INTERCONNECTION OF EPITHELIAL-MESENCHYMAL TRANSITION AND SENESCENCE IN PANCREATIC NEUROENDOCRINE LESIONS

Ioanna Angelioudaki[1], Agapi Kataki[2], Efthymios Koniaris[3], Alexandros-Georgios Tzingounis[1], Alexandros Mitrousias[1], Loukas Stoupis[1], MM Konstadoulakis[1]

[1] *Second Department of Surgery, Aretaieion Hospital, Medical School, NKUA, Greece*
[2]*First Department of Propaedeutic Surgery, "Hippokratio" General Hospital of Athens, Medical School, NKUA, Greece*
[3]*Department of Pathology-Anatomy, Hippocration General Hospital of Athens, Greece*

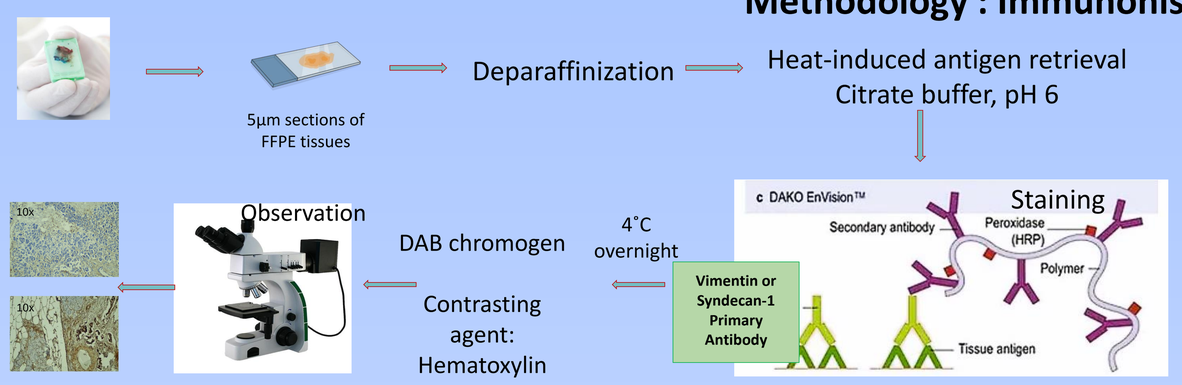
Introduction: PNENs represent a heterogeneous group of rare tumors (3-5% of all cases) consisting primarily of pancreatic neuroendocrine tumors (pNETs) and pancreatic neuroendocrine carcinomas (pNECs). During the last decades, their incidence is increasing as a consequence of improved imaging techniques. In terms of overall survival (OS), pNENs are mostly benign (95% 4.1 years, CI: 3.9–4.4), contrary to the more aggressive and most common type of pancreatic cancer (>90%), Pancreatic Ductal Adenocarcinoma (PDAC), which presents a median 6-month survival. PNENs are characterized by late diagnosis due to the absence of specific symptoms, aggressive and rapid progression of the disease. In 50-80 % of these patients metastases occur months or years after the primary tumor is diagnosed, probably due to senescence, although the exact mechanisms remained undefined.

Patients : Study was approved by the scientific committee of General Hospital of Athens 'Hippocration'. Protein expression profiles were studied immunohistochemically in paraffin-embedded tissues from 25 patients undergoing surgery for pNEN (15 pNETs and 10 pNECs). All pNEN cases were revaluated according to the latest 2019 WHO definition.

Aim: As Epithelial to Mesenchymal Transition (EMT) seems to be an important factor during the metastatic process, and senescence to be responsible for late recurrence, the expression profiles of Vimentin and Syndecan-1 which has been recently associated to play a role in the regulation of cellular senescence, were analysed in the current study, aiming to investigate a possible interconnection between them.

Type of Pancreatic Lesion	Number of samples	Mean Age	Sex		Grade		
			male	female	I	II	III
pNECs	10	60.5 ± 3.44	5	5	0	0	10
pNETs	15	56.6 ± 4.03	10	5	10	5	0

Methodology : Immunohistochemical detection



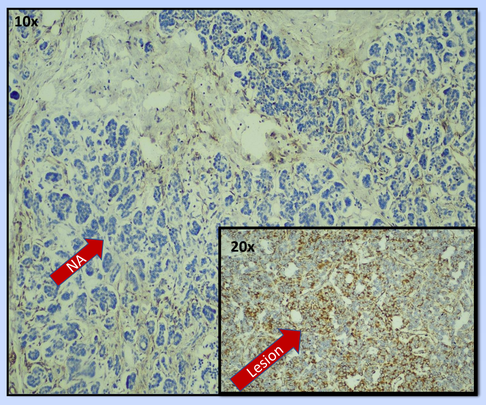
Vimentin primary antibody [1/100, M0725, DAKOPATTS a/s, Denmark]
Syndecan-1 primary antibody [1/500, NB100-64980, Novus Biologicals, USA]

