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Case Report

Pancreatic Adenocarcinoma with Co-Occurrence of *KRAS* and *EGFR* Mutations: Case Report and Literature Review

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Keywords
Pancreatic duct cell carcinoma · *KRAS* · *EGFR* · Case report · Erlotinib hydrochloride

Abstract

Introduction: Mutation in *Kristin ras sarcoma virus (KRAS)* oncogene is the main driver in pancreatic ductal adenocarcinoma (PDAC) and is present in nearly 90% of patients with PDAC. *Epidermal growth factor receptor* (*EGFR*) mutation is rare in PDAC and is mostly present in the absence of *KRAS* mutation. Co-occurrence of *KRAS* and *EGFR* mutations is extremely rare, and the value of EGFR inhibition in these cases is unknown. ***Case Presentation:*** Here, we present a case of metastatic PDAC with co-occurrence of *KRAS* G12V and *EGFR* L730R. Despite primary resistance to folinic acid, fluorouracil, irinotecan, oxaliplatin, and gemcitabine/nab-paclitaxel, this patient had a biochemical response (decrease in carbohydrate antigen 19-9) and disease control of 7 months on gemcitabine/erlotinib (an EGFR inhibitor). This outcome is remarkable in the late-line PDAC treatment setting and is unusual after the progression of the tumor on gemcitabine/nab-paclitaxel chemotherapy. ***Conclusion:*** This case suggests that gemcitabine/erlotinib could be an effective treatment in patients with PDAC and co-occurrence of *EGFR* and *KRAS* mutations.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a deadly cancer with a 5-year survival rate of about 12% [1]. It mostly presents as advanced or metastatic disease, and conventional palliative chemotherapy remains the mainstay of therapy [2]. Gemcitabine/erlotinib is a

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chemotherapy/targeted therapy combination with FDA approval in advanced/metastatic PDAC [3]. Due to only modest clinical benefit with this treatment (median progression-free survival of 3.75 months in gemcitabine/erlotinib vs. 3.55 months in gemcitabine alone), and the emergence of active chemotherapies such as folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX) and gemcitabine/nab-paclitaxel, this regimen is not commonly used in clinical practice and is not covered by insurance in some countries [4, 5].

PDAC is a molecularly complex disease, with high dependence on the receptor tyrosine kinase/RAS/mitogen-activated protein kinase signaling pathway [6]. In nearly 90% of PDAC tumors, activation of this pathway happens through mutations in the *Kristin ras sarcoma virus (KRAS)* oncogene. In the remaining 10% of PDAC tumors without *KRAS* mutation (*KRAS* wild-type), receptor tyrosine kinase/RAS/mitogen-activated protein kinase pathway activation is still common (~40%) and typically occurs through *BRAF* alterations, kinase gene fusions, and less commonly through mutations in other genes such as e*pidermal growth factor receptor* (*EGFR*) [6]. Due to the redundancy in function, alterations of *EGFR* and *KRAS* in PDAC are mostly mutually exclusive with *KRAS* mutations [6]. Here, we present a unique case of PDAC with co-occurrence of *KRAS* and *EGFR* mutations with clinically meaningful disease stability of 7 months with gemcitabine/erlotinib in metastatic late-line setting despite having tumor progression after gemcitabine/nab-paclitaxel chemotherapy.

