A Promising Diagnostic Role of Immunohistochemical Expression of Insulin-Like Growth Factor II mRNA Binding Protein 3 (IMP3) in Pancreatic Lesions Using Endoscopic Ultrasound-Guided Fine Needle Aspiration (EUS-FNA) Cytology

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Abstract

Background Poor prognosis and short survival of patients harboring pancreatic cancer emerge how advanced disease it is. In a trial to achieve the earliest and most accurate diagnosis to manage this progressive disease, we proposed that using endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) with an adjuvant diagnostic immunohistochemical marker would give better diagnostic results. IMP3 has gained recently wide attention, as many studies found that IMP3 has not only diagnostic but also prognostic role in different types of malignancies.

Aim of the Study This prospective work is to assess the diagnostic role of EUS-FNA combined with the immunohistochemical expression of IMP3 on different benign and malignant pancreatic lesions.

Material and Method The included pancreatic lesions (n = 140) were obtained by EUS-FNA technique and stained for IMP3 immunohistochemically. Paraffin blocks from patients who underwent excision (n = 92) or core biopsies (n = 48) were performed for confirming diagnosis.

Results The combined method for diagnosis showed that IMP3 was positive in 78.7%, 91.7%, 100% PAC, mucinous neoplasm with high grade dysplasia, and IPMN with high grade dysplasia, respectively, while almost all benign lesions showed negative IMP3. Also, this method showed sensitivity (78.26%), specificity (95.83%), and accuracy (84.3%).

Conclusion EUS-FNA cytology with IMP3 could be a reliable diagnostic tool especially for assessment of malignant pancreatic lesions.

Keywords IMP3 · Endoscopic ultrasound-guided fine needle aspiration · Pancreatic cancer · Immunohistochemistry

Introduction

Pancreatic cancer (PC) is considered one of the most lethal cancers with high mortality and morbidity. In 2021, an estimated 60,430 new cases of PC will be diagnosed in the USA and 48,220 people will die from the disease. The death rate for PC has increased slightly (by 0.3% per year) since around 2000 [1]. The 5-year relative survival of PC decreases with advanced stages at time of diagnosis, as the survival in localized disease is 39.4%, while apparently declines with regional (13.3%) and distant disease (2.9%) [2].

Patients with PC are usually presented with an advanced disease, so they are inoperable at time of diagnosis. An early and feasible diagnostic tool for diagnosis is needed. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is considered a safe and effective procedure for diagnosis of pancreatic lesions which is very important because of the risk for simultaneous or later malignancy development associated with benign lesions [3].

Insulin-like growth factor II messenger ribonucleic acid (mRNA) binding protein 3 (IMP3), a member of IMP family which involves IMP1, IMP2, and IMP3, is an oncofetal protein that contributes to different organs development including intestine, thymus, pancreas, and kidneys during embryogenesis [4, 5].
The evaluation of immunohistochemical markers like IMP3 protein to reach an appropriate discrimination between malignant and benign pancreatic lesions would essentially help in early diagnosis of pancreatic cancer and optimum patient management as several studies concluded that IMP3 is a promising marker for various malignancies [6–9]. Overexpression was frequently seen in different tumor types and typically related to progressive tumor features. However, IMP3 was not expressed in various normal tissues, e.g., heart, striated muscle, uterus, esophagus, stomach, colon, kidney, urinary bladder, ovary, fat, skin, oral cavity, ectocervix, gallbladder, liver, pancreas, bone marrow, prostate, lung, breast, thyroid gland, cerebellum, and cerebrum [10].

The aim of this work was to assess the diagnostic value of EUS-FNA procedure with the immunohistochemical expression of IMP3 in pancreatic lesions then comparing results with surgical resected specimens or core biopsies of unresectable specimens to reach an early and accurate diagnosis.

Material and Method

Patients’ Selection

This prospective study was held up in Pathology, Tropical and Surgical Departments, Faculty of Medicine, Zagazig University, Egypt, including 140 patients with pancreatic lesions. Samples were obtained by EUS-FNA procedure, and cytology specimens and/or cell blocks were prepared. Specimens from patients who underwent surgical resection or core biopsies were histopathologically evaluated for reaching the gold standard diagnosis; however, cases that did not undergo either procedure were excluded. Approval has been obtained from the Institutional Review Board (IRB), Faculty of Medicine, Zagazig University (approval number: 6130, May 30th, 2020). Patients’ data was assessed including age, sex, site of the lesion, and duct communication.

