

Correlation of Inverse Expression of E-Cadherin and Autocrine Motility Factor Receptor with Increased Dedifferentiation of Pancreatic Adenocarcinoma

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Abstract : Pancreatic adenocarcinoma though relatively rare, have dismal prognosis. With intention to find if simultaneous occurrence of destruction of intercellular adhesion is associated with propagation of carcinomatous cells, we studied different grades and stages of pancreatic adenocarcinoma and noted expression of E-cadherin (ECAD), strongest intercellular adhesion molecule of epithelial cells and Autocrine Motility Factor Receptor (AMFR), the known propagator of cancer cell with aid of immunohistochemistry in a retrospective study. Paraffin blocks of 19 patients who were treated with Pancreaticoduodenectomy (Whipple procedure), Distal pancreatectomy, Total pancreatectomy was processed through standardized protocols and scrutinized with predetermined parameters. Normally in non-malignant pancreatic epithelium, strong ECAD and Weak AMFR is visible, with tumour dedifferentiation, reverse manifested. In comparison to Grade 3 tumours, Grade 1 Pancreatic Duct Adenocarcinomas in our study revealed strong ECAD (52.6% vs. 5.2%) and less AMFR (36.8% vs. 100%) expression. Increment of tumour stage was found associated with strong AMFR and Weak ECAD expression. Study of coexpression of these two molecules could partly explain different histologic grades of pancreatic adenocarcinoma, their properties as well as indicated towards their synergistic critical play in process of progression of cancer cell.

Keywords: E-cadherin, Autocrine Motility Factor Receptor, Pancreatic adenocarcinoma

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I. Introduction

Pancreatic cancer is a devastating disease with a dismal prognosis and early detection remains a challenge. With the exception of the small bowel, the pancreas is less likely to develop cancer than any other gastrointestinal organ. Nevertheless, the remote location of the organ, the lack of any specific diagnostic markers, the difficulty in establishing a tissue diagnosis, and the aggressive nature of pancreatic adenocarcinomas, which respond poorly to both chemotherapy and radiotherapy, contribute to the exceptionally high mortality associated with this type of cancer. (1)

Based on the GLOBOCAN 2012 estimates, Pancreatic cancer causes more than 331000 deaths per year (accounts for 4.0% of all deaths), ranking as the seventh leading cause of cancer death in both sexes together. About 338000 people had pancreatic cancer in 2012, making it the 11th most common cancer. The estimated 5-year survival rate for pancreatic cancer is less than 5% (2). The incidence of pancreatic cancer in India is 0.5–2.4 per 100,000 men and 0.2–1.8 per 100,000 women (1). The incidence and mortality of pancreatic cancer worldwide correlated with increasing age and was slightly more common in men than in women. In the past decades, pancreatic cancer mortality has been increasing in both genders (for example, in the United States, European countries, Japan, China). (2) Survival rates are among the worst of neoplastic lesion, being the mortality to incidence ratio of 98%. It is among the tumors with worst survival rates (1).

In early stage of pancreatic cancer it does not show any symptoms. With further advancement of the disease nonspecific symptoms such as pain in the abdomen, weight loss, fever, itchiness, loss of appetite, diarrhea, nausea, jaundice are most common presenting symptoms. (3) Lack of specific diagnostic marker and association of vague presenting symptoms contributes to the late detection of the disease at fairly advanced stage.

Resection surgery does lead to about a 20% 5-year survival, but because of the presence of widespread local disease or metastasis, only 10–20% of patients undergo pancreatic resection. Furthermore, in addition to the limited curative potential of surgery, chemotherapy and radiation therapy, there is a paucity of molecular markers for targeted therapy. Consequently, Pancreatic adenocarcinoma has high morbidity and dismal prognosis

(1) and a new look at the results of epidemiological and experimental studies is important to establish strategies for precise prognostic categorization.

