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

Richard C *et al*. *EGFR* amplification induces sensitivity to anti *EGFR* therapy

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**Abstract**

Pancreatic acinar cell carcinoma (PACC) is a rare cancer. When tumor is metastatic few therapeutic option 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 to finding new therapeutic option for rare cancer is an emerging field. We have reported here the cases of a patient bearing a multi-treated metastatic PACC. This patient underwent somatic and constitutional exome analyses. The analyses revealed in the liver metastasis an amplification of *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 resistance mechanism to anti *EGFR* therapy. Our results suggest that exome analysis may be helpful to highlight target in rare cancer such as PACC. *EGFR* amplification in this pathology should be determined and could be used as biomarker to propose anti *EGFR* therapy.

**Key words:** [Pancreatic](https://www.f6publishing.com/ArticlesByKeywords?type=2&pageNumber=1&keyword=Colorectal+cancer) cancer; Acinar cell carcinoma; [Exome](https://www.f6publishing.com/ArticlesByKeywords?type=2&pageNumber=1&keyword=Exome+analysis); [Genetic mutations](https://www.f6publishing.com/ArticlesByKeywords?type=2&pageNumber=1&keyword=Genetic+aberrations); Precision medicine

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**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* mAb in this pathology.

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**INTRODUCTION**

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

Despite the absence of response to chemotherapy, recent publication suggest 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. Eigthy-eight patients underwent surgical resection. Overall survival rate was 43.9% at five years and median overall survival was 41 months. However, for unresectable pancreatic acinar cell carcinoma we found several studies, which described the usage of chemotherapy used for the treatments for pancreatic ductal adenocarcinoma[1,4-7]. However, due to small sample size the level of evidence is limited. Recent advances in genetic testing unravel that Pancreatic acinar cell carcinoma could have genetic mutation that could be targetable in 30% of cases. Here we provide first report to our knowledge of an *EGFR* amplification in a metastatic Pancreatic acinar cell carcinoma with exceptional and rapid response only in metastasis harboring only *EGFR* amplification.

**CASE REPORT**

Fifty-four year old man with past history of nephroblastoma in the young age treated by surgery and chemotherapy presented a diarrhea associated with important low weight of 10 kg. On June 2017, a CT scan revealed 2 liver metastasis and voluminous mass of the head of the pancreas without compression of 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 surround small lumina. The malignant cells are monomorph with round nuclei and prominent nucleoli with eosinophil cytoplasm. Immunohistochemically, it showed expression of EMA, cytokeratin 7 and absence of WT1, synaptophysin, and chromogranin A markers. Ki67 is expressed in 30% of tumor nuclei. The diagnostic of metastatic acinar cell pancreatic cancer was given. The patient received 4 cycles of FOLFIRINOX, which results in tumor progression, and then 2 cycles of gemcitabine plus nabpaclitaxel with tumor progression. The patient was included in EXOMA trial (NCT02840604). A biopsy of a liver metastasis was performed with a blood withdraw. Then patient benefited from somatic and constitutive exome sequencing. The tumor mutational burden was 410 mutations. We limited our analysis on a list of 324 genes. These genes were selected due to their role in prediction of response or resistance to therapy or their association with cancer predisposition. Our gene list was inspired from the recently published gene list of the MD Anderson used for clinical trial of precision medicine[8]. We observed an unknown mutation in *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[9]. CUL2 is a cullin protein. Cullins are associating with RING proteins and ubiquitin E3 ligases. This complex regulates in various cellular processes, including proliferation, differentiation, and apoptosis. Loss of *PBRM1* activity is also associated with chromosomal instability due to its inability to promote cohesion[10]. Because of the presence of *PBRM1* mutation, we search for chromosomal instability using TITAN software. Titan is a Python/R package for analyzing subclonal copy number alterations (CNA) and loss of heterozygosity (LOH) in whole genome and exome sequencing of tumors[11]. We observed a ploidy near 3, 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 of one. Interestingly, we observed a large chromosome 7 amplification containing *EGFR* gene locus, resulting in the presence of 3 copies of the *EGFR* gene (Figure 1A). Extensive analysis of 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. Two weeks 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 contrast, we did not observe any changes in tumor characteristic 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), thus suggesting the presence of intrinsic tumor resistance mechanism to anti *EGFR* therapy.

The primary tumor contains 2 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 of about 25%[12,13]. Because of the rarity of the disease, few trials address the therapeutic strategy to treat metastatic PACC. 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 few information on underlying genetic alterations that dictate the development of pancreatic acinar cell carcinoma. Only a study of 23 cases of PACC 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 do not observe any mutations in these genes in our patient.

Pancreatic acinar cell carcinoma presents frequently large number of chromosomal alterations and a major intratumoral heterogeneity. These data suggest that these tumors are chromosomally unstable[15], although mechanism (s) which explain chromosomal instability is 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 cases, 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 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 neither on *KRAS* nor on *NRAS* gene in our patient. We observed for the first time that amplification in *EGFR* locus in a PACC. 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 bioinformatics analysis of copy number alterations. Indeed, this analysis underlined that primary tumor contained 2 clones while liver metastasis contained only the anti EGFR sensitive clone. 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 amplification16. 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 is the first description of a major and rapid response of PACC to anti *EGFR* therapy related to *EGFR* amplification. This report also gives rational to perform multiple biopsy 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 *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***

CT-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 target in rare cancer 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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**Figure 1 Representation of chromosomal amplification and deletion in chromosome 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 mansion by a red arrow.



**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 mansion by a black arrow.