EUS-FNA Specimens

EUS-FNA was performed with a 19, 22, or 25 gauge needle and an average of 3.1 ± 1.0 passes per session. The aspirate material was smeared onto a glass slide by air pressure and fixed with 95% ethanol for cytological evaluation. Cytology/cell blocks were fixed in formalin then embedded in paraffin. Staining with hematoxylin and eosin was done for histopathological diagnosis and with IMP3 marker for evaluation of protein expression. The diagnosis was considered as benign and malignant. Cystic fluid aspirates were investigated for levels of amylase enzyme and tumor markers CEA and CA19-9, IgG4.

IMP3 Immunohistochemical Staining

Formalin-fixed paraffin-embedded cell blocks were serially sectioned into 3–5 μm and deparaffinized in xylene, then rehydrated in descending series of alcohols. For antigen retrieval processing, 10 mM citrate buffer (pH 6.0) at the microwave for nearly 20 min was used. Blocking of endogenous peroxidase was done by using 3% hydrogen peroxide for 10 min. Repeated washing in PBS was performed, then the slides were incubated with primary antibody for mouse monoclonal antibody IMP3 (IGF2BP3 (E-2): sc-365640, 1:100 dilution, Santa Cruz Biotechnology). The polymer detection system; Dako EnVisionTM kit (Dako, Copenhagen, Denmark) was used. Finally, the tissue sections were counterstained with Meyer’s hematoxylin.

IMP3 cytoplasmic expression was assessed semi-quantitatively according to both the extent of positively stained cancer cells and the intensity of stain at ×100 then ×400 HPF. The intensity of staining was none, weak, moderate, and strong considered as 0, 1, 2, and 3, respectively. The percentage of positive cells was calculated as <5%; ≥5–<25%; ≥25–<50%; and ≥50% and evaluated as 0, 1, 2, and 3, respectively. A score was set by adding the two previous scores. A final score was considered as negative if <2, and positive if ≥2 [11].

Gold Standard Diagnosis (Surgically Resected Specimens or Core Biopsies)

The pancreatic specimens from patients who underwent surgical excision (n=92) and core biopsies (n=48) were collected, fixed in formalin, embedded in paraffin, and then stained with hematoxylin and eosin for setting the gold standard diagnosis relying on the clinical presentation and radiological findings. Then, the diagnosis was considered as benign and malignant to compare results with cytologic diagnosis and combined method.

Statistical Analysis

All data were collected, tabulated, and statistically analyzed using SPSS 22.0 for windows (IBM Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Diagnostic performance of cytology, IMP3 IHC, and their combination in diagnosis of pancreatic lesions was calculated depending on sample 2×2 contingency tables generation using the Tru-cut needle biopsy/surgical specimen pathology as the reference (gold) standard. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and accuracy were calculated to compare between them. All tests were two sided. p-value < 0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS), and p-value ≥ 0.05 was considered statistically non-significant (NS).
Results

Patients’ Characteristics

This study included 140 specimens of different pancreatic lesions. The incidence rate of pancreatic lesions is higher in males (53.6%). The malignant lesions were higher in age group 55 years with slightly higher incidence in males. Diagnosis of these lesions comprises malignant lesions (n = 92): pancreatic adenocarcinoma carcinoma (PAC) (n = 47), intraductal papillary mucinous carcinoma (IPMN) with low (n = 6) and high grade dysplasia (n = 12), mucinous cystic neoplasm (MCN) with low (n = 6) and high grade dysplasia (n = 12), solid pseudopapillary neoplasm (SPN) (n = 9), and benign lesions (n = 48): serous microcystic adenoma (SMA) (n = 9), pseudocyst (n = 19), autoimmune pancreatitis (n = 12), and chronic pancreatitis (n = 8). The most common site for malignant lesions was the head followed by the body-tail (50%, 28.6%). Grossly, the pancreatic lesions were; mass nature (50%) are slightly higher than cystic lesions (45.7%) while the least common form is the mixed pattern (4.3%). Most of lesions present without duct communication (86.4%) (Tables 1, 2, 3, and 4).