At cellular level, progression of malignancy is dependent variably on many cellular properties including intercellular adhesion, motility and proteolysis.(4) Reduction of intercellular adhesion and increment of cell motility appeared two necessary simultaneous incidents for infiltration of malignant cell into surrounding stroma. It is established that E-cadherin (ECAD) is strongest intercellular adhesion molecule in epithelial cell.(5) which is regulated by ECAD and ECAD associated proteins including catenins.(6,7). Many researchers have indicated that correlation between infiltration of malignant cell and diminished ECAD and catenins both in vitro and in vivo in malignant lesion of various organs(6-11) is modulated by property of cell motility-which in turn is affected by various motility factors like Hepatocyte Growth factor, Epidermal growth factors(12-14). Silletti et al. found that loss of intercellular adhesion up regulates the protein expression and promoter activity of AMFR(15).

Autocrine Motility Factor (AMF) has been purified from the culture media of various tumor cells as a specific motility modifier.(16,17) The receptor for AMF (AMFR) has been identified as a cell surface glycoprotein (gp78; molecular weight, 78,000) on the B16-F1 melanoma cell line with high metastatic ability.(16,17) Autocrine Motility Factor Receptor (AMFR) concentrates on the leading edge of the cell surface, then is phosphorylated and internalized by binding with AMF.(18) Finally, it induces rearrangement of integrin, causing cells to move.(19) In this pathway, G protein might be involved, since cell motility is inhibited by a Bordetella pertussis toxin.(19) Up-regulation of AMFR and its implication in cancer progression in human cancers of various origin, including the large intestine, placenta, esophagus, and stomach,(20-24) has been reported.

Review of literature confirmed that in epithelial cell, ECAD is strongest intercellular adhesion molecule(5), association between ECAD and AMFR is studied in various epithelial malignancies i.e. carcinomas and simultaneous loss of ECAD and increase in AMFR is found in cultured cell lines of Urinary Bladder carcinomas.(25) This simultaneous alteration of ECAD and AMFR, if they are situated on the common signal, enables us to understand that method of cancer progression in more details and provide clue to ascertain process of malignant cell invasion and metastasis.

Many researchers concentrated to find association between destruction of intercellular adhesion and propagation of carcinomatous cell and studied simultaneous co expression of ECAD and AMFR gene in Colon, Rectal, Breast, and Gastric adenocarcinoma with aid of immunohistochemistry. We are yet to find similar study in Pancreatic adenocarcinoma. We tried to find if there is any significant association of expressions of these two molecules in different grades and stages Pancreatic adenocarcinoma and evaluated immunohistochemical expression of ECAD and AMFR protein to that end in our study.

II. Material And Methods

The study population consisted of 19 patients who were finally treated with Pancreaticoduodenectomy (Whipple procedure), Distal pancreatectomy, Total pancreatectomy. In this retrospective study (conducted between 2010 to 2016), in Medical College, Kolkata, we selected only those patients who underwent endoscopic evaluation followed by Final surgery. Interval between endoscopy and final surgery in our study varied from 22 to 69 days. Most patients underwent Final surgery within 37 days of the endoscopic evaluation.

To reduce influence on natural history of the disease, we selected only those cases who have received no anticancer therapy prior to the surgery. We had to exclude quite a few cases from our study who received various types of indigenous so-called anti-cancer medications and non-regulated chemotherapy between endoscopic diagnosis and final surgery and such led us to conclusion of necessity of separate study to determine effects of such non-regulated /non-conventional therapy in this malignancy.

Clinical data including copy of histopathology requisition slips were collected from tertiary treatment center in Kolkata. Fresh Copy of Hematoxyline and Eosin stained tissue sections of different types of pancreatectomy / pancreaticoduodenectomy specimens were prepared from paraffin blocks. Team of Physicians, Surgeon and Pathologist in Medical College, Kolkata went through the clinical data and tissue sections as per previously fixed protocol and parameters.