Case Report

Our patient was a 64-year-old Caucasian woman, non-smoker, with adenocarcinoma of the pancreas. Figure 1 represents the timeline of events in this patient. She initially presented with a mass in the head of the pancreas causing jaundice (staging per TNM 8th edition 2017: T3, N0, M0; stage IIA) and needed biliary stent placement. Carbohydrate antigen 19-9 (CA19-9) level upon normalization of bilirubin was 673 (normal CA19-9 is ≤ 35 units/mL). The patient was treated with 12 cycles of neoadjuvant-modified FOLFIRINOX, which decreased CA19-9, but without normalization (CA19-9 81 U/mL at this point). Following Whipple surgery, CA19-9 normalized. Surgical pathology showed 4.1 cm moderately differentiated ductal adenocarcinoma arising in the pancreatic head with invasion of peripancreatic soft tissue and extension into ampulla wall, without significant therapy-related response, and 3 of 15 lymph nodes positive for metastatic carcinoma. Margins of surgery were negative, and TNM staging was ypT3, ypN1. The patient was treated with adjuvant concurrent chemoradiation with weekly gemcitabine. In less than 3 months after completion of treatment, however, CA19-9 started to rise with serial imaging showing the emergence of multiple pulmonary nodules. Nearly 8 months after completion of adjuvant therapy, the patient underwent robotic-assisted left thoracoscopy with wedge resection of two of the lung nodules, to establish the diagnosis of lung metastasis and to provide further tissue for genomic profiling of the tumor. Pathology confirmed that the lung nodules were of pancreatic origin. The tissue obtained from the wedge resection was sent for clinical-grade comprehensive genomic profiling to Tempus [7], with the report showing the presence of *EGFR* p.L730R, *ELF2* p.T129fs, *CDKN2A* p.H83N, *TP53* p.C124R, *SMAD4* p.S178*, and *KRAS* p.G12V mutations in the tumor (Table 1). A follow-up blood-based tumor-normal paired analysis showed that the *EGFR* p.L730R was a germline mutation. Family history was positive for pancreatic cancer in the father (no germline evaluation was performed for the father). Considering the lack of response to FOLFIRINOX on the surgical pathology, she was started on gemcitabine/nab-paclitaxel therapy. Unfortunately, the tumor progressed on this treatment in 2 months (radiographic progression with emergence of multiple new pulmonary and hepatic

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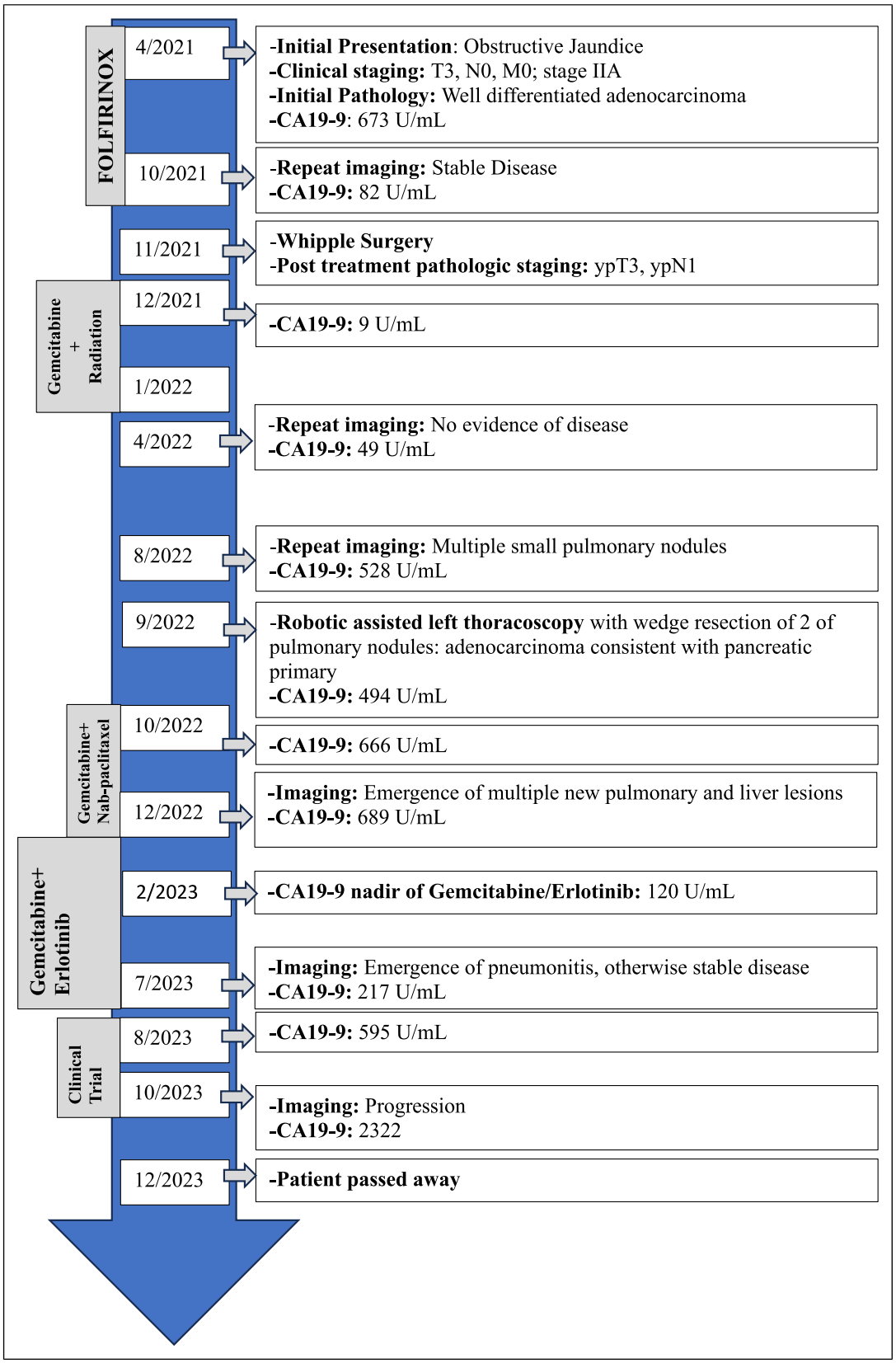

