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ABOUT COVER

David W Townsend, MD, Professor, Department of Medicine, Bigelow Lab Ocean Sci, Mckown Point, Boothbay Harbor, ME 04575, United States

AIM AND SCOPE

World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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CASE REPORT

EGFR amplification induces sensitivity to anti*EGFR* therapy in pancreatic acinar cell carcinoma

Corentin Richard, Julie Niogret, Romain Boidot, Francois Ghiringhelli

Corentin Richard, Romain Boidot, Francois Ghiringhelli, Platform of Transfer in Oncology, Center GF Leclerc, Dijon 21000, France

Corentin Richard, Romain Boidot, Francois Ghiringhelli, INSERM U1231, Dijon 21000, France

Corentin Richard, Francois Ghiringhelli, University of Bourgogne Franche Comte, Dijon 21000, France

Julie Niogret, Francois Ghiringhelli, Department of Medical Oncology, Georges Francois Leclerc Cancer Center, Dijon 21000, France

ORCID number: Corentin Richard (0000-0001-9732-0219); Julie Niogret (0000-0002-3563-4658); Romain Boidot (0000-0001-9956-1737); Francois Ghiringhelli (0000-0002-5465-8305).

Author contributions: Boidot R and Ghiringhelli F designed the report; Richard C and Niogret J performed the genetic analyses; Ghiringhelli F collected the patient's clinical data; Boidot R and Ghiringhelli F analyzed the data and wrote the paper.

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Correspondence to: Francois Ghiringhelli, MD, Professor, Department of Medical Oncology, Georges Francois Leclerc Cancer Center, 1 Rue Pr Marion, Dijon 21000, France. fghiringhelli@cgfl.fr
Telephone: +33-380-393353
Fax: +33-380-393434

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Abstract

Pancreatic acinar cell carcinoma (PACC) is a rare cancer. When the tumor is metastatic, few therapeutic options are available. Precision medicine using next-generation sequencing is defined by the administration of drugs based on the tumor genetic mutations. The usage of precision medicine for finding new therapeutic options for rare cancers is an emerging field. We have reported here the case of a patient bearing a multitreated metastatic PACC. This patient underwent somatic and constitutional exome analyses. The analyses revealed in the liver metastasis an amplification of the *EGFR* gene. Accordingly, the patient was treated with off-label usage of panitumumab. We observed rapid response with necrosis of the liver metastasis, while no efficacy was observed in the primary tumor. An exome analysis of the primary tumor revealed amplification of *HER2* and *MET* with *EGFR* amplification. Such amplifications are known as a resistance mechanism to anti*EGFR* therapy. Our results suggest that exome analysis may be helpful to highlight targets in rare cancers, such as PACC. *EGFR* amplification in this pathology should be determined and could be used as a biomarker to propose anti*EGFR* therapy.

Key words: Pancreatic cancer; Acinar cell carcinoma; Exome; Genetic mutations; Precision medicine

Core tip: The role of genetic profiling for therapy of rare cancer for precision medicine is currently under investigation. This case report reports, for the first time, that pancreatic acinar cell carcinoma could benefit from precision medicine and that *EGFR* gene amplification could be targetable by anti*EGFR* monoclonal antibody in this pathology.

Richard C, Niogret J, Boidot R, Ghiringhelli F. *EGFR* amplification induces sensitivity to anti*EGFR* therapy in pancreatic acinar cell carcinoma. *World J Gastrointest Oncol* 2018; 10(4): 103-107 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i4/103.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i4.103

INTRODUCTION

Pancreatic acinar cell carcinoma is a rare cancer. This cancer accounts for about 1% of all cases of pancreatic cancers. Patients at diagnosis often present a large tumor with distant metastases in the liver or in other organs[1]. No standard treatments have been proposed in metastatic settings.

Despite the absence of response to chemotherapy, a recent publication suggested that the prognosis of pancreatic acinar cell carcinoma could be better than classical pancreatic ductal adenocarcinoma[2]. Another report[3] described 112 cases of pancreatic acinar cell carcinoma. Eighty-eight patients underwent surgical resection. The overall survival rate was 43.9% at 5 years and the median overall survival was 41 mo. However, for unresectable pancreatic acinar cell carcinoma we found several studies describing the usage of chemotherapy for treatment of pancreatic ductal adenocarcinoma[1,4-7]. However, due to small sample sizes, the level of evidence is limited. Recent advances in genetic testing have revealed that pancreatic acinar cell carcinoma could have genetic mutation that could be targetable in 30% of cases. Here, we provide the first report (to our knowledge) of an *EGFR* amplification in a metastatic pancreatic acinar cell carcinoma, with exceptional and rapid response only in metastases harboring only *EGFR* amplification.

CASE REPORT

A 54-year-old man with past history of nephroblastoma at young age that had been treated by surgery and chemotherapy presented with diarrhea associated with important low weight of 10 kg. On June 2017, a CT scan revealed two liver metastases and voluminous mass in the head of the pancreas, without compression of the biliary tract or duodenum. The patient benefited from pancreatic biopsy upon endoscopic ultrasound. Histology revealed a tumor with large area of fibrous stroma. Acinar architecture was observed with pyramidal-shaped cells surrounding small lumina. The malignant cells were monomorph, with round nuclei and prominent nucleoli having eosinophil cytoplasm. Immunohistochemically, expression of EMA, cytokeratin 7 and absence of WT1, synaptophysin, and chromogranin A markers were shown. Ki67 was expressed in 30% of the tumor nuclei. The diagnosis of metastatic acinar cell pancreatic cancer was given.

The patient received four cycles of FOLFIRINOX, which resulted in tumor progression, and then two cycles of gemcitabine plus nabpaclitaxel, again with tumor progression. The patient was included in the EXOMA trial (NCT02840604). A biopsy of a liver metastasis was performed with a blood withdraw. Then, the patient benefited from somatic and constitutive exome sequencing. The tumor mutational burden was 410 mutations. We limited our analysis to a set of 324 genes, selected due to their roles in prediction of response or resistance to therapy or their associations with cancer predisposition. Our gene list was inspired from the recently published gene list of the MD Anderson Cancer Center used for clinical trial of precision medicine[8].

We observed an unknown mutation in the *CUL2* and *PBRM1* genes. *PBRM1* encodes a tumor suppressor and component of the SWI/SNF chromatin protein complex. Inactivating mutations of *PBRM1* are frequently found in renal tissues[9]. CUL2 is a cullin protein. Cullins are associated with RING proteins and ubiquitin E3 ligases. This complex regulates various cellular processes, including proliferation, differentiation and apoptosis. Loss of *PBRM1* activity is also associated with chromosomal instability, due to inability to promote cohesion[10]. Because of the presence of *PBRM1* mutation, we searched for chromosomal instability using TITAN software. Titan is a Python/R package for analyzing subclonal copy number alterations and loss of heterozygosity in whole genome and exome sequencing of tumors[11].

We observed a ploidy near 3, where 21 chromosomal fragments of more than 10 mB were amplified and 4 chromosomal segments of more than 10 mB were deleted. The number of clones in this tumor was one. Interestingly, we observed a large chromosome 7 amplification containing the *EGFR* gene locus, resulting in the presence of three copies of the *EGFR* gene (Figure 1A). Extensive analysis of the amplifications revealed that only *EGFR* but not *MET* (Figure 1A) nor *ERBB2* (Figure 1B) were amplified. Based on this observation, anti*EGFR* (panitumumab) treatment was given.

At 2 wk after the first injection, we observed clinical improvement for the patients, with 2 kg weight gain and disappearance of liver pain. After two cycles of chemotherapy, we observed a dissociated response with complete necrosis of the liver metastasis, which was tested for exome analysis (Figure 2A and B). In

