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Liquid biopsy in periampullary carcinoma

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ABSTRACT

Periampullary cancers are rare tumors arising within 2 cm of the major papilla of the duodenum. In this case report, we describe the use of liquid biopsy to analyze cell-free tumor DNA and exosomal microRNA to guide treatment selection in a patient with periampullary adenocarcinoma. To our knowledge, this is the first time such case report has been described in the literature.

Key words: Cell free DNA, Liquid biopsy, MicroRNA

Introduction

Periampullary carcinoma is a widely used term to define a heterogeneous group of neoplasms arising from the head of the pancreas, the distal common bile duct, and the duodenum.

Medical treatment decisions are generally derived from pancreatic cancer chemotherapy protocols and consist mainly of traditional chemotherapy drugs with targeted therapy having limited role. In many cancers, next generation sequencing of circulating nucleic acids has recently made it possible to better understand the cancer biology and elucidate tumor signatures which can provide therapy guidance.

Case Report

A 69-year-old male was diagnosed with periampullary carcinoma in the year 2002 and was treated by Whipple surgery along with 6 cycles of leucovorin, gemcitabine, and 5-fluorouracil. At the time of recurrence in 2015, he presented with multiple metastases and raised serum cancer antigen 19.9 (CA19.9) level of 3290 U/ml. He was started on protein-bound paclitaxel and gemcitabine. However, after 3 weeks and 3 doses of chemotherapy CA19.9 levels increased to 5277 U/ml (Figure 1).

A liquid biopsy was performed to know the current molecular profile of the disease. Cell-free DNA (CfDNA) obtained from plasma was used for enrichment of targeted regions of 61 genes using Ion AmpliSeq™ Kit (Thermo Fisher) as per user recommended protocol. One hundred picomoles of exome library was further subjected to template preparation with Ion OneTouch 2 and sequenced on Ion PI semiconductor chip (Thermo Fisher). Exosomal RNA was used for targeted miRNA analysis with Taqman miRNA assays using Quant studio 12K flex (Thermo Fisher) and relative gene expression was obtained by CancerTrack™ analysis platform.

The liquid biopsy identified driver mutations in KRAS (G12D), PIK3CA (K567E), and KIT (K818R) genes. The miRNA profile showed the presence of a significant number of miRNAs suggestive of potential benefit from cisplatin therapy (Table 1 and 2). The patient on receiving cisplatin therapy instead of gemcitabine showed significant clinical improvement. Post-cisplatin therapy CA19.9 levels started declining. The CA19.9 levels reduced to 1500 U/mL in 2 weeks and further reduced to 90 U/ml at eight weeks post-cisplatin therapy along with radiological disease response.

It is now well established that fragments of tumor DNA and RNA are shed in the peripheral bloodstream. These are emerging as critical biomarkers in cancer management. They have potential to play a role in selecting optimum therapy, to detect acquired resistance or early detection of disease progression. They help to know the molecular profile of the tumor where biopsy is not feasible.

The patients with pancreatic and biliary carcinomas lack personalized treatment options, in part because biopsies are often inadequate for molecular characterization and sometimes difficult to obtain. Liquid biopsy enables a precision oncology approach in these settings. The cfDNA sequencing diagnostic accuracy of 97.7%, with average sensitivity of 92.3%, and specificity of 100% across five informative genes was shown recently by Zill *et al*.[1] in pancreatobiliary carcinomas.

It has been shown that KRAS mutations at codon 12 are specific to pancreatic cancers and the other tumors in the

Table 1: Blood-based miRNA expression profile as a biomarker in the diagnosis of pancreatic cancer - miRNAs differentially expressed in current case and reported previously in literature for blood-based diagnosis of pancreatic cancer

microRNA	Expression in serum/plasma	Reference
miR-16	Up regulation	Liu, *et al.*
miR-210	Up regulation	Wang, *et al.*
miR-21	Up regulation	Wang, *et al.*
miR-18	Up regulation	Morimura, *et al.*
miR-221	Up regulation	Kawaguchi, *et al.*
miR-20, miR-21, miR-24, miR-25, miR-185, miR-191	Up regulation	Liu, *et al.*

miRNA: microRNA

Table 2: microRNA expression profile suggestive of chemotherapy response in current case

microRNA	Chemotherapy drug	Expression	Chemo response	Reference
Gemcitabine				
miR-21	Gemcitabine	Up regulation	Resistance	Wang, *et al.*
miR-29	Gemcitabine	Up regulation	Resistance	Nagano, *et al.*
miR-365	Gemcitabine	Up regulation	Resistance	Hamada, *et al.*
miR-221	Gemcitabine	Up regulation	Resistance	Park, *et al.*
miR-200	Gemcitabine	Up regulation	Resistance	Meng, *et al.*
Cisplatin				
miR-21	Cisplatin	Up regulation	Resistance	Wang, *et al.*
miR-29	Cisplatin	Up regulation	Sensitive	Zhang, *et al.*
miR-152	Cisplatin	Up regulation	Sensitive	Xiang, *et al.*
miR-185	Cisplatin	Up regulation	Sensitive	Xiang, *et al.*
miR-106	Cisplatin	Up regulation	Sensitive	Rao, *et al.*
miR-451	Cisplatin	Up regulation	Sensitive	Bian, *et al.*
miR-186	Cisplatin	Up regulation	Sensitive	Sun, *et al.*
miR-130	Cisplatin	Up regulation	Sensitive	Zhang, *et al.*
miR-148	Cisplatin	Up regulation	Sensitive	Sui, *et al.*

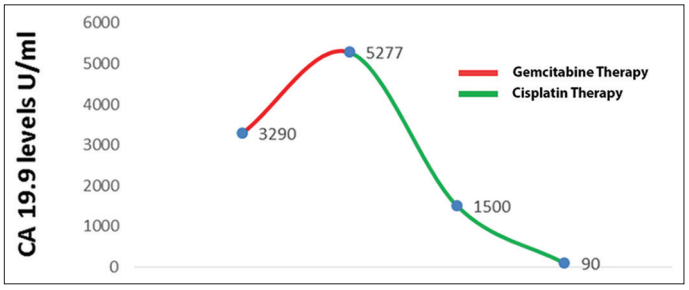

Figure 1: Trend in cancer antigen 19.9 levels with change of therapy from gemcitabine to cisplatin

periampullary region have not frequently demonstrated this alteration. Thus, the presence of KRAS mutation suggests the probable pancreatic origin of this periampullary tumor rather than distal common bile duct or duodenum. The presence of KRAS mutation has been identified in previous studies as a predictive biomarker for pancreatic cancer patients who received either first-line gemcitabine-based chemotherapy or gemcitabine plus erlotinib combination chemotherapy.[2]

The study of a class of small non-coding RNA molecules, named microRNAs (miRNAs), has advanced our understanding of many of the fundamental processes of cancer biology and the molecular mechanisms underlying tumor initiation and progression. The use of miRNA signatures has been studied in the diagnosis and prognosis of various types of cancers. Another area of immense importance is miRNAs as markers for therapy response.

Various miRNAs, such as miR-16, miR-210, miR-21, miR-18a, and miR-221, which are independently or in combination reported as blood-based diagnostic makers for pancreatic cancer were upregulated in patient's plasma.[3] A blood-based signature of seven upregulated miRNA was identified by Liu *et al*. which distinguished pancreatic cancer patients from healthy controls with a diagnostic accuracy of 83.6%.[4] Six out of these seven miRNA signature were also found to be upregulated in patient's sample. Many miRNAs suggestive of a lack of response to gemcitabine and likely response to cisplatin therapy were detected.[5]

In this case of periampullary carcinoma, cfDNA and miRNA analysis helped in cancer management at many levels. The identification of KRAS G12D mutation suggested likely pancreatic origin for this periampullary tumor. The exosomal miRNA profile reinforced the finding of lack of response to the gemcitabine therapy. Furthermore, many miRNAs reported in literature to be associated with cisplatin sensitivity were detected. The potential benefit of the cisplatin therapy indicated by the liquid biopsy was clinically translated with clinical, radiological, response and CA19.9 improvement.

Conclusion

This case highlights the potential of liquid biopsy as an important cancer management tool. The liquid biopsy can help in most optimum therapy selection, acquired resistance detection, real-time molecular profiling of cancer. In patients with unavailability of tumor tissue for molecular profiling liquid biopsy can provide the molecular footprints of cancer from blood. It also can help in certain situations to arrive at a probable diagnosis. Thus, liquid biopsies can be great value add to the current cancer management.

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