Staining Intensity	X	Score of (%) Stained cells	=	Final score
1 | 2 | 3		1 = 0-10% 2 = 11-50% 3 = 51-80% 4 = 81-100%		0 - 12

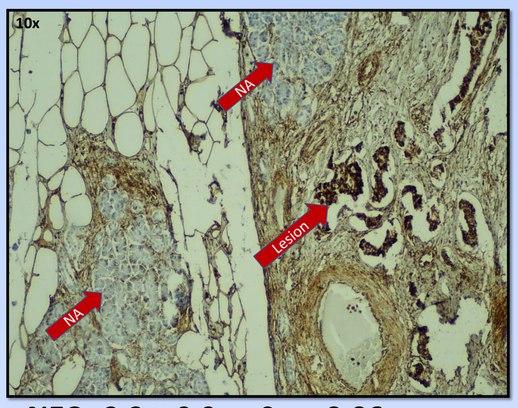
Data were statistically analysed with SPSS 26

Results

➢ **In all cases NA epithelium was scored negative for Vimentin expression**

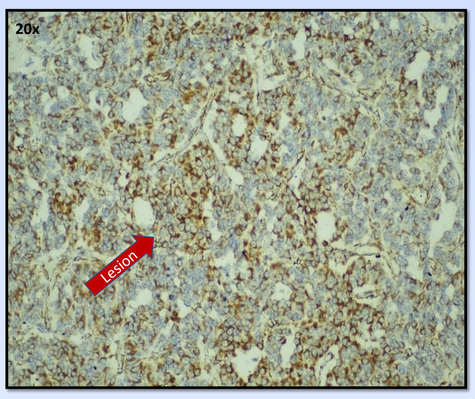


pNETs: 2.47±0.66 vs 0 **p=0.026**

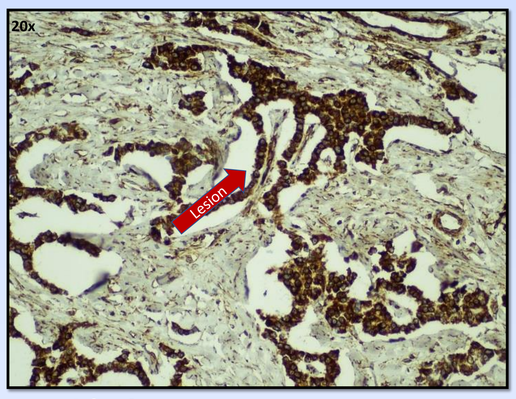


pNECs:3.3 ± 0.9 vs 0**, p=0.06**

➢ **84% of pNEN patients' presented Vimentin expression in lesions' epithelium**



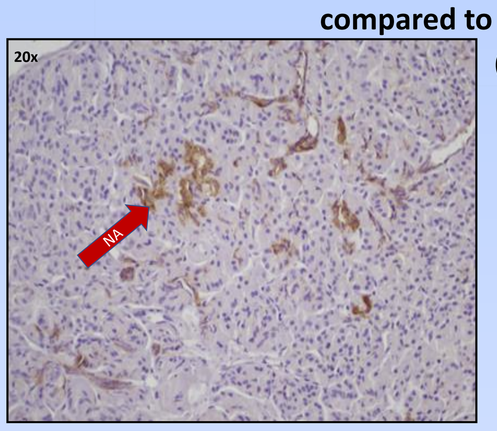
pNET lesion



pNEC lesion

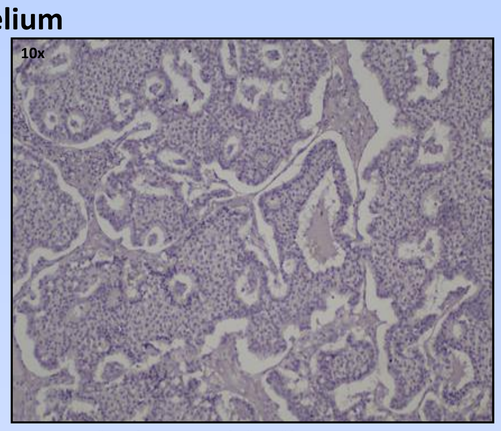
Vimentin expression profile did not significantly differ between pNET and pNEC (2.47±0.66 vs. 3.3 ± 0.9, p=0.268)

