



# A case report of microsatellite instability (MSI)-high, *HER2* amplified pancreatic adenocarcinoma with central nervous system metastasis

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**Abstract:** Pancreatic adenocarcinoma commonly presents as metastatic disease and harbors a dire prognosis due to its aggressive behavior, propensity for resistance to therapies, and lack of targetable driver mutations. Additionally, despite advances in other cancers, immunotherapy has been ineffective in this disease thus far and treatment remains centered around cytotoxic chemotherapy. Here, we present a case of a patient with pancreatic adenocarcinoma harboring both high microsatellite instability (MSI-H) and *HER2* amplification. After an initial response to standard-of-care chemotherapy with FOLFIRINOX followed by progression, she was treated with dual immune checkpoint blockade, which resulted in a period of disease control. This was complicated by the development of autoimmune hypophysitis and an incidental finding of brain metastasis on magnetic resonance imaging (MRI). Her extracranial disease progressed while receiving stereotactic radiosurgery, with findings of lymphangitic spread in her lungs, and her treatment was changed to gemcitabine/nab-paclitaxel with trastuzumab. This resulted in a degree of extracranial disease control, though she experienced progressive brain metastases despite radiation and therapeutic switch to lapatinib and trastuzumab. Ultimately, the patient developed leptomeningeal disease which was not controlled by intrathecal trastuzumab. Given the rarity of central nervous system metastasis, *HER2* amplification, and MSI in pancreatic cancer, this patient's presentation represents a confluence of multiple unique features. This case highlights the clinical value of up-front next-generation sequencing in metastatic pancreatic cancer and the ability of pancreatic cancer with actionable molecular variants to develop atypical sites of disease and adaptive resistance.

**Keywords:** Microsatellite instability (MSI); pancreatic cancer; *HER2* amplification; brain metastasis; case report

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most deadly malignancies, frequently presenting as metastatic disease with over 57,000 new diagnoses and

47,000 deaths a year, as most patients with stage IV disease survive for less than 1 year (1). The vast majority lack targetable genomic variants, and the standard of care for patients with metastatic disease is cytotoxic chemotherapy. High microsatellite instability (MSI-H) occurs in roughly

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1% of PDAC cases, the majority of which have Lynch syndrome (2). In colon cancers which are MSI-H, response rates to anti-PD-1 antibody treatment approach 50% and are frequently durable (3); however, in PDAC, response rates are approximately 18% with dramatically shorter progression free survival, indicating that other immune resistance mechanisms play a role (4).

*HER2* (*ERBB2*) amplification is observed in approximately 2% of patients with PDAC (5) and evidence for anti-HER2 therapies in this patient population is limited. Further, *KRAS* mutations, which are common in metastatic PDAC, may attenuate the activity of anti-HER2 therapeutic strategies as has been observed with *HER2* amplified and *KRAS* mutated metastatic colorectal cancer (6). *HER2* amplification rarely co-occurs with MSI. In the Genomics, Evidence, Neoplasia, Information, Exchange (GENIE) database of over 90,000 advanced solid tumors only 105 patients (0.1%) had both *HER2* amplification and MSI-H (7).

Despite the aggressive behavior of PDACs, the disease rarely progresses to the central nervous system (CNS) (8). It is possible with prolonged therapy, more patients will develop CNS metastasis later in their disease course, however this event remains exceedingly uncommon in this population. Here, we describe a patient with MSI-H, *HER2* amplified pancreatic cancer. After progression on FOLFIRINOX, this patient responded to immunotherapy, then relapsed with brain metastasis. The patient then experienced a brief response to chemotherapy and anti-HER2 therapy, followed by progression with leptomeningeal disease. This case highlights the importance of obtaining up-front genomic profiling on patients with metastatic pancreatic cancer and exemplifies tumor adaptation under selective pressure. It also demonstrates the refractory nature of this malignancy and the need for a more sophisticated understanding of molecular drivers of treatment resistance.

We present the following case in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/acr-20-154>).