Results of the Combined Method of Diagnosis (EUS-FNA with IMP3 Immunohistochemistry)

The results of cytologic sampling obtained by EUS-FNA demonstrated that from 47 PAC, 72.3% were malignant by cytology compared by 78.7% by combined method (EUS-FNA with IMP3 immunohistochemistry). Regarding high grade MCN and IPMN, 1 case of MCN and 3 cases were detected by IMP3 immunohistochemistry over cytologic diagnosis. Two cases of low grade MCN, 2 of low grade IPMN, and 2 of solid-pseudopapillary neoplasms were mistakenly considered benign by cytology, and correctly diagnosed as malignant depending on IMP3 expression. As regards the benign lesion, including serous microcystic adenoma, pseudocyst, chronic pancreatitis, and autoimmune pancreatitis were accurately benign by cytology, but only 1/9 of serous microcystic adenoma and 1/8 of autoimmune pancreatitis were positive for IMP3 and considered malignant (Tables 5 and 6).

Considering benign and malignant diagnosis only by the three methods, the results of combined method showed higher efficacy in diagnosing the malignant pancreatic lesions than depending on cytology only, and that was proved by reaching 78.2% of malignant lesions diagnosis compared with 64.1% by cytology only (Table 6; Figs. 1, 2, and 3).

Table 1  Comparison between benign and malignant pancreatic lesions regarding serum markers

| Serum marker | All studied patients (N=140) | Gold standard diagnosis | Testa | p-value (sig.) |
|--------------|-----------------------------|-------------------------|-------|----------------|
|              | No %                        | Malignant (N=92)        | Benign (N=48) |                          |
| Serum amylase|                             |                         |       |                |
| Low          | 107 76.4%                   | 79 85.9%                | 28 58.3% | 13.276a < 0.001 (HS) |
| High         | 33 23.6%                    | 13 14.1%                | 20 41.7% |                 |
| Serum CA19-9 |                             |                         |       |                |
| Low          | 68 48.6%                    | 26 28.3%                | 42 87.5% | 48.095a < 0.001 (HS) |
| High         | 71 50.7%                    | 66 71.7%                | 5 10.4% |                 |
| Not done     | 1 0.7%                      | 0 0%                    | 1 2.1%  |                 |
| Serum CEA    |                             |                         |       |                |
| Low          | 68 48.6%                    | 26 28.3%                | 42 87.5% | 44.313a < 0.001 (HS) |
| High         | 72 51.4%                    | 66 71.7%                | 6 12.5% |                 |
| Serum IG4    |                             |                         |       |                |
| Low          | 130 92.9%                   | 90 97.8%                | 40 83.3% | 17.090a < 0.001 (HS) |
| High         | 8 5.7%                      | 0 0%                    | 8 16.7% |                 |
| Not done     | 2 1.4%                      | 2 2.2%                  | 0 0%   |                 |

aChi-square test

Table 2  Gold standard diagnosis of the studied patients (N=140)

| Gold standard diagnosis | The studied patients (N=140) |
|-------------------------|-----------------------------|
|                         | Number | Percent |
| Pancreatic adenocarcinoma | 47     | 33.6%   |
| Mucinous neoplasm with high grade dysplasia | 12     | 8.6%    |
| Mucinous neoplasm with low grade dysplasia | 6      | 4.3%    |
| IPMN with low grade dysplasia | 6      | 4.3%    |
| IPMN with high grade dysplasia | 12     | 8.6%    |
| SPN | 9 | 6.4% |
| Serous microcystic adenoma | 9 | 6.4% |
| Pseudocyst | 19 | 13.6% |
| Pancreatitis | 12 | 8.6% |
| Autoimmune pancreatitis | 8 | 5.7% |
| Total | 140 | 100% |

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Assessment of Sensitivity, Specificity, and Accuracy

Regarding using cytology (EUS-FNA) only for diagnosis of pancreatic lesions, the sensitivity was 64.13%; the specificity was (100%), and the accuracy was 89%. But the combination of cytological diagnosis using EUS-FNA with the expression of IMP3 in diagnosis showed sensitivity (78.26%), specificity (95.83%), and accuracy (84.3%). So, IMP3 with cytology has higher sensitivity, while cytology has more specificity and accuracy (Table 7).

