Biomarkers for Pancreatic Ductal Adenocarcinoma

Munaim Ashb Shahid

1st Year MBBS, Islamabad Medical and Dental College, Islamabad Pakistan.

Key Points
➢ Incidence of pancreatic cancer ➢ Types of pancreatic cancer ➢ Risk factors and symptoms ➢ Diagnostic biomarkers

Pancreatic cancer is one of the most aggressive and lethal malignancies. Currently, it is the most lethal tumor entity with 458,918 new cases followed by 432,242 deaths in 2018.[1] Henceforth becoming the seventh leading cause of cancer-related deaths due to late diagnosis, poor survival rates, and high incidence of metastasis. Its global burden has more than doubled over the past 25 years and highest incidence regions include North America, Europe and Australia.[2,3]. Mortality is close to incidence and patient survival after diagnosis stands at an approximate of five months. Blood-based biomarkers include one of the many factors that could improve this dismal situation as they possess several advantages over tissue-based markers. While disease symptoms are subjective, biomarkers provide an objective and measurable way to characterize the affliction.

Types of Pancreatic Cancer

There are two main categories for pancreatic tumors: endocrine and exocrine. Endocrine tumors are rare and are mostly initiated in hormone-producing cells. Exocrine pancreatic tumors are developed from cells that make up the enzyme-producing glands or the ducts of the pancreas. One of them is acinar cell carcinoma, which is relatively sporadic.

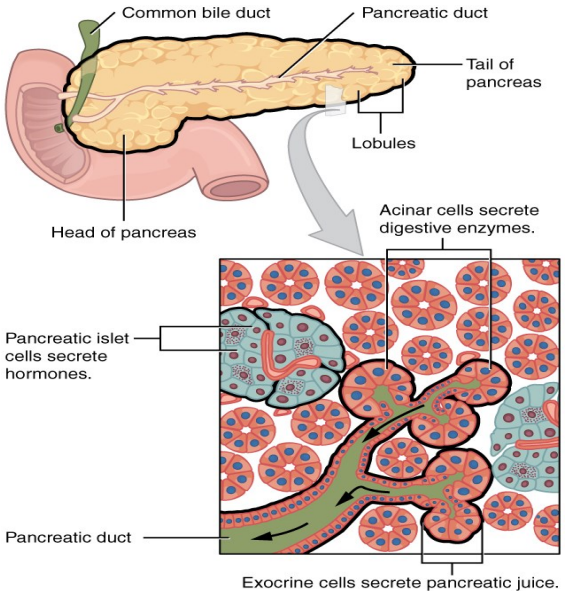

Figure:1

The pancreas has many functions, served by the endocrine cells in the islets of Langerhans and the exocrine acinar cells. Pancreatic cancer may arise from any of these and disrupt any of their functions.[1]

Similarly infrequent are the benign or less malignant pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). All three may, upon specific stimuli, transform into malignant tumors. The most common exocrine neoplasm constituting 90–95% of all pancreatic cancer cases is pancreatic ductal adenocarcinoma (PDAC); about 10% of them have a familial background.[4]

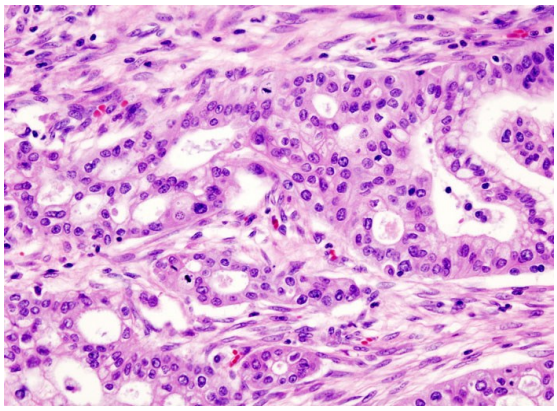

Figure: 2

Micrograph of pancreatic ductal adenocarcinoma (the most common type of pancreatic cancer), H&E stain.[2]

Risk Factors & Symptoms

In spite of the advancements in research and analysis of disease management, the overall 5-year survival rate with regards to PDAC remains low for 5–9% of the patients. Smoking, diabetes and chronic pancreatitis along with family history of cancer are major risk factors for tumor development. Obesity and heavy alcohol consumption are also found to be associated with increased probability of the ailment. It is important to note that pancreatic cancer manifestations are nonspecific- this means that PDAC cases are diagnosed at advanced stages so that only 10–20% of tumors are eligible for surgery. The most widespread symptoms include back pain, weight loss, jaundice, nausea and the onset of diabetes.[5]

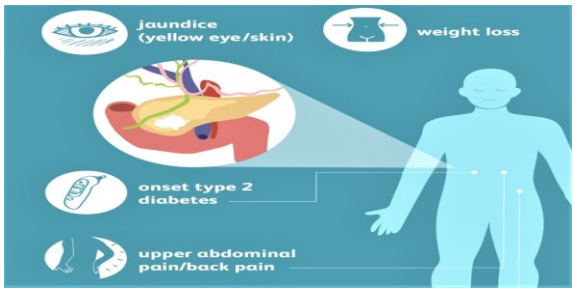

Figure:*3*

Common Symptoms of Pancreatic Cancer.[3]

Diagnosis & Biomarkers

Initially, diagnosis usually relies on imaging techniques such as MRI and Multidetector Computed Tomography Scan. With appropriate screening processes in place, it may even be possible to pinpoint healthy individuals that may have a molecular predisposition to develop PDAC. The current standard of care for diagnosing PDAC involves examination of tumor tissue either by fine needle aspiration cytology or histological examination of biopsies or surgical specimens. The aforementioned procedures are invasive thus entailing a risk of complications.