Hematoxyline and Eosin stained 0.5 micrometer thick tissue sections were studied and Tumor was classified in Well differentiated (Grade 1), Moderately differentiated (grade 2) and Poorly differentiated (grade 3) type based on histomorphology. Depth of Tumour invasion was noted following established WHO Guideline. Sections for immunohistochemistry was selected among the paraffin blocks which were taken from invasive margins of tumor, and had tumor in 50% or more of total section area.

Immunohistochemistry was performed on sections obtained from representative block of formalin-fixed paraffin-embedded tissue using the Avidin-biotin complex technique. The sections were deparaffinized in xylene, and rehydrated in a graded ethanol series. Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide. The slides were subsequently incubated at room temperature with reagents. After washing in

a 0.05-mol/L concentration of phosphate-buffered saline (PBS), they were incubated with 3% normal rabbit serum for AMFR or 3% normal mouse serum for ECAD for 30 minutes to block nonspecific conjugation in the tissues. The specimens were incubated sequentially with the primary anti-AMFR monoclonal antibody, 3F3A19, or antihuman ECAD antibody, HECD1 (Takara Shuzo, Kyoto, Japan), at 4°C overnight. After washing with PBS, they were incubated with biotinylated rabbit anti-rat IgG for AMFR or rabbit anti-mouse IgG (Vectastain ABC Kit, Vector, Burlingame, CA), diluted 1:250 in PBS, for 30 minutes at room temperature and with ABC reagent (Vectastain ABC Kit) for 30 minutes at room temperature. The immune conjugate was visualized with a 0.05-mol/L concentration of tris(hydroxymethyl)-aminomethane (Tris)-hydrochloric acid (pH 7.6) containing 0.02% (wt/vol) 3,3'-diaminobenzidine tetrahydrochloride and 0.03% (vol/vol) hydrogen peroxide, and counterstaining was performed with Meyer's hematoxylin.

During immunohistochemical evaluation of ECAD and AMFR tumour cell were designated positive or negative as per predetermined criteria. ECAD is normally expressed at ductal lining epithelium-which made us to fix 90% of ECAD expression as cut-off criteria of positive expression. On the other hand, AMFR is only mildly expressed in normal ductal cell and we fixed its 50% expression as cut-off margin for same purpose.

For statistical analysis, differences between the 2 groups were assessed by the Mann-Whitney U test, and correlations between 2 parameters were evaluated by the Spearman rank correlation test.

Expression of Autocrin Motility Factor Inhibitor Receptor(AMFR) and E-Cadherin(ECAD)

III. Table

	AMFR				ECAD			
	Strong		weak		Strong		Weak	
Histopathologic Grade (n =19)								
Grade1(n=14)	7	36.8%	7	36.8%	10	52.6%	4	20.1.3%
Grade2(n=4)	1	5.2%	3	15.8%	2	10.5%	2	10.5%
Grade3 (n=1)	1	5.2%	0	-	0	-	1	5.2%
Depth of Invasion								
T1(n=12)	3	15.8%	9	15.8%	9	47.3%	3	15.8%
T2(n=6)	3	31.6%	3	31.6%	2	10.5%	4	21%
T3(n=1)	1	5.2%	0	-	0	-	1	5.2%

Table:1

	ECD Strong		ECAD Weak		Total
AMFR Strong	3	33.3%	6	66.7%	9
AMFR Weak	6	66.7%	4	21%	10
Total	9		10		19

Table:2

IV. Results

In non-malignant Pancreatic tissue, ECAD is strongly expressed at intercellular border. In contrast to ECAD expression, AMFR, in such cases is seen in some foci of proliferating zone. (Image 1,2.) In Pancreatic Adenocarcinoma cells, AMFR frequently was expressed in the cell surface and cytoplasm and ECAD expression frequently was reduced in a homogenous or heterogeneous fashion. Thus, the alteration in Pancreatic Adenocarcinoma was follows: 9 cases (47.4%) showed strong expression of AMFR, and 10 cases (52.6%) showed weak ECAD expression. The expressions of AMFR and ECAD molecules were correlated with morphologic variant as well as depth of tumor invasion in Pancreatic Adenocarcinoma [Table 2]. Strong expression of AMFR was observed more frequently in poorly differentiated adenocarcinomas (1/1 [100%]) and in (1/4[25%]) moderately differentiated adenocarcinoma than in well differentiated type (7/14 [36.8%]).