Discussion

PC is characterized by poor prognosis, decreased survival, and inoperable advanced stages. Presenting at advanced stages is considered a crucial point in patients’ survival. Therefore, an early and accurate diagnosis is needed for those patients, hoping for early management that could improve prognosis and prolong survival. A study done by Pasiliao et al. [12] observed a decrease in motility, invasion, and matrix adhesion following IMP3 knockdown suggesting...
that IMP3 promotes PAC progression by enhancing the pro-
metastatic behavior of tumor cells. Moreover, the immu-
nohistochemical IMP3 expression was considered a poor
prognostic predictor in different malignancies as mucoepi-
dermoid carcinoma of salivary glands, duodenal papillary
carcinoma, and pilocytic and pilomyxoid astrocytomas
[13–15].

Also confirming the diagnostic importance of IMP3,
using quantitative real-time RT-PCR by Yantiss et al. [16]
showed that mRNA IMP3 was highly expressed in pancre-
atic carcinomas (79%). Also, Wang et al. [17] demonstrated
that increased mRNA IMP3 expression was associated with
poor overall survival and considered as an independent risk
factor and they suggested that combination with microdis-
section techniques to evaluate IMP3 mRNA expression in
frozen pancreatic lesions can be worthy for diagnosis of PC.

EUS-FNA combined with evaluation of IMP3 immuno-
histochemical expression is a promising tool for achieving
discriminating malignant from benign lesions. As Yantiss et al.
[20] demonstrated that EUS-FNA for PAC expressed IMP3
in 92% of the cases, while all cases of chronic pancreatitis
were IMP3 negative. Zhao et al. [21] found that all benign
cases expressed negative IMP3; IMP3 was expressed in 88%
of PAC; suspicious cases were positive for IMP3; and cytolo-
y results combined with IMP3 expression revealed 95%
positivity in PAC. IMP3 staining was positive in 97%, 79%
of PAC, high grade dysplasia, respectively, while in mild to
moderate dysplasia, IMP3 showed negative staining. Gener-
ally, IMP3 showed strong to moderate intensity [16]. These
results were agreeing with ours, as we found that high IMP3
was expressed in 77.8%, 78.7%, 91.7%, and 100% of SPN,
PAC, mucinous neoplasm with high grade dysplasia, and
IPMN with high grade dysplasia, respectively.

In low grade dysplasia, 2/6 cases of mucinous neoplasm
and 3/6 cases of IPMN were positive for IMP3 staining.
However, benign lesions showed negative staining in all
cases of benign lesions except one case of serous microcystic
adenoma and a case of autoimmune pancreatitis which were
diagnosed by cytology as benign. Also, a study analyzed the
expression of 26 immunohistochemical markers confirmed
the diagnosis of PAC in both surgical and fine-needle aspi-
ration specimens using the best diagnostic panel of immu-
nomarkers including pVHL, maspin, S100P, and IMP3.
IMP3 was 90% positive (intermediate to weak intensity) in
PAC in surgical specimens and normal pancreatic ducts were
usually negative for IMP3, while in FNA specimens, IMP3
was positive in 93% of PAC compared with 77% and 10% for
suspicous and benign cases, respectively [22].

The incidence of pancreatic cystic lesions is rising due to
increase use of imaging techniques as part of routine clinical
practice. Some cystic lesions have the potential for mali-
gnant neoplastic transformation and are considered mali-
gnant precursor for pancreatic ductal adenocarcinoma such as
IPMNs and MCNs whereas serous cystic neoplasms (SCNs)
are considered benign lesions. Ezzat et al. [23] and Senoo
et al. [24] demonstrated sensitivity and specificity of IMP3
on cytology specimens for PAC were 91.2%, 86.7%, and
87.9%, 100%, respectively, with total accuracy 90.3% and
90.8%, respectively. Our findings concluded that using of

| Table 5 Comparison between cytological diagnosis and gold standard diagnosis |
|-------------------------------------------------------------|
| Cytologic diagnosis                         | Gold standard diagnosis | Total |
|                                             | Malignant | Benign | Malignant | Benign |
| Malignant                                  | No        | 59     | 0        | 59     |
|                                             | %         | 42.1%  | 0%       | 42.1%  |
| Benign                                     | No        | 33     | 48       | 81     |
|                                             | %         | 23.6%  | 34.3%    | 57.9%  |
| Total                                      | No        | 92     | 48       | 140    |
|                                             | %         | 65.7%  | 34.3%    | 100%   |
| Testc                                      | 31.030    |        |          | <0.001 (HS) |
| p-value (sig.)                             | <0.05 is significant |
| sig significance                           |           |
| cMcNemar’s test                            |           |