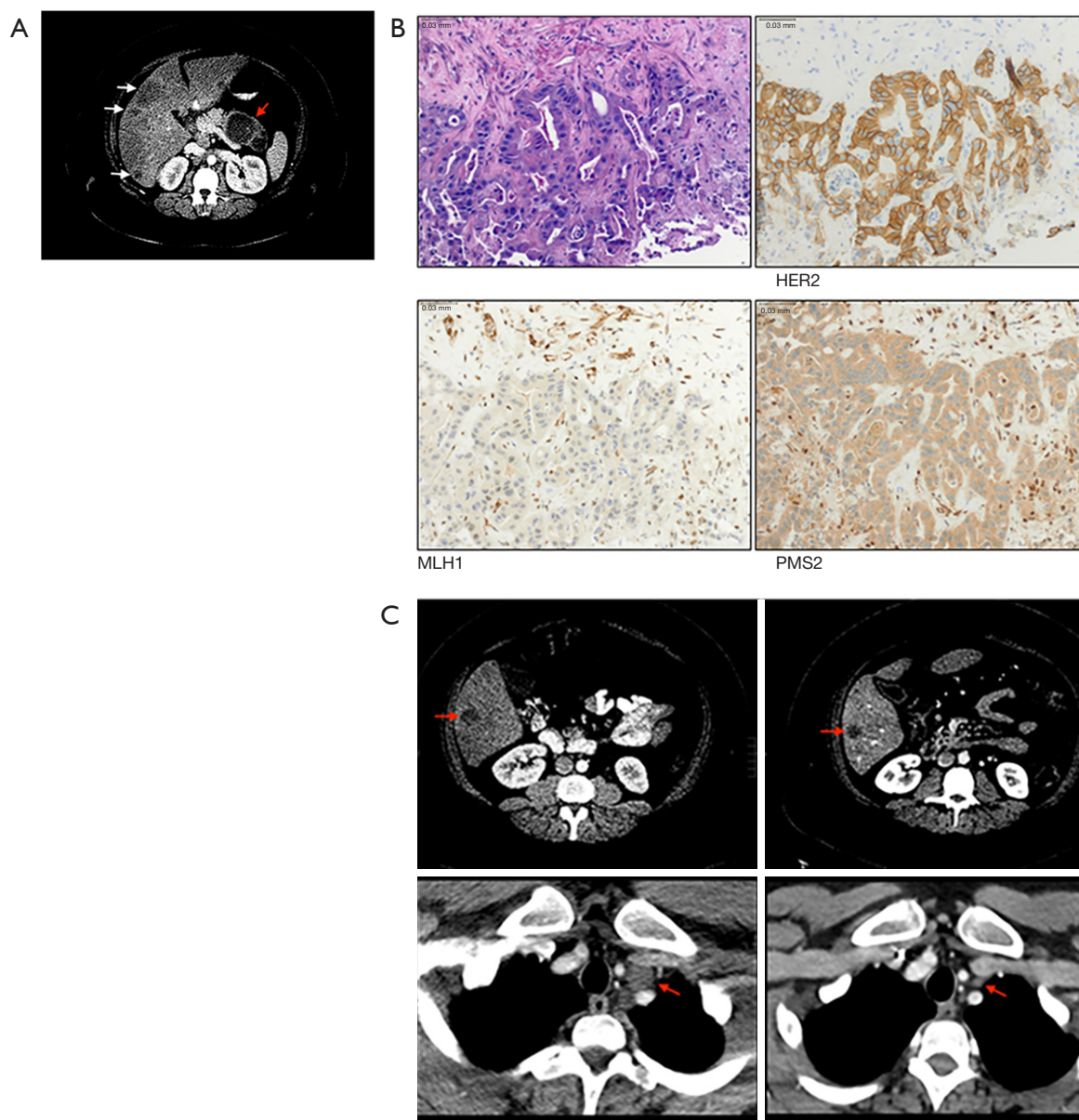
## Case presentation

A 43-year-old female with a history of hypertension, hyperlipidemia, and a 2-year history of type 2 diabetes mellitus presented with acute, intermittent mid-back pain over 2 months. After a visit to her primary care doctor, she underwent a workup for possible pulmonary embolism including a computed tomography (CT) pulmonary

arteriogram which was unremarkable. A CT of the abdomen and pelvis confirmed a septated pancreatic body/tail mass with multiple liver lesions (*Figure 1A*). Endoscopic ultrasound (EUS) with biopsy of pancreatic and liver masses confirmed adenocarcinoma, CK7<sup>+</sup>/CK20<sup>-</sup>, consistent with pancreatic primary and thus stage IV disease. CA19-9 was elevated at 6,600 U/mL. Upon presentation, she noted a weight loss of 15 pounds over a month, worsening glucose control, and fatigue. Next-generation sequencing (NGS; FoundationOneCDx, 2018) results from the liver metastasis revealed *KRAS* G12D and *TP53* W146 mutations as well as *ERBB2* amplification. Tumor mutational burden could not be determined. Immunohistochemistry (IHC) revealed 3+ staining for HER2 in 75% of tumor cells (*Figure 1B*). IHC for mismatch repair proteins showed loss of MLH1 and PMS2 expression (*Figure 1B*). MSI-H status was confirmed by PCR testing, which revealed an increased number of novel repeat lengths. *MLH1* was negative for promoter methylation. Germline testing for heritable mutations was negative (Invitae Custom Pancreatic Panel, 2018).