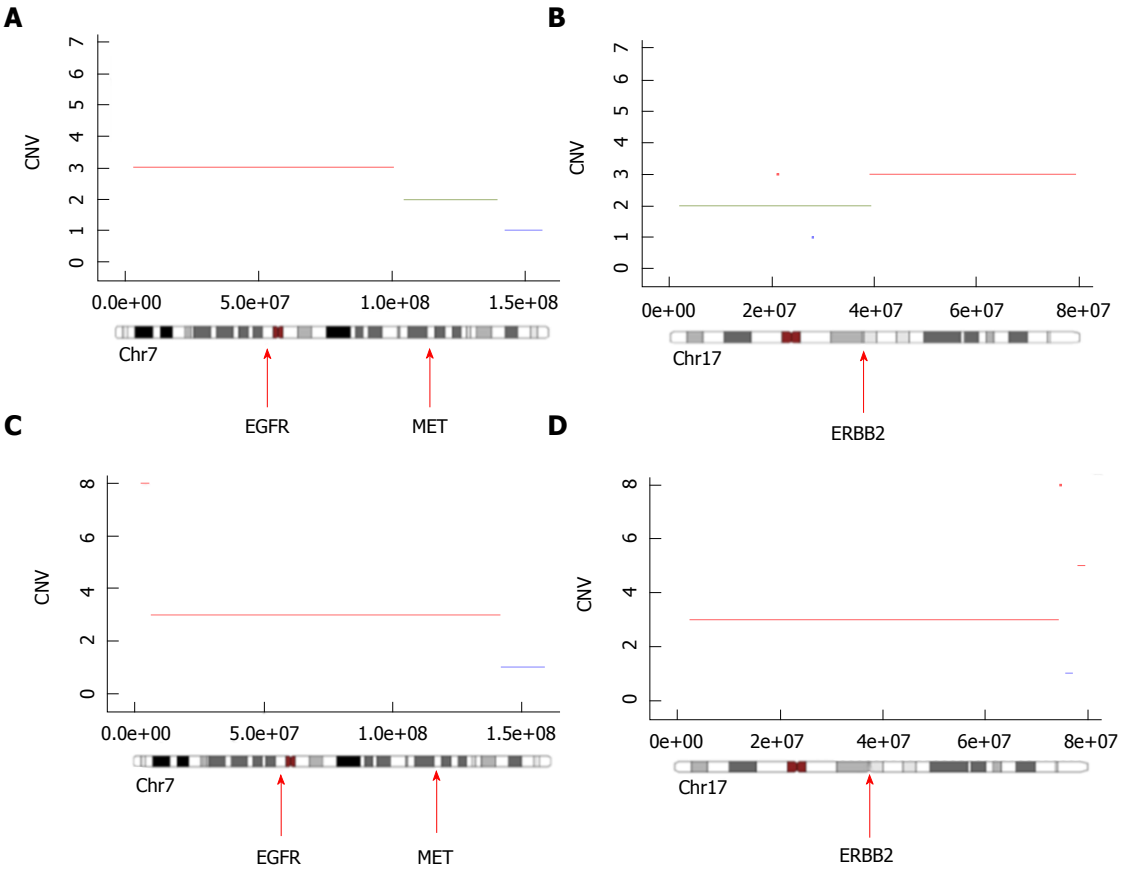

Figure 1 Representation of chromosomal amplification and deletion in chromosomes 7 (A, C) and 17 (B, D) in the primary tumor (C, D) and the liver metastasis (A, B). Portions in red are amplified, portions in blue are deleted and portions in green are diploid. Genes of interest are indicated by a red arrow.

contrast, we did not observe any changes in the tumor characteristics of the primary tumor (Figure 2C and D). A second exome analysis was performed on the primary tumor. Interestingly, we observed in this tumor *EGFR* amplification but concomitant amplification of *ERBB2* and *Met* loci (Figure 1C and D), suggesting the presence of an intrinsic tumor resistance mechanism to anti*EGFR* therapy.

The primary tumor contained two clones, including one with strong similarly to the liver metastatic one, suggesting that only one clone was at the origin of the metastasis process.

DISCUSSION

Pancreatic acinar cell carcinoma is a rare disease of the pancreas. This is a tumor with poor prognosis, like ductal adenocarcinoma. The mean survival is around 2 years and the 3-year survival rate is about 25%[12,13]. Because of the rarity of the disease, few trials address the therapeutic strategy to treat metastatic pancreatic acinar cell carcinoma. Classically, these tumors are considered as chemoresistant ones. Patients are treated with first-line therapy, like pancreatic ductal adenocarcinoma, and then proposed for palliative care.

In contrast to ductal adenocarcinoma of the pancreas, we have little information on the underlying genetic alterations that dictate the development of pancreatic acinar cell carcinoma. Only a study of 23 cases of pancreatic acinar cell carcinoma was extensively characterized by exome sequencing fluorescence *in situ* hybridization and microsatellite instability analysis[14]. This study underlined some mutations that could be targetable, such as those in genes coding for members of the Fanconi anemia pathway and mutations in genes such as *BRCA2*, *PALB2, BAP1*, *ATM*, *BRAF* and *JAK1*. Such mutations could be targetable by PARP inhibitors, BRAF inhibitors and JAK1 inhibitors respectively. However, we did not observe any mutations in these genes in our patient.

Pancreatic acinar cell carcinoma presents frequently with a large number of chromosomal alterations and a major intratumoral heterogeneity. These data suggest that these tumors are chromosomally unstable[15], although the mechanism(s) which explain chromosomal instability is(are) unclear. We could suspect that it may explain its aggressive behavior and resistance to therapy[16]. In this report, the presence of *PBRM1* mutation, which is classically associated with chromosomal instability, could explain this instability. Such instability should induce some amplification of oncogenes that could be targetable. In this case, the liver metastasis presented amplification of *EGFR*, which could be oncogenic but also a target for anti*EGFR* therapy.