Likewise, the frequency of weak expression of ECAD was higher in poorly differentiated type carcinomas (1/1 [100%]) and in moderately differentiated adenocarcinoma (2/4[50%]). Such expression in than in well differentiated-type carcinomas (4/14 [28.6%]). such The alterations of these molecules were associated

with poorly and moderately type differentiated carcinomas, which imply a loss of differentiation ($P = .005$ and $P = .0217$ for AMFR and ECAD respectively). Strong expression of AMFR was observed less frequently in superficial (T1) cancer (3/12 [25%]) than those with deeper infiltration (T2,) (3/6 [50%]) and T3(1/1[100%]). There was a significant positive correlation between the depth of invasion and the expression of AMFR ($P = .0384$); however, the proportion of ECAD reduction (weak expression) was similar in superficial and deep infiltrating tumors.

When the expression of ECAD and AMFR are compared (Table 3), strong expression of AMFR was more frequent in tumors with weak expression of ECD (6/19 [31.6%]) than in tumors with strong expression of ECD (3/19 [15.8%]), thereby showing a significant negative correlation ($P = .0034$). When other morphometric parameters were reevaluated according to the coexpression pattern of these molecules, tumors with strong AMFR and weak ECAD expression showed deep tumor invasion (T2,3) more frequently than tumors with weak AMFR and strong ECAD expression.

V. Discussion

Histologically, pancreatic adenocarcinoma are classified into different grades-Grade 1, Grade 2 and Grade 3. Mucinous component is seen both grade 2 and 3 types tumour. Grade 3 type of tumours showed diffuse pattern of growth and signet ring cell component. We find slight male preponderance (male= 11, female=8) in our study. Mean age of detection pancreatic adenocarcinoma was mostly more than 58 years with variation between 49 to 73 years-which in concordance with global trend.(2)

The E-cadherins (ECAD), or “classical” cadherins of type I, belong to the large family of cadherins, transmembrane or membrane-associated glycoproteins, mediating intercellular adhesion and playing a pivotal role in epithelial cell behavior and tissue morphogenesis or remodeling (26-32). Transcriptional ECAD reprogramming in epithelial cells leads to decreased adhesion to facilitate migration at the epithelial-to-mesenchymal transition (EMT) interface during cancer progression (33). It is the characteristic of high grade tumors that the function of ECAD is disturbed, even in the presence of its protein expression,(9) because of ECAD gene mutation or tyrosine phosphorylation of ECAD binding proteins.(7) Accordingly, as mentioned previously, loss of cell-cell adhesion induces transcription of the AMFR gene. In the present study, we found more AMFR overexpression in Grade 3 (poorly differentiated) than in Grade 1 (Well differentiated) tumours. This probably is a consequence of a functional or expression disorder of ECAD.

In concordance with previous researchers we found necessity of setting cutoff line of ECAD at 90% for ECAD expression, as such protein is expressed normally on cell surface.(20,34) AMFR, on the other hand was expressed only slightly in normal epithelium and gradually increased in cancer cells, and 50% cutoff was sufficient for separating AMFR expression into 2 groups.(7) In the present study, we found overexpression of AMFR in half of the patients with pancreatic adenocarcinoma and association of AMFR with tumouredifferentiation and deeper infiltration. Our observation was in concordance with similar study of Hirono Y et. al. in evaluation of gastric adenocarcinoma.(23)

The mechanism for regulation of AMFR is not fully understood. The AMFR gene is located on 16q2130. In cultured cell lines, cell-cell contact dramatically down-regulated the protein expression and messenger RNA transcription of the AMFR gene.(15) Researchers performed an AMFR promoter assay and found it was suppressed by high cell density. They could not precisely identify the transcription factor but speculated that c-Myc was a candidate, since the amount of c-Myc was correlated inversely with cell density.(24) There is another report that retinoic acid down-regulates AMFR expression.(35) Since retinoic acid induces differentiation in various types of cells, differentiation might be another factor that regulates AMFR expression.