To alleviate her symptoms and expeditiously treat her, she was initiated on standard-of-care first line FOLFIRINOX with modest radiographic response after 4 cycles of treatment (*Figure 1C*). After 4 additional cycles, FOLFIRINOX was discontinued due to rising CA19-9 and clinical progression (*Figure 2A*). Given her MSI-H disease, she was switched to ipilimumab 1 mg/kg and nivolumab 3 mg/kg. This was chosen over anti-PD-1 monotherapy due to the inadequacy of response in non-colorectal MSI-H cancers (4). Shortly after initiating immunotherapy, her CA19-9 declined precipitously (*Figure 2A*) to 2,000 U/mL with substantially improved pain. After the fourth dose, she developed pruritis and a severe headache with blurry vision. A brain magnetic resonance imaging (MRI) revealed hypophysitis and multiple punctate brain metastases; cortisol was low (0.4 µg/dL), as was adrenocorticotropic hormone (ACTH) (19 pg/mL), follicle-stimulating hormone (FSH) (6.8 mIU/mL), luteinizing hormone (LH) (2.4 mIU/mL), and thyroid stimulating hormone (TSH) (0.04 µIU/mL). Her headache resolved with hydrocortisone and she was continued on maintenance nivolumab. After a month, she developed worsening gait instability. A subsequent brain MRI demonstrated isolated progression in two cerebellar lesions which were treated with stereotactic radiosurgery (SRS) (*Figure 2B*).

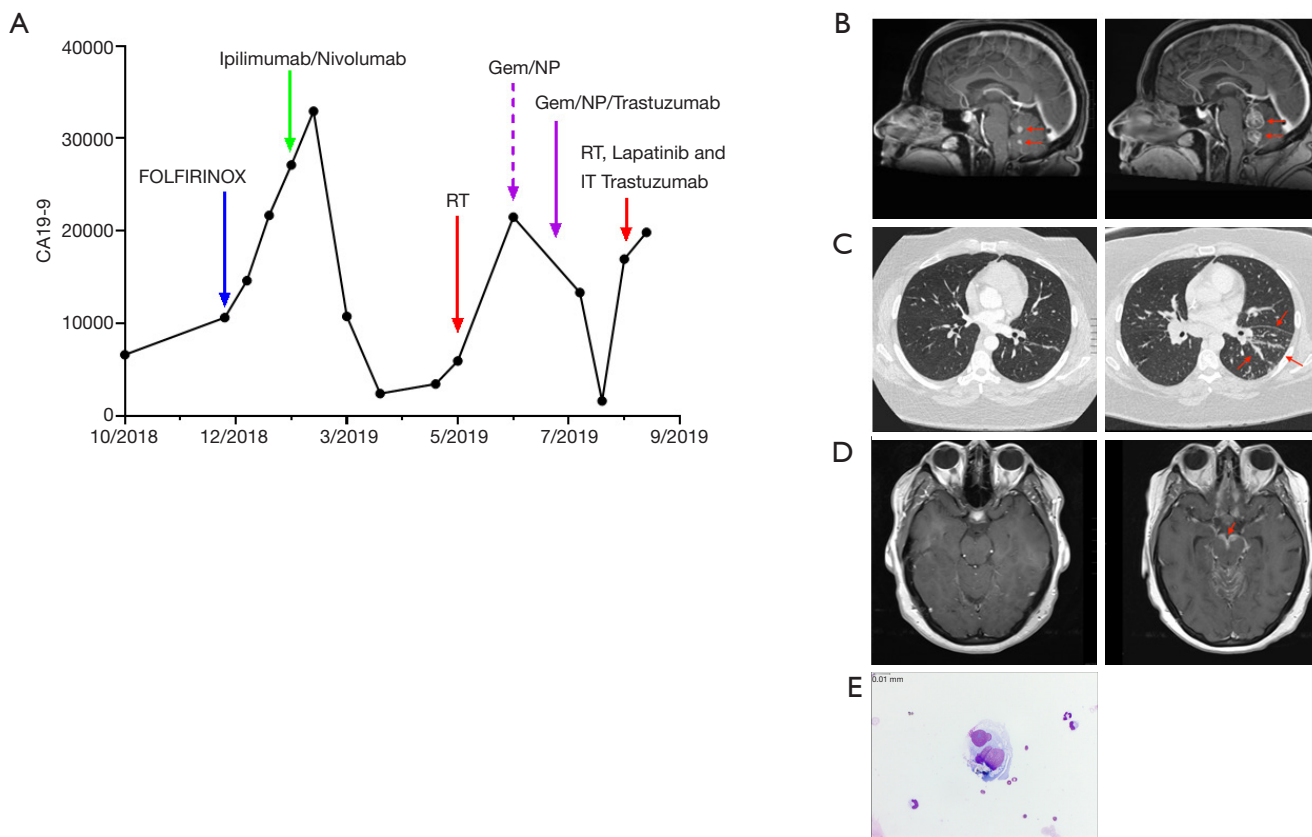
Following SRS, a restaging CT demonstrated marked disease progression in the liver and lymph nodes, a new renal infarct, and lymphangitic spread in the lungs (*Figure 2C*).