Blood-based tests are minimally invasive, involving only limited unease, and have no major impediments. They can easily be repeated to allow close monitoring of the disease and to evaluate response to treatment or early detection of recurrence.[6]

Biomarkers may include a wide range of components in a biological specimen, including nucleic acids (e.g., microRNA) and its modifications (e.g., DNA methylation), proteins, peptides or their isoforms and variants, as well as cells (e.g. circulating tumor cells) or exocellular vesicles, such as exosomes. Blood has also been an appealing and plausible biomarker because of its stability and accessibility.[7]

As a result, research on biomarker analysis has become an investigation of blood-based molecules, termed liquid biopsy. Carbohydrate antigen 19–9 (CA19-9) is the only blood-based biomarker that is being used for the management of pancreatic cancer patients on a routine basis.[7] However CA19-9 is not completely detectable in approximately 6% of patients due to a lack of fucosyltransferase (an enzyme that transfers an L-fucose sugar from a GDP-fucose (guanosine diphosphate-fucose) donor substrate to an acceptor substrate) activity in individuals who have homozygous mutations in gene FUT3. Other carbohydrate antigens, such as

CA242, have been studied, but did not surpass the performance of CA19-9.[8]

Protein Biomarkers

ELISA (enzyme-linked immunoassay) is the top tier standard for the detection of protein biomarkers. Either monoclonal or polyclonal antibodies can be used for the capture and detection of disease in ELISA systems as it provides strong clinical diagnostics.[9] Additionally, given the molecular complexity of pancreatic tumors in general, as well as taking into account the disparity between the genetic backgrounds of patients; it is more probable that a group of markers is required for a precise and robust diagnosis.[8]

Soluble siC3b, another protein-based biomarker, is highly significant with respect to early diagnosis of PDAC. The membrane-bound protein activates the complement system during the binding of auto-antibodies to tumor cells. In a detailed research, it predicted tumor growth four months before radiological evidence became available.[10]

Protein level alterations have the ability to act as biomarkers more than functionally unrelated molecules. Inflammatory factors in blood can also be used as biomarkers, although they might have a lesser accuracy.[11]

Conclusion

In reference to pancreatic ductal adenocarcinoma (PDAC), clinical research suggests that due to the nature of its malignancy, it is very challenging to identify symptoms that initially point towards pancreatic cancer specifically. As a result, the tumor has normally reached advanced levels of metastasis by the time of diagnosis.[12]

References

1. AP., K. (2021 Jul). Pancreatic cancer epidemiology: Understanding the role of lifestyle and inherited risk factors. Nature Reviews Gastroenterology & Hepatology , 18(7):493-502.
2. Björling E, U. M. (2008 Oct 1). Antibodypedia, a portal for sharing antibody and antigen validation data. Molecular & Cellular Proteomics , 7(10):2028-37.
3. Costache MI, C. C. (2017 Apr). Which is the best imaging method in pancreatic adenocarcinoma diagnosis and staging-CT, MRI or EUS? Current health sciences journal , 43(2):132.
4. E Poruk K, Z. G. (2013 Mar 1). The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. Current molecular medicine , 13(3):340-51.
5. EP., D. (2012 Dec). The failure of protein cancer biomarkers to reach the clinic: why, and what can be done to address the problem? BMC medicine , 10(1):1-5.
6. Guerra C, C. M.-P.-J. (2011 Jun 14). Barbacid M. Pancreatitis-induced inflammation contributes to pancreatic cancer by inhibiting oncogene-induced senescence. Cancer cell , 19(6):728-39.
7. Henriksen SD, T.-U. O. (2021 Jun). Cell-Free DNA Methylation as Blood-Based Biomarkers for Pancreatic Adenocarcinoma—A Literature Update. Epigenomes , 5(2):8.
8. Hidalgo M, C. S. (2015 Jan 1). Addressing the challenges of pancreatic cancer: future directions for improving outcomes. Pancreatology , 15(1):8-18.
9. Marten A, B. M. (2009 May 20). Soluble iC3b as an early marker for pancreatic adenocarcinoma compared to CA 19.9 and radiology. Journal of Clinical Oncology , 27(15_suppl):4626-.
10. Nimse SB, S. M. (2016). Biomarker detection technologies and future directions. Analyst , 141(3):740-55.
11. Rawla P, S. T. (Feb 2019). Epidemiology of pancreatic cancer: global trends, etiology and risk factors. 10(1):10.
12. Ryan DP, H. T. (2014 Sep 11). Pancreatic adenocarcinoma. New England Journal of Medicine , 371(11):1039-49.