Efficacy of anti*EGFR* therapy is restrained by the

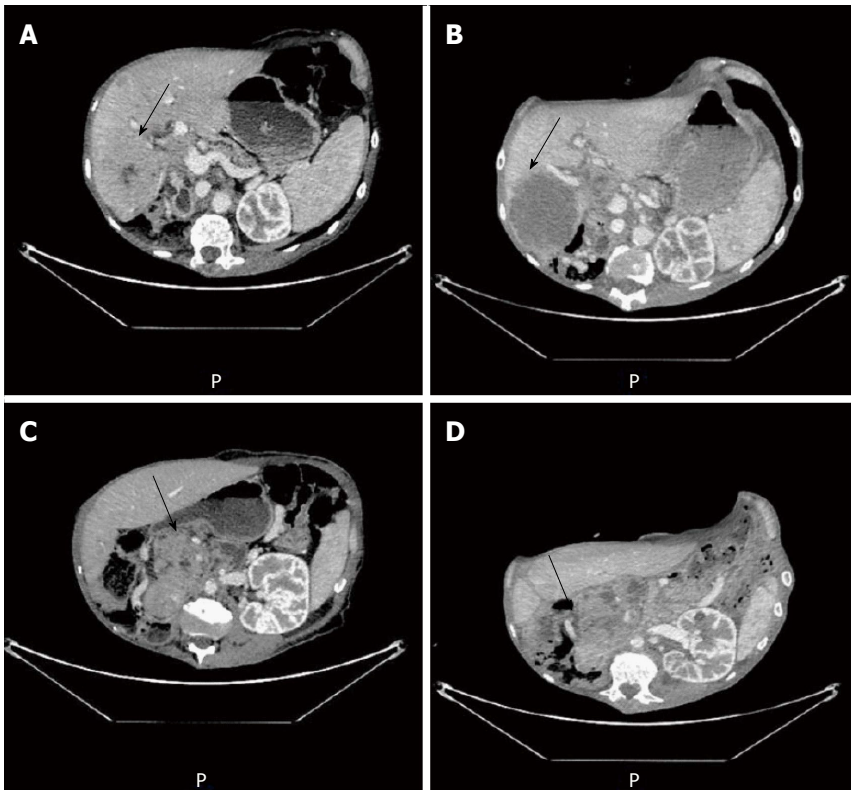

Figure 2 Primary tumor and liver metastasis response to FOLFIRI plus panitumumab. A and B: CT scan axial images of liver metastasis at baseline and 4 wk of therapy; C and D: Axial images of at primary pancreatic tumor at baseline and 4 wk of therapy. Lesions are indicated by a arrow.

presence of *KRAS-NRAS* mutations[17]. However, none of the pancreatic acinar cell carcinomas had *KRAS* mutation in previous series, in contrast to ductal adenocarcinomas[18-20].

Accordingly, we did not detect mutation either on *KRAS* or on *NRAS* in our patient. We observed, for the first time, amplification in the *EGFR* locus in a pancreatic acinar cell carcinoma. In colorectal cancer, *EGFR* amplification was previously described as a biomarker associated with anti*EGFR* efficacy[21,22]. The presence of a dissociation response between liver metastasis and primary tumor suggest the presence of a clonal heterogeneity between the two tumor sites, confirmed by our bioinformatic analysis of copy number alterations. Indeed, this analysis underlined that the primary tumor contained two clones, while the liver metastasis contained only the antiEGFR-sensitive clone. The mechanism of resistance to anti*EGFR* therapy is pleiotropic and includes presence of *KRAS* and *NRAS* mutations, *PIK3CA* and *PTEN* alterations, mutation in the extracellular domain of EGFR, HER2 and MET amplification 16. The presence of both *HER2* and *MET* amplifications gave strong rational to explain the resistance of the primary tumor to anti*EGFR* therapy.

Together, this report provides the first description of a major and rapid response of pancreatic acinar cell carcinoma to anti*EGFR* therapy related to *EGFR* amplification. This report also gives rationale to perform multiple biopsies or liquid biopsy to address tumor heterogeneity, which could explain dissociated response.

ARTICLE HIGHLIGHTS

Case characteristics
A pancreatic cancer with liver metastasis.

Clinical diagnosis
Amplification of the *EGFR* gene is targetable in pancreatic acinar carcinoma.

Differential diagnosis
Histology and molecular biology are required for the diagnosis.

Laboratory diagnosis
Genetic testing provides information on targetable tumor mutation.

Imaging diagnosis
Computed tomography scan underlines liver metastasis necrosis.

Treatment
The patient was treated with off-label usage of panitumumab.

Term explanation
This is the first report of *EGFR* amplification in acinar cell pancreatic cancer, and the first report of panitumumab efficacy in such disease.

Experiences and lessons
Our findings suggest that exome analysis may be a helpful tool to highlight targets in rare cancers, such as pancreatic acinar cell carcinoma. *EGFR*

amplification in this pathology should be determined and could be used as biomarker to propose anti*EGFR* therapy.

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