These phenomena lead us to the possibility that ECAD is involved in transcriptional regulation of AMFR. For example, ECAD is the strongest cell-cell adhesion molecule (5) and beta-catenin, an ECAD binding protein, is reported to be associated with c-Myc transcription. (36) Retinoic acid is known to up-regulate ECAD expression.(37) Although the suppression of AMFR transcription by ECAD has not been proven directly, the inverse correlation of ECD and AMFR expression has been reported in bladder carcinomas.(38),gastric carcinoma(23). It appears that as ECAD itself is strong repressor of cancer invasion and metastasis, the reduction of ECAD induces cancer invasion and metastasis, both by the function itself and by the regulatory mechanism for AMFR expression.

VI. Conclusion

This study signifies importance of simultaneous examination of both ECAD and AMFR molecules. Complicated histologic types of Pancreatic adenocarcinoma and its properties could partly be explained by inverse association between expression of these two molecules. Synergistic effects of these molecules seems to be critical for progression of malignant cell and varying prognosis of Pancreatic adenocarcinoma.

IMAGES

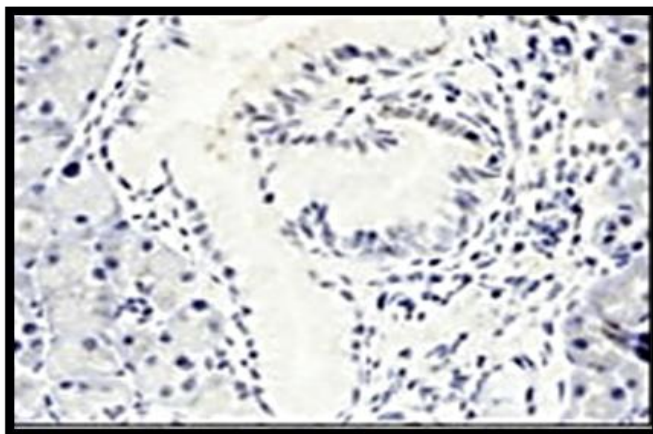


Image 1: AMFR expression in normal Pancreatic Duct (x400)

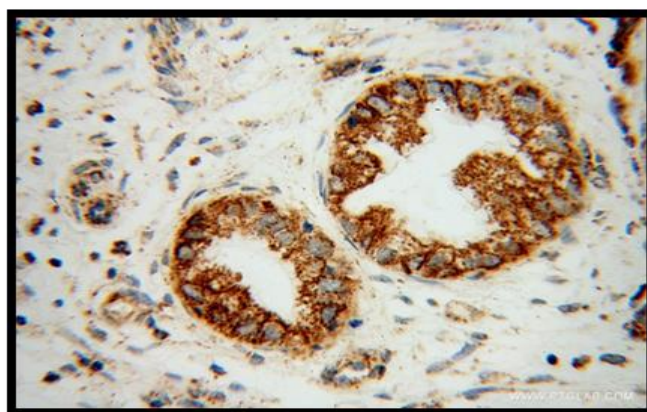


Image 2: ECAD expression in normal Pancreatic Duct(x400)