➢ **Syndecan-1 membrane staining was diminished in pNETs epithelium compared to NA epithelium**



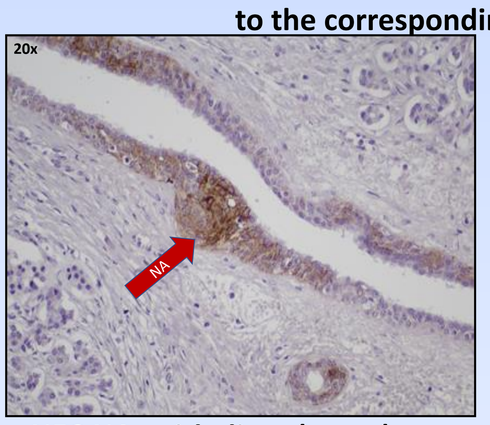
pNET NA epithelium

(p=0.014)



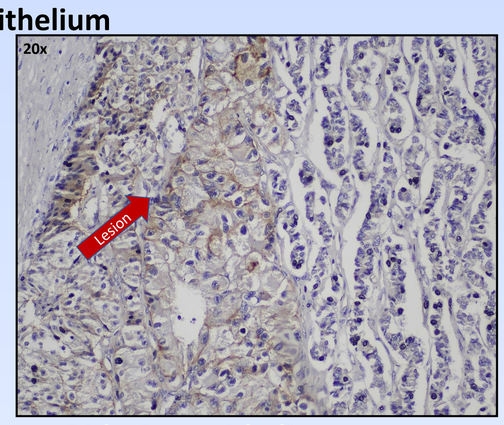
pNET lesion epithelium

➢ **Syndecan-1 membrane staining in pNECs epithelium compared to the corresponding NA epithelium**



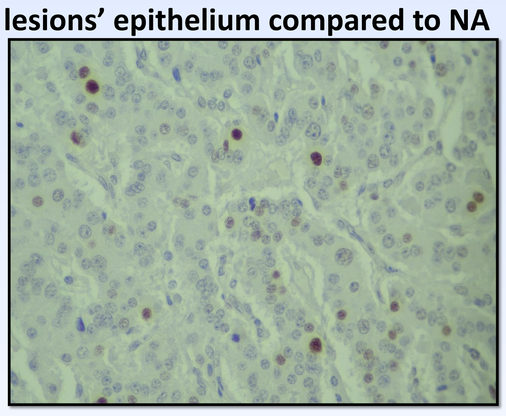
pNEC NA epithelium (pores)

(p=0.49)



pNEC lesion epithelium

➢ **p21 increased expression in pNEN lesions' epithelium compared to NA**



pNET lesion

Discussion

Accumulating evidence supports that "quasi-mesenchymal" cells which display both epithelial and mesenchymal characteristics, are the most capable for metastasis and formation of new tumors throughout the body. Our results indicate the presence of EMT process, as presented by the increased Vimentin expression in most pNENs lesions' epithelium. In addition, in pNET epithelium an increased number of senescent cells were detected (p21 positive expression). As both expression profiles parallel the detected depletion of Syndecan-1 expression in neoplastic compared to the normal adjacent epithelium, an association of Syndecan-1 with tumor development and a mechanism for tumor cells to escape/bypass senescence through EMT can be speculated.

Limitation: Further research is required to elucidate the interrelation of these two mechanisms as our cohort of patients is small.

References

1. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76(2):182–8.
2. Yan J, Yu S, Jia C, Li M, Chen J. Molecular subtyping in pancreatic neuroendocrine neoplasms: New insights into clinical, pathological unmet needs and challenges. Biochim Biophys Acta - Rev Cancer 2020;1874(1):188367.
3. Fujii T, Shimada K, Tatsumi Y, Hatakeyama K, Obayashi C, Fujimoto K, et al. microRNA-145 promotes differentiation in human urothelial carcinoma through down-regulation of syndecan-1. BMC Cancer. 2015;15(1):1–8.
4. Paul R, Dorsey JF, Fan Y. Cell plasticity, senescence, and quiescence in cancer stem cells: Biological and therapeutic implications. Pharmacol Ther. 2022 Mar;231:107985. .

Acknowledgment: This project is part of **NExT project** which has received funding from the GSRT (Greece) within the **Transcan-2 program ERA-NET' Translational research on rare cancers",** as well as from the **European Union's Horizon 2020** research and innovation programme under grant agreement No 857381, project **VISION**

ERA-NET on Translational Cancer Research (TRANSCAN-2)