Fig. 1. Timeline of events in our patient.

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Table 1. List of mutated genes

NGS vendor	Genomic alterations (VAF), *n* (%)	Type of mutation[a]
Tempus[b]	*EGFR* p.L730R (47)	Exon 19 missense mutation – GOF
	KRAS p.G12V (6.8)	Exon 2 missense mutation – GOF
	CDKN2A p.H83N (7.6)	Missense mutation – LOF
	ELF2 p.T129fs (12.4)	Frameshift – LOF
	SMAD4 p.S178* (7.4)	Stop gain – LOF
	TP53 p.C124R (7.5)	Missense mutation – LOF

GOF, gain of function; LOF, loss of function; NGS, next-generation sequencing; VAF, variant allele frequency. [a]As identified on original Tempus report. [b]Total 648 genes tested; pertinent negative mutations: *ATM*, *BRCA1/2*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *STK11*.

lesions). Considering the presence of *EGFR* p.L730R mutation, treatment was changed to gemcitabine (1,000-600 mg/m^2, adjusted per cytopenia; first 2 cycle days 1, 8, and 15 of 28-day cycle, cycles 3, and onward every other week due to the emergence of cytopenia) and erlotinib (a tyrosine kinase and EGFR inhibitor; applied dosage: 100 mg daily, approved dosage: 100 mg daily). Fortunately, this was followed by stabilization of the tumor size on imaging and declining CA19-9 (Fig. 2). The patient remained on this treatment for 7 months, after which treatment was discontinued due to the emergence of pneumonitis, a known potential side effect of this combination therapy. This was followed by the progression of the tumor based on both imaging and serial CA19-9 levels (Fig. 2). The patient had a resolution of pneumonitis after a course of corticosteroids. She went on to receive treatment then as part of a clinical study (NCT05802069), but unfortunately had continued progression of the disease. She passed away in December 2023. As a side note, a completed CARE Checklist has been completed by the authors for this case report, and it has been attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536552).

