case reports

Exceptional Clinical Response to Alectinib in Pancreatic Acinar Cell Carcinoma With a Novel ALK-KANK4 Gene Fusion

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INTRODUCTION

Pancreatic acinar cell carcinoma (PACC) is a rare cancer accounting for approximately 1% of exocrine pancreatic tumors.[1] If compared with the most frequent pancreatic ductal adenocarcinoma (PDAC),[2] patients affected by PACC are diagnosed at a significantly younger age, present with an earlier stage disease, and, thus, are more likely to undergo potentially curative resection. Even if presenting in advanced unresectable stage, patients affected by PACC maintain a better prognosis than those with PDAC with a 5-year survival rate of 22%.[3] However, evidence regarding systemic treatments is limited in this rare subtype of pancreatic neoplasms, so the role of chemotherapeutic regiments for PACC remains poorly defined, and novel therapies are urgently needed.[4]

Initial whole-exome sequencing analysis of resected PACC revealed potentially actionable genetic alterations in more than one third of these cases, including mutations in *BRCA2*, *PALB2*, *ATM*, *BAP1*, *BRAF*, and *JAK1*.[5] More recent comprehensive genomic profiling of a larger series of PACC identified recurrent rearrangements involving the actionable genes *BRAF* and *RAF1* in approximately 23% of tumors. These *RAF* genomic alterations were mutually exclusive with inactivating alterations in DNA repair genes observed in 45% of PACC.[6] Small-molecule inhibitors with activity against RAF demonstrated clinical activity in patients with PACC-positive for RAF1 gene fusions.[7]

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that can be mutated in several tumors, more commonly in 3%-7% of non–small-cell lung cancer (NSCLC), resulting in dysregulation and inappropriate signaling through the ALK kinase domain. Activation of the *ALK* gene can occur by rearrangements with partner genes, point mutations, or amplification. The most common partner gene is echinoderm microtubule-associated protein-like 4 (*EML4*), although a variety of other fusion partners have been identified.[8] Alectinib is an oral ALK tyrosine kinase inhibitor approved as a first-line therapy option for patients with ALK-positive metastatic NSCLC.[9]

Rearrangements of ALK genes are extremely rare events in PDAC accounting for only 0.16% of the case. ALK rearrangements are mutually exclusive with mutations of KRAS and are present exclusively in patients younger than 50 years.[10] Patients with ALK-positive PDAC had clinical response if treated with first- or second-generation ALK inhibitors including alectinib. In patients developing resistance under alectinib, acquired point mutations of resistance (G1202R and V1180L) have been identified in addition to ALK translocation. These patients, however, demonstrated clinical benefit on the third-generation ALK inhibitor lorlatinib.[11]

Here, we present the first case in literature of a patient affected by advanced PACC with a novel ALK fusion partner, KN Motif And Ankyrin Repeat Domains 4 (*KANK4*), who achieved a major response under treatment with alectinib.

CASE REPORT

A 62-year-old man with no relevant medical history and no family cancer history was diagnosed with a mass at the head of the pancreas in January 2019. He underwent duodenocephalopancreasectomy, and the histologic report revealed a PACC, pT3N1, and R1. Grossly, the tumor presented as a 4.5-cm mass located into the pancreas head. On microscopic examination, tumor cells were arranged in nodules separated by thin bundles of stroma (Fig 1A). At higher magnification, tumor cells described luminal spaces, and cytologically, they presented quite regular round nuclei with fine chromatin and prominent nucleoli (Fig 1B). Morphologic features were consistent with a PACC. However, alternative diagnosis of neuroendocrine neoplasm was considered, but it was subsequently rejected because of the negative immunohistochemical stains for chromogranin A and synaptophysin (Figs 1C and 1D).

In March 2019, basal computed tomography (CT) scan for the potential postoperative treatment revealed two liver metastases. There are no standard guidelines for chemotherapeutic treatment in this rare pancreatic

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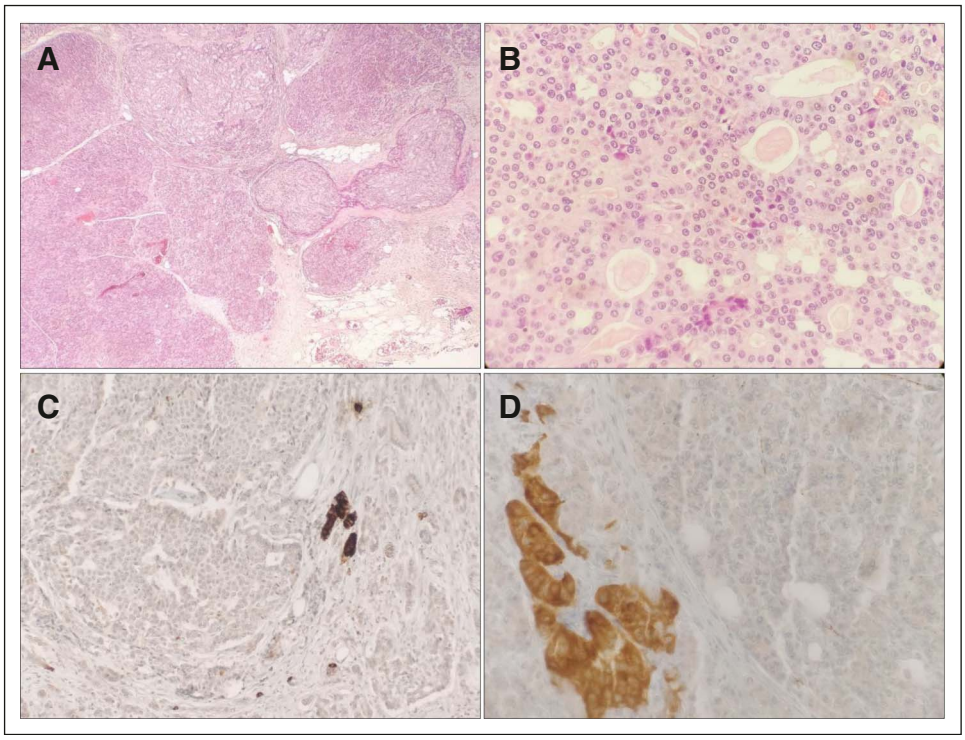

FIG 1. Histologic features of the tumor. (A) Micrograph of the lesion, consisting of large nodules of tumor cells. (B) Micrograph of the tumor at higher magnification, showing tumor cells disposed in acinar structures and characterized by rounded nuclei with finely dispersed chromatin and conspicuous nucleoli. (C) Negative immunohistochemical reaction for chromogranin A with some scattered non–neoplastic-positive cells. (D) Negative immunohistochemical stain for synaptophysin with a remaining cluster of non–neoplastic-positive cells.

neoplasia. Although patients with PACC are generally excluded from the pancreatic cancer pivotal trials, standard treatment for PDAC is also commonly used in this uncommon histology. Therefore, the patient received first-line chemotherapy with a gemcitabine plus nab-paclitaxel regimen for three cycles from April to July 2019. Because of a RECIST disease progression, the patient received second-line chemotherapy with fluorouracil, leucovorin, and irinotecan. After 3 months of treatment, the patients achieved with a partial response as documented at CT scan in October 2019. The patient continued the treatment for another 3 months until February 2020 when CT imaging showed disease progression as enlargement of the liver lesions and of abdominal lymph nodes. The patient was then switched to fluorouracil, leucovorin, and oxaliplatin but showed a further disease progression as enlargement of the liver lesions and of abdominal lymph nodes at CT scan in September 2020.

The patient referred to our unit in November 2020, and next-generation sequencing (NGS) was performed on archival tissue from last resection by using a FoundationOne CDxF1CDx assay (F1CDx). The patient consent was obtained for publication of his genomic and clinical data. This NGS assay detected several genomic alterations, including an additional sex combs-like 1 (*ASXL1*) R596fs*107 and a BCL6 corepressor-like 1 (*BCORL1*) V937fs*10 point mutations and, in particular, a novel *KANK4-ALK* gene fusion. Fluorescence in situ hybridization confirmed that more than 90% of tumor cells showed separated green and red signals or single red signals of rearranged *ALK* (Fig 2A). Cytoplasmic expression of the protein was detected in tumor cells by immunohistochemistry analysis while the rest of cells were completely negative (Fig 2B). On the basis of this finding, he was switched to therapy with alectinib 600 mg twice daily. Treatment received approval by local ethics committee.

At baseline to alectinib in December 2020, CT scan imaging showed a progression of disease if compared with previous examination of September 2020 as a novel bulky supraclavicular left lymph node (Fig 3A) and a further enlargement of the liver lesions (Fig 3D) and of the abdominal lymph nodes (Fig 3G), compatible with the absence of active treatment during these months. This radiologic progression paralleled a clinical deterioration with anorexia, weight loss, and onset of pain. Gamma-glutamyl transferase and alkaline phosphatase serum levels increased to 346 UI/L and 544 UI/L, respectively. The cancer antigen 19.9 level was 43.1 U/mL.

