 单项检测。

本组结果提示诊断肺腺癌所致恶性胸腔积液以胸腔积液 CEA + CYFRA21-1(按平行试验)价值最高,其次依次为胸腔积液 CEA + CYFRA21-1 联合检测(按序列试验)、胸腔积液 CEA + NSE + CYFRA21-1 联合检测(按平行试验)、胸腔积液 CEA 单项检测及胸腔积液 CYFRA21-1 单项检测。

本研究结果还提示诊断肺鳞癌所致恶性胸腔积液以胸腔积液 CYFRA21-1 + CEA(按平行试验)价值最高,其次依次为胸腔积液 CYFRA21-1 单项检测、胸腔积液 NSE + CYFRA21-1 + CEA 联合检测(按平行试验)、胸腔积液 CYFRA21-1 + CEA 联合检测(按序列试验)及胸腔积液 CEA 单项检测。

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