| Table 6 Comparison between cytologic + IMP3 and gold standard diagnosis |
|-------------------------------------------------------------|
| Cytologic + IMP3 diagnosis                                  | Gold standard diagnosis | Total |
|                                                           | Malignant | Benign | Malignant | Benign |
| Malignant                                                 | No        | 72     | 1.4%     | 52.9% |
|                                                           | %         | 51.4%  | 1.4%     | 52.9% |
| Benign                                                    | No        | 20     | 32.9%    | 66     |
|                                                           | %         | 51.4%  | 32.9%    | 66     |
| Total                                                     | No        | 92     | 48       | 140    |
|                                                           | %         | 65.7%  | 34.3%    | 100%   |
| Testc                                                     | 13.136    |        |          | <0.001 (HS) |
| p-value (sig.)                                            | <0.05 is significant |
| sig significance                                          |           |
| cMcNemar’s test                                           |           |
Fig. 1 Pancreatic adenocarcinoma (PAC). A Cytology of PAC showed loose cluster of malignant epithelial cells with pleomorphic hyperchromatic nuclei and some abnormal mitotic figures (H&E stain ×400, scale bar 40 μm). B Cell block of PAC showing small clusters of malignant epithelial cells expressing positive cytoplasmic IMP3 (IMP3 immunohistochemical stain ×400, scale bar 40 μm)

Fig. 2 High grade mucinous cystic neoplasm (MCN). A Cell block of high grade MCN showed glandular epithelium with dysplastic mucinous cells (high grade dysplasia) (H&E stain ×400, scale bar 40 μm). B Cell block of high grade MCN showed mucinous cells expressing positive cytoplasmic IMP3 (IMP3 immunohistochemical stain ×400, scale bar 40 μm)

Table 7 Diagnostic performance of cytology and cytology + IMP3 IHC for diagnosis of malignant pancreatic lesions

|                      | Cytology | Cytology + IMP3 IHC |
|----------------------|----------|---------------------|
| TP                   | 59       | 72                  |
| FP                   | 0        | 2                   |
| TN                   | 48       | 46                  |
| FN                   | 33       | 20                  |
| SN                   | 64.13%   | 78.26%              |
| (95% CI)             | (53.457–73.867) | (68.44–86.187) |
| SP                   | 100%     | 95.83%              |
| (95% CI)             | (92.06–100) | (85.746–99.49) |
| PPV                  | 100%     | 97.297%             |
| (95% CI)             | (90.225–99.293) |                 |
| NPV                  | 59.259%  | 69.69%              |
| (95% CI)             | (52.354–65.654) | (60.843–77.296) |
| Positive LR (95% CI) | 18.78 (4.871–73.255) |                 |
| Negative LR (95% CI) | 0.359 (0.273–0.471) | 0.227 (0.153–0.336) |
| Accuracy (95% CI)    | 89% (52.2–97.6) | 84.3% (74.4–90.7) |
| AUC                  | 0.821    | 0.870               |
| (95% CI)             | (0.747–0.88) | (0.803–0.921) |

TP true positive, FP false positive, TN true negative, FN false negative, SN sensitivity, SP specificity, PPV positive predictive value, NPV negative predictive value, LR likelihood ratio, AUC area under curve, CI confidence interval
combined IMP3 immunohistochemical staining with cytology diagnosis of malignant and benign pancreatic lesions has sensitivity and specificity of 78.2% and 95.8% with total accuracy 84.3% compared with 64.1%, 100%, and 89% sensitivity, specificity, and total accuracy of cytology diagnosis only, respectively.

**Limitations of the Study**

Many problematic issues may arise due to limited skills of the endoscopy operator in terms of insufficient tissue yield and targeting error, misinterpretation and misdiagnosis by pathologists, and absence of on-site cytopathologists for adequacy assessment.

In conclusion, for diagnosing malignant pancreatic lesions, IMP3 expression based on EUS-FNA sampling could be very valuable. However, benign lesions rely more accurately on cytologic findings by EUS-FNA than IMP3 expression. Further research is recommended on largest samples of malignant and benign pancreatic lesions.

**Declarations**

**Competing Interests** The authors declare no competing interests.

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