**Figure 1** Radiology and pathology at diagnosis, initial response to treatment with FOLFIRINOX. (A) Representative images of pancreatic mass (red arrows) and liver metastasis (white arrows) at diagnosis. (B) Representative pathology images including H&E (top left), IHC for HER2 (top right), MLH1 and PMS2 (bottom left and right, respectively). Scale bars are located in the top left of each image. (C) Representative images from initial response to FOLFIRINOX, liver lesion (top, red arrows), mediastinal lymph node (bottom, red arrows). H&E, hematoxylin and eosin; IHC, immunohistochemistry.

She was initiated on gemcitabine and nab-paclitaxel, and trastuzumab was added in cycle 2. After 2 cycles, her CA19-9 decreased to 13,000 U/mL and abdominal pain improved. At cycle 4, she developed dizziness and gait imbalance. MRI revealed enlargement of previously treated cerebellar lesions. Circulating tumor DNA was analyzed via NGS

and revealed *CDK6*, *CCNE1*, and *KIT* amplifications, as well as the *TP53* W146\* mutation [mutant allele frequency (MAF) =35.6%] and *KRAS* G12D mutation (MAF =22.1%) consistent with the patient’s baseline tumor tissue NGS. *HER2* amplification and MSI-H were not detected. Due to CNS progression, treatment with lapatinib and trastuzumab



**Figure 2** Treatment course and images of progression after immunotherapy and then trastuzumab based chemotherapy. (A) Time course of CA19-9 changes and treatments received; (B) progressive cerebellar lesions after relapse on immunotherapy; (C) development of pulmonary lymphangitic carcinomatosis; (D) development of leptomeningeal carcinomatosis after relapse on Gem/NP/trastuzumab; (E) representative image of CSF cytology demonstrating a pancreatic cancer cell (H&E). Gem, gemcitabine; NP, nab-paclitaxel; RT, radiotherapy; IT, intrathecal; CSF, cerebrospinal fluid.

was initiated. To treat leptomeningeal disease (*Figure 2D,E*), intrathecal trastuzumab was administered. After a very brief period of relief, the patient continued to experience worsening nausea, headaches, gait instability, and developed horizontal nystagmus along with visual difficulties. The decision was subsequently made to enroll in hospice, and she passed peacefully with her family.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

## Discussion

PDAC confers a high mortality rate and propensity for

early metastasis, emphasizing the urgent need for improved therapeutic options. Unfortunately, targetable molecular alterations are rare. Given the limited treatment options available in this malignancy, NGS can be transformative for a small subset of patients. We highlight a case of MSI-H metastatic PDAC displaying concurrent *HER2* amplification. Her disease responded and relapsed on tailored therapeutic approaches, with treatment failure in the CNS.

While many patients with MSI-H cancers have durable responses to anti-PD-1 treatment, up to half experience either *de novo* or acquired resistance (3,9). This is particularly relevant in non-colorectal cancer cohorts such as PDAC, indicating that tumor-driven immune evasion beyond T cell exhaustion and the lack of neoantigens is driving immunotherapy resistance. Indeed, this is further

supported by the fact that vaccines have elicited neoantigen specific T cell responses without meaningful clinical benefit in this patient population (10). Given the heterogeneous, immunosuppressive microenvironment of pancreatic cancer, a myriad of possible mechanisms could be contributing to these findings. Regulatory T (Treg) cells and myeloid-derived suppressor cells (MDSCs) contribute to immune suppression and disease progression in pancreatic cancer, and have a well-established role in immune checkpoint inhibitor resistance (11,12). Tumor associated macrophages, which occupy the majority of leukocytes in the pancreatic tumor microenvironment, are frequently polarized toward an M2 phenotype which facilitates disease progression and mitigates T cell responses (11,13). Finally, advanced pancreatic cancers show a scarcity of dendritic cells (DCs) (14), which differentiate tumor from self and are required for successful immune checkpoint blockade (15). Tumors may also co-opt DCs to induce a tolerogenic state which dampens CD8<sup>+</sup> T cell proliferation and promotes Treg generation (16). Our patient experienced an initial response to immunotherapy followed by relapse, which could be due to one or more of the microenvironmental alterations discussed above. The loss of MSI-H may represent tumor evolution under selective pressure, or it was not detected by ctDNA, which has a sensitivity of 95% (17). Microsatellite instability is thought to be a driver event, and MSI-H loss has not been previously described in the literature nor was tissue confirmation feasible in this patient. Notably, the tumor lacked any known mutations associated with checkpoint inhibitor resistance, suggesