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*RESEARCH ARTICLE*

# HIGH HE4 CYSTIC FLUID/SERUM RATIO: A PREDICTOR OF MALIGNANCY IN PANCREATIC CYSTIC LESION? A CASE REPORT.

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## *Abstract*

Pancreatic cystic lesions are discovered frequently on modern imaging, posing a clinical problem because they might lead to ductal adenocarcinoma. The evaluation of cystic fluid carcinoembryonic antigen (CEA) concentration and cytology have low sensitivity in distinguishing mucinous from non-mucinous cysts.

Recently, some authors reported that circulating HE4 (Human epididymis protein 4) levels were higher in subjects with pancreatic adenocarcinoma than in the controls.

We reported here the observation of elevated HE4 levels in pancreatic cyst fluid of malignant origin encountered in our laboratory medicine practice.

The sample showed high HE4 cyst fluid levels and low serum HE4 values. The high fluid/serum ratio value in this patient was associated with malignant lesion. Interestingly, the same patient showed high CEA cyst fluid/serum ratio. This patient had mucinous cystadenomas and developed lung and liver metastasis in less than 3 years, Both HE4 and CEA cystic fluid/serum ratios are high. This preliminary observation suggested the need to perform further studies on large population to assess whether cystic fluid/serum ratio of HE4, as well as CEA, might perform as cancer-specific biomarker for pancreatic cystic lesions.



## Introduction:-

Pancreatic cystic lesions pose a clinical relevant problem, because they are discovered frequently on modern imaging and because they might be precursors of pancreatic ductal adenocarcinoma [1]. These lesions are generally classified into 2 main groups: 1) mucinous (intraductal mucinous neoplasm or mucinous cystic neoplasm) which have malignant potential and 2) serous (serous cystadenomas) that are nearly always benign. Therefore, the clinically relevant problem of evaluating pancreatic cysts is to make this distinction, which determine further management (surgery, surveillance, or neither).

Currently, imaging techniques, cytology, and biochemical analysis [including carcinoembryonic antigen (CEA)] of pancreatic cyst fluid obtained by endoscopic ultrasound (EUS)-pancreatic fine needle aspiration (FNA) are used to differentiate pancreatic cystic lesions with malignant potential.

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Cystic fluid carcinoembryonic antigen (CEA) concentration and cytology have low sensitivity in distinguishing mucinous from non-mucinous cysts [2], leading to frequent misdiagnoses and unnecessary surgical interventions [3]. The new AGA (American Gastroenterological Association) guidelines [4] advocate a more selective use of invasive testing, surgery and surveillance.

Therefore, the management of pancreatic cysts requires new tools for risk stratification of malignant potential. Recently, some authors reported that HE4 (Human epididymis protein 4) could be a potential biomarker to improve the diagnostic power for pancreatic adenocarcinoma. In particular, HE4 was significantly higher expressed in the human pancreatic carcinoma tissues than in both normal and adjacent non-tumorous tissues and circulating HE4 levels were higher in subjects with pancreatic adenocarcinoma than in the controls [5].

**Case Description:-**

The observation of elevated HE4 levels in pancreatic cyst fluid of malignant origin is reported here that was recently encountered in our laboratory medicine practice.

We investigated pancreatic cyst fluid samples obtained by ultrasound-guided fine needle aspiration during routine investigation. Samples were stored at -20 °C and were thawed and vortex-mixed before analysis. HE4 was measured by HE4 immunometric assay (Lumipulse G, Fujirebio Diagnostics AB, Gothenburg, Sweden).

In our institution, all pancreatic cystic FNAs are routinely performed according to a reference protocol wherein a cytopathologist prepares on site an ethanol-fixed smear for Papanicolaou staining and aliquots the residual material to measure the CEA levels. We used this material also to determine mucins and HE4 levels.

As shown in table 1, this sample exhibited high HE4 cyst fluid levels and low serum HE4 values. Worthy of attention was the calculation of HE4 cyst fluid/serum ratio. In fact, we observed high ratio value in this patient harboring malignant lesion. Interestingly, the same patient showed high CEA cyst fluid/serum ratio. This patient had mucinous cystadenomas and developed lung and liver metastasis in less than 3 years, Both HE4 and CEA cystic fluid/serum ratios are high, whereas mucins ratios even showed an opposite trend. This observation suggested that HE4 and CEA perform as more cancer-specific biomarker for pancreatic cystic lesions. Probably, using both CEA and HE4 levels delivered the highest diagnostic properties. However, such a question required a number of patients undergoing surgical resection of pancreatic cysts and, since the incidence of pancreatic cysts is low, probably a multi-center survey is heartily recommended.

**Table 1:** CEA, Mucins and HE4 levels in pancreatic cyst fluid and serum

| Cyst fluid | | | | | Serum | | | | | Cyst fluid/Serum ratio | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **CEA** | **Ca19-9** | **Ca15-3** | **Ca125** | **HE4** | **CEA** | **Ca19-9** | **Ca15-3** | **Ca125** | **HE4** | **CEA** | **Ca19-9** | **Ca15-3** | **Ca125** | **HE4** |
| ng/ml | U/ml | U/ml | U/ml | ng/ml | ng/ml | U/ml | U/ml | U/ml | ng/ml | ng/ml | U/ml | U/ml | U/ml | ng/ml |
| 3312 | 40000 | 7,6 | 8,6 | 429 | 26,2 | 7065 | 47,9 | 74,9 | 61 | 127 | 5,6 | 0,1 | 0,1 | 7 |

## Conclusions:

To the best of our knowledge, this is the first observation of high HE4 levels in pancreatic cyst fluids. Our findings suggest that HE4 cyst fluid/serum ratio can be used as a marker of neoplastic transformation of epithelial cells in pancreatic cysts. Our observation encourages further studies on large population to assess the clinical usefulness of HE4 measurement alone and in combination with CEA in EUS-FNA samples of pancreatic cysts.

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