In January 2021, the patient started the treatment with alectinib, in the absence of adverse events. The 2-month follow-up CT imaging showed a RECIST partial response with a decrease in size of the supraclavicular left lymph node (48-23 mm; Fig 2B) of the liver lesions (83-44 mm; Fig 3E) and complete resolution of the abdominal lymph nodes (Fig 3H). Furthermore, the 4-month follow-up CT imaging in May 2021 confirmed a RECIST partial response with a decrease in size of the supraclavicular left lymph node (11 mm; Fig 3C) of the liver lesions (21 mm; Fig 3F) and complete resolution of the abdominal lymph nodes (Fig 3I). His clinical conditions rapidly improved with complete resolution of pain, weight gain, and subjective well-being. He did not present any adverse event by alectinib. Gamma-glutamyl transferase

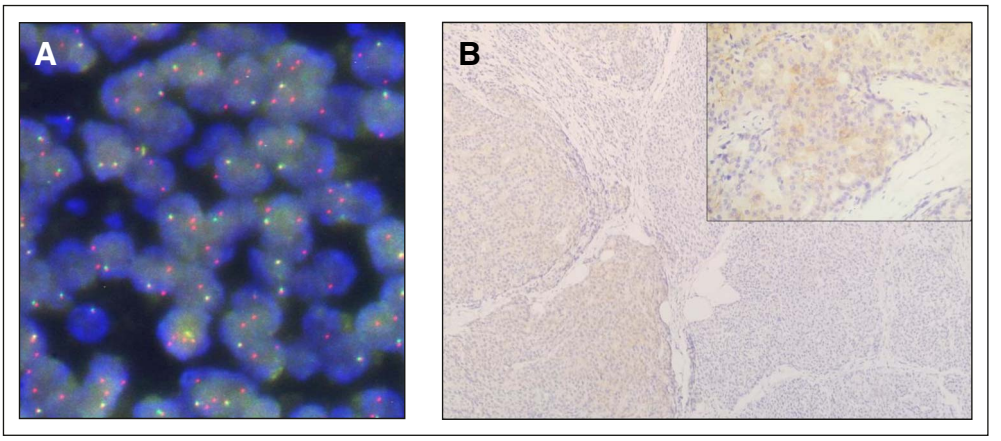

FIG 2. (A) Fluorescence in situ hybridization analysis using a break-apart probe. A fusion of the red and green signals corresponds to the intact chromosome, and the split signals are indicative of the *ALK* rearrangement. (B) Immunohistochemistry for ALK by using 5A4 antibody. Tumor cells show cytoplasmic expression of the protein (40×) while the rest of cells are completely negative (10×). ALK, anaplastic lymphoma kinase.

and alkaline phosphatase decreased to normal values. The cancer antigen 19.9 level dropped at 28.3 UI/mL. The patient is alive and well at the time of writing; the duration of survival from diagnosis is currently 32 months.

DISCUSSION

Adoption in clinical diagnostics of comprehensive tumor molecular profiling obtained by applying NGS technologies has led to benefiting a greater fraction of patients with cancer with personalized treatment approaches. In this novel scenario, cancers of the pancreas still remain as largely orphan diseases, mainly allocated to standard chemotherapeutic treatments with often disappointing disease responses. In patients affected by PDAC, the most frequent actionable mutations present in approximately 15% of tumor samples belong to the family of genes involved in DNA repair, potentially leading to a sensitivity to poly (ADP-ribose) polymerase-1 inhibitors.[7] In PACC, however, a radically different mutational landscape has been identified if compared with the more frequent PDAC, with recurrent rearrangements involving the actionable genes *BRAF* and *RAF1* in 23% of the cases.[6]