Discussion

PDAC is largely driven by *KRA*-activating mutations [6]. *EGFR* mutation is a rare occurrence in PDAC and most commonly occurs in patients with *KRAS* wild-type tumors [6]. In a study that included 3594 PDAC samples, *EGFR* mutation prevalence was categorized by *KRAS* mutational status. *EGFR* mutation was detected in 4.3% of *KRAS* wild-type tumors and 0.35% of *KRAS*-mutated tumors [6]. The potential clinical value of EGFR inhibition in patients with *KRAS* wild-type PDAC and *EGFR* mutation has been previously reported in case reports, with responses lasting 12–13 months [8, 9]. The value of EGFR inhibition in PDAC patients with co-occurrence of *EGFR* and *KRAS* mutations is less clear, mostly due to its rarity. Most data in this setting come from the Asian population due to the increased prevalence of *EGFR* mutation in this population, in general [10]. In a study of Chinese patients with PDAC (83/88 with *KRAS* mutation), treatment with gemcitabine/erlotinib in 26 patients with *EGFR* mutation was associated with a median progression-free survival of 5.9 months [10]. In our patient with co-occurrence of *KRAS* G12V and *EGFR* L730R mutations, treatment with gemcitabine/erlotinib was associated with progression-free survival of 7 months. In the clinical trial that established the role of gemcitabine/erlotinib combination in patients with metastatic and advanced PDAC (biomarker unselected patients), treatment with gemcitabine/erlotinib in the first-line setting

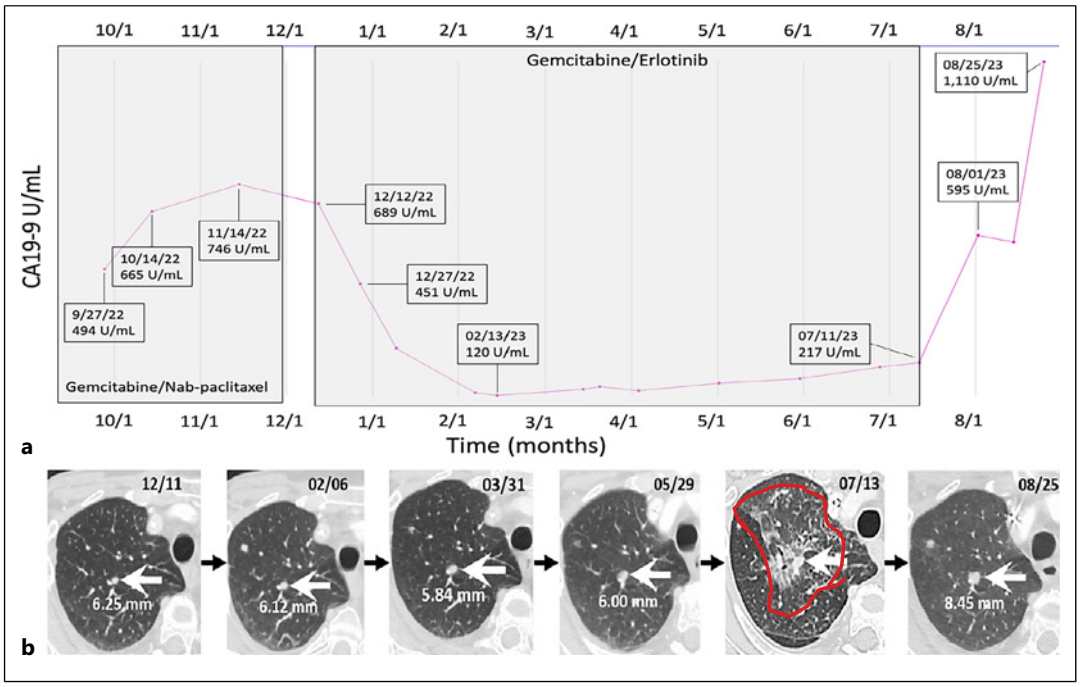

Fig. 2. Serial imaging and tumor marker (CA19-9) while on gemcitabine/erlotinib. **a** CA19-9 level declined on gemcitabine/erlotinib (indicating response), with a fast rise after discontinuation of this treatment (indicating disease progression). **b** The white arrow points to a represented right upper lobe pulmonary nodule (area of metastasis of pancreatic cancer to the lung). The represented nodule was stable while on gemcitabine/erlotinib (size is measured by the radiologist on the same axis in all images and is indicated in each image). The CT scan taken on 07/13 represents the emergence of pneumonitis (representative area marked by red lining) at which time gemcitabine/erlotinib was discontinued. CT scan on 08/25 shows resolution of pneumonitis with steroid treatment but an increase in the size of the represented nodule (indicating tumor growth). Innumerable other sub-centimeter nodules in bilateral lungs progressed within the same timeline after discontinuation of gemcitabine/erlotinib (not shown here).

was associated with median progression-free survival of 3.75 months [3]. Notably, in the multivariable Cox regression analysis in this study, female sex was associated with longer overall survival. The same effect was not reported for progression-free survival [3]. The CA19-9 response to gemcitabine/erlotinib and the disease stability of 7 months in our case in late-line treatment of PDAC are therefore intriguing, specifically in the setting of previous chemotherapy and gemcitabine resistance.

Most data about the role of EGFR inhibition in the presence of *EGFR* mutation come from non-small cell lung cancer (NSCLC). Even in NSCLC, however, co-occurrence of *KRAS* and *EGFR* mutations is rare. In a study from China evaluating 5,125 patients, co-occurrence of *KRAS* and *EGFR* was reported in 30 patients (0.6%) [11]. Benesova et al. [12] reported on the outcomes of 3 patients with NSCLC and co-occurrence of *KRAS* and *EGFR* mutations, treated with EGFR tyrosine kinase inhibitors. EGFR inhibition was associated with partial response in all three, lasting for 3–7 months. The authors speculated that the response might have been due to the presence of subpopulations of cells bearing only a single mutation at a time (*EGFR* or *KRAS*). They argued that the initial response might be due to the response of *EGFR*+ and *KRAS*- cells, and the later progression was due to the dominance of *EGFR*-/*KRAS*+ or *EGFR*+/*KRAS*+ tumor cells [12]. While this could explain the rationale behind disease stability for 7 months on gemcitabine/erlotinib in the case of our patient, this hypothesis cannot be verified without

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evaluation of molecular alterations at a single-cell setting. Furthermore, while the presence of *KRAS* mutation in PDAC is associated with poor prognosis, its predictive value regarding response to EGFR inhibition is debated [13]. Post hoc biomarker analysis of the CONKO-005 trial (gemcitabine +/− erlotinib as adjuvant therapy for PDAC) did not show *KRAS* mutation status as a reliable biomarker of response to erlotinib [13].

KRAS G12V mutation which was present in our patient presented in this case report is a missense mutation in exon 2 of the *KRAS* gene. This is the second most common pathogenic *KRAS* mutation in PDAC, following *KRAS* G12D mutation [14]. There is debate about the prognostic value of *KRAS* G12V mutation in PDAC. Available literature so far supports favorable prognosis associated with *KRAS* wild-type, and *KRAS* G12R-mutated tumors, as opposed to *KRAS* G12D-mutated tumors [15]. *KRAS* G12V mutation is associated with resistance to EGFR inhibition in colorectal cancer [16, 17].

EGFR L730R is a missense mutation in exon 19 of the *EGFR* gene. This is an extremely rare mutation, currently classified as a variant of unknown significance as a germline cancer-predisposing gene based on the ClinVar database [18]. While interpreted as somatic, this gene was reported as a gain of function mutation in the Tempus report of our patient. Somatic mutations in this gene are reported in NSCLC case reports [19–21]. The role of *EGFR* L730R in the prediction of erlotinib response in NSCLC remains controversial. Oyaert et al. [20] reported a case of NSCLC with co-occurrence of *EGFR* L858R, L730R, and T790M, with partial response to erlotinib lasting for 11 months. de Wit et al. [19] identified this mutation in 2 patients, both of whom had disease progression after 2 months of erlotinib. The disease stability on erlotinib in our case might suggest erlotinib sensitivity with *EGFR* L730R mutation. However, due to a lack of functional and drug response evaluations at a cellular level, this correlation remains hypothetical.

Our case report represents one example of how next-generation sequencing can facilitate the utilization of targeted therapy directed against the unique molecular features of the tumor in an individual. Presently, the identification of certain alterations in PDAC can lead to the application of certain FDA-approved treatments [22]. Patients with *KRAS* wild-type tumors have numerous targeted therapy options dependent on the driver mutation in their tumors [22]. PARP inhibition can be utilized in those with *BRCA*1/2 and *PALB*2 mutations [23]. Immunotherapy can be utilized in patients with mismatch repair deficient tumors [24]. With the emergence of KRAS inhibitors, and novel KRAS-targeted immunotherapies, the percentage of patients that could benefit from personalized targeted and immunotherapy will expand further [25]. Considering the sub-optimal outcomes with chemotherapy, the emergence of multiple new novel systemic therapies, and the refractoriness of disease to treatment in the late-line setting, early and universal utilization of genomic profiling and genetic testing should be considered in all patients with PDAC [26].

Our patient unfortunately eventually passed away from her pancreatic cancer. Considering the uniqueness of her case, and uncertainties along the way, it took great bravery, trust, and hope on her part to proceed with the treatment. She cherished the extra months that this treatment provided her, spent it with her family, and continued the activities that were dear to her throughout treatment. Fortunately, she did not experience a significant financial burden from the performance of genomic profiling, or the administration of genomic profiling-based treatment as the treatment in her case was otherwise FDA-approved for pancreatic cancer.

Our article is based on data from a single patient which limits our study. Therefore, it should be interpreted with caution. Considering the lack of single-cell molecular evaluations, our understanding of the tumor heterogeneity and clonality in this case is limited. Furthermore, without functional characterization of *EGFR* L730R mutation and its response to erlotinib at the cellular level, the role of *EGFR* L730R mutation in response to erlotinib remains hypothetical.

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Conclusion

With the wide and timely availability of NGS, targeted therapies such as erlotinib can be utilized more selectively in patients with PDAC. In biomarker unselected PDAC patients, the clinical benefit of erlotinib in addition to gemcitabine remains debated. In our current case, the presence of *EGFR* L730R mutation in the tumor led to the decision to use gemcitabine/erlotinib. This was associated with disease stability of 7 months, an outcome which is remarkable in late-line metastatic PDAC treatment. The patient's lack of progression on gemcitabine/erlotinib (despite having tumor progression after gemcitabine/nab-paclitaxel chemotherapy) might reflect the sensitivity of *EGFR* L730R, and extremely rare mutation in cancers specifically PDAC, to erlotinib. This case furthermore suggests a potential value for the combination of gemcitabine/erlotinib in patients with PDAC with co-occurrence of *KRAS* and *EGFR* mutations. Lastly, this case represents the value of genomic profiling in patients with PDAC.

Statement of Ethics

An informed consent was obtained from the patient prior to passing to participate in this study as part of the MCW Master Predict protocol (NCT05802069) approved by Medical College of Wisconsin Institutional Review Board, which would allow for publication of the details of their medical case and any accompanying images. This study followed the Medical College of Wisconsin Internal Review Board-approved observational protocol (NCT05802069; MCW Master Predict [Profile Related Evidence Determining Individualized Cancer Therapy]), approval number PRO00044894. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images prior to her passing away.

Conflict of Interest Statement

Kamgar M. receives research funding from Cornerstone Pharmaceuticals. Mody J. declares no conflict of interests.

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Author Contributions

Contributed to conception and interpretation of data: Kamgar M. Contributed to manuscript preparation: Mody J. and Kamgar M.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons. They are available from Dr. Mandana Kamgar, MD, MPH (corresponding author), upon request.