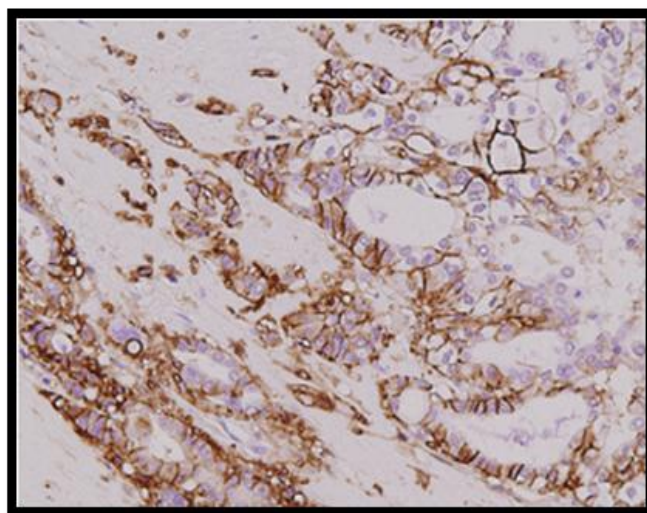


Image 3: AMFR expression in Pancreatic Duct Adenocarcinoma Grade 2(x400)

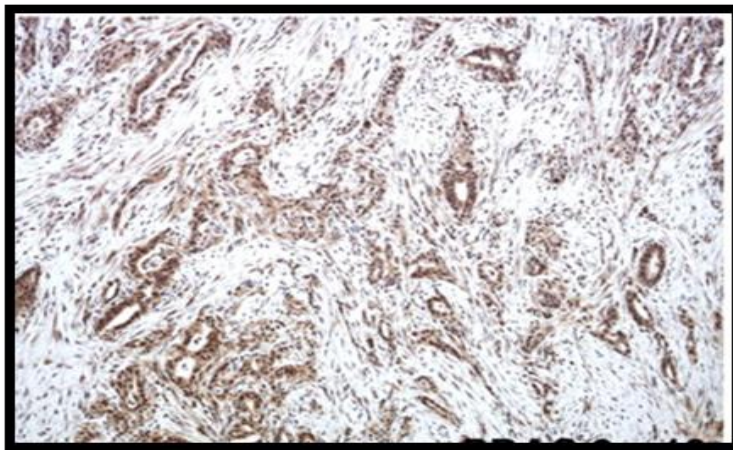


Image 4: ECAD expression in Pancreatic Duct Adenocarcinoma Grade 2(x400)

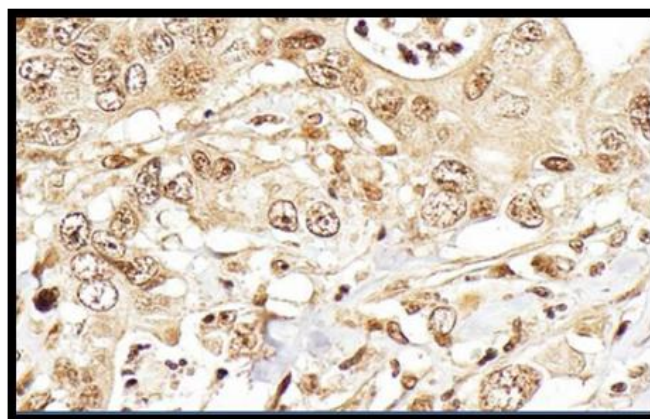


Image 5: AMFR expression in Pancreatic Duct Adenocarcinoma Grade 3(x400)

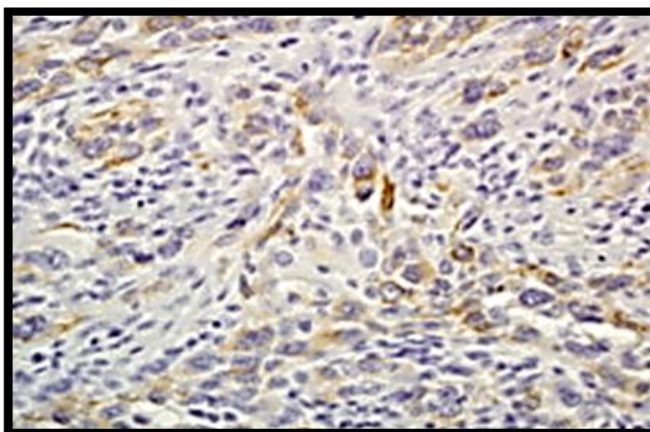


Image 6 ECAD expression in Pancreatic Duct Adenocarcinoma Grade 3(x400)

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