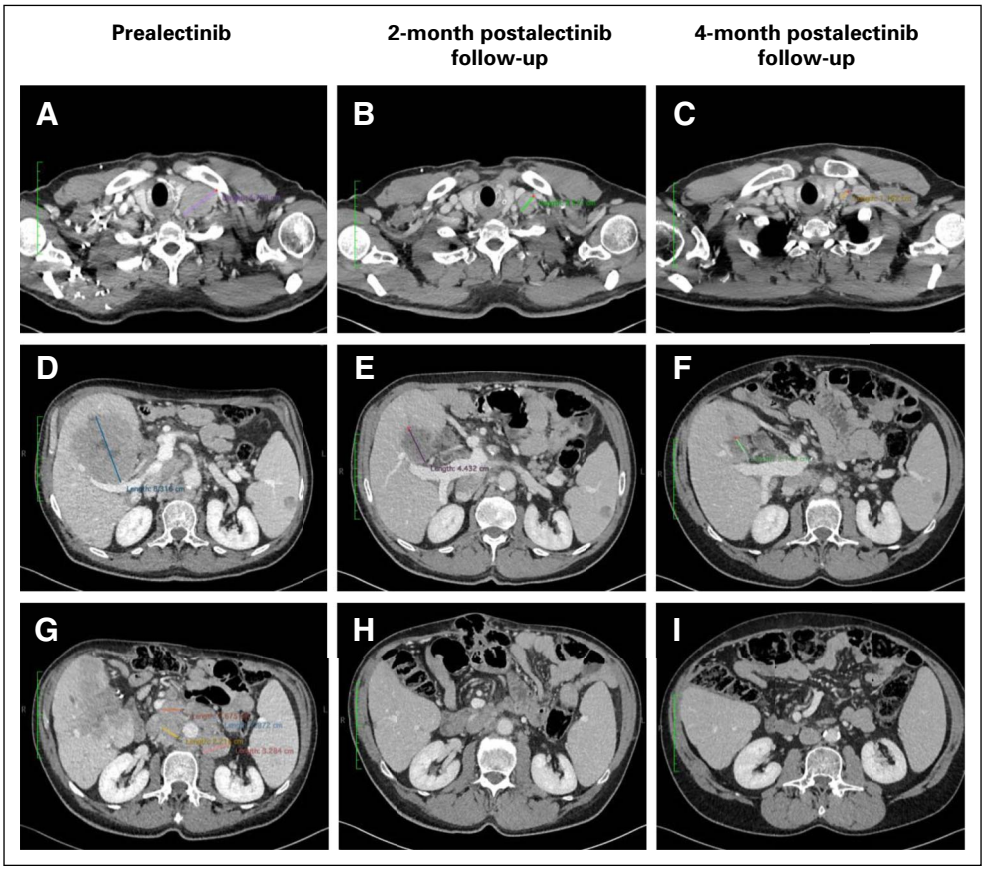

FIG 3. CT scan showing (A) supraclavicular left lymph node, (D) liver, and (G) abdominal lymph nodes before and during treatment with alectinib after the detection of a novel KANK4-ALK genes fusion. After (B, E, and H) 2 and (C, F, and I) 4 months of alectinib, CT scan detected decreasing of target metastasis. Colored lines indicate lesions' major diameters. CT, computed tomography.

ALK rearrangements are extremely rare in PDAC, with only five cases positive of 3,170 cases in the largest series studied.[10] To our knowledge, here, we reported for the first time the detection of an *ALK* rearrangement in a patient affected by PACC.

The most common partner genes in *ALK* rearrangements detected in NSCLC as well as in PDAC is *EML4*, but other ALK fusion proteins have also been described, including KIF5B-ALK, TFG-ALK, KLC1-ALK, PTPN3-ALK, and STRN-ALK.[12] In our case of PACC, *ALK* presented a rearrangement with *KANK4*, a new partner not previously detected in other ALK-mutated cancers. More interestingly, we recently identified a different case of PACC-positive for a rearrangement of *KANK4* with *RAF1*. This novel fusion gene was pathogenetic, and the patient achieved a radiologic partial response maintained for almost 1 year with the RAF inhibitor sorafenib.[7] The reasons for these frequent fusion genes involving *KANK4* in PACC deserve further explorations.

Most importantly, the *KANK4-ALK* fusion gene identified in this PACC was highly pathogenetic. Treatment with the ALK inhibitor alectinib obtained a radiologic partial response after 2 months of treatment and continued at 4 months. This paralleled with a significant improvement in the clinical performance status of the patient. The deepness of the response obtained with alectinib in this patient was far greater than those obtained with previous chemotherapeutic regimens, considering also that the longest period of treatment with the same scheme of chemotherapy lasted no more than 6 months.

In conclusion, this is, to our knowledge, the first report for a *KANK4-ALK* rearrangement as an oncogene driver in solid tumors, the first description of an *ALK* rearrangement in PACC, and the first reported patient with PACC to be treated with alectinib.

There is no current indication to perform tumor multigene NGS in patients with advanced pancreatic neoplasms.[13] However, comprehensive genomic profiling of PACC revealed potentially actionable genetic alterations in a significant proportion of patients. The detection of druggable molecular targets as *ALK* rearrangements, despite the low frequency of these alterations, might offer to patients with PACC a chance of good clinical and objective responses with a gain in survival and quality of life and contribute to strength the recommendation for the use of NGS also in this dismal disease.[14] This case report corroborates the indication for patients affected by these rare tumors to be treated in higher-volume cancer centers to provide patients with more experience and access to NGS diagnostic resources. Most importantly, it raises enthusiasm and hope toward precision medicine and tailored treatments for patients with PACC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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