References

1 Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48.
2 Kamgar M, Chakrabarti S, Shreenivas A, George B. Evolution of systemic therapy in metastatic pancreatic ductal adenocarcinoma. Surg Oncol Clin N Am. 2021;30(4):673–91.
3 Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25(15):1960–6.
4 Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
5 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
6 Singhi AD, George B, Greenbowe JR, Chung J, Suh J, Maitra A, et al. Real-time targeted genome profile analysis of pancreatic ductal adenocarcinomas identifies genetic alterations that might Be targeted with existing drugs or used as biomarkers. Gastroenterology. 2019;156(8):2242–53.e4.
7 Beaubier N, Tell R, Lau D, Parsons JR, Bush S, Perera J, et al. Clinical validation of the tempus xT next-generation targeted oncology sequencing assay. Oncotarget. 2019;10(24):2384–96.
8 Park R, Al-Jumayli M, Miller K, Saeed A, Saeed A. Exceptional response to Erlotinib monotherapy in EGFR Exon 19-deleted, KRAS wild-type, Chemo-refractory advanced pancreatic adenocarcinoma. Cancer Treat Res Commun. 2021;27:100342.
9 Patel GK, Perry JB, Abdul-Rahim O, Frankel AE, Cameron D, Taylor W, et al. Epidermal growth factor receptor-activating mutation(E746_T751>VP) in pancreatic ductal adenocarcinoma responds to erlotinib, followed by epidermal growth factor receptor resistance-mediating mutation (A647T): a case report and literature review. J Cancer Res Ther. 2020;16(4):950–4.
10 Wang JP, Wu CY, Yeh YC, Shyr YM, Wu YY, Kuo CY, et al. Erlotinib is effective in pancreatic cancer with epidermal growth factor receptor mutations: a randomized, open-label, prospective trial. Oncotarget. 2015;6(20):18162–73.
11 Li S, Li L, Zhu Y, Huang C, Qin Y, Liu H, et al. Coexistence of EGFR with KRAS, or BRAF, or PIK3CA somatic mutations in lung cancer: a comprehensive mutation profiling from 5125 Chinese cohorts. Br J Cancer. 2014;110(11):2812–20.
12 Benesova L, Minarik M, Jancarikova D, Belsanova B, Pesek M. Multiplicity of EGFR and KRAS mutations in non-small cell lung cancer (NSCLC) patients treated with tyrosine kinase inhibitors. Anticancer Res. 2010;30(5):1667–71.
13 Hoyer K, Hablesreiter R, Inoue Y, Yoshida K, Briest F, Christen F, et al. A genetically defined signature of responsiveness to erlotinib in early-stage pancreatic cancer patients: results from the CONKO-005 trial. EBioMedicine. 2021;66:103327.
14 Witkiewicz AK, McMillan EA, Balaji U, Baek G, Lin WC, Mansour J, et al. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. Nat Commun. 2015;6:6744.
15 Ardalan B, Ciner A, Baca Y, Darabi S, Kasi A, Lou E, et al. Prognostic indicators of KRAS G12X mutations in pancreatic cancer. J Clin Oncol. 2023;41(4_Suppl l):735.
16 Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008;359(17):1757–65.
17 McFall T, Stites EC. Identification of RAS mutant biomarkers for EGFR inhibitor sensitivity using a systems biochemical approach. Cell Rep. 2021;37(11):110096.
18 Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018;46(D1):D1062–7.
19 de Wit M, Gao Y, Mercieca D, de Heer I, Valkenburg B, van Royen ME, et al. Mutation and drug-specific intracellular accumulation of EGFR predict clinical responses to tyrosine kinase inhibitors. EBioMedicine. 2020;56:102796.
20 Oyaert M, Demedts I, Boone E, Dedeurwaerdere F, Vandorpe J, De Laere E, et al. Antitumoral activity of tyrosine kinase inhibitors in patients with non-small cell lung cancer harbouring rare epidermal growth factor receptor mutations. Mol Diagn Ther. 2015;19(5):267–72.
21 VandenBussche CJ, Illei PB, Lin MT, Ettinger DS, Maleki Z. Molecular alterations in non-small cell lung carcinomas of the young. Hum Pathol. 2014;45(12):2379–87.
22 Di Federico A, Tateo V, Parisi C, Formica F, Carloni R, Frega G, et al. Hacking pancreatic cancer: present and future of personalized medicine. Pharmaceuticals. 2021;14(7):677.
23 Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381(4):317–27.
24 Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409–13.
25 Bannoura SF, Uddin MH, Nagasaka M, Fazili F, Al-Hallak MN, Philip PA, et al. Targeting KRAS in pancreatic cancer: new drugs on the horizon. Cancer Metastasis Rev. 2021;40(3):819–35.
26 Tempero MA. NCCN guidelines updates: pancreatic cancer. J Natl Compr Canc Netw. 2019;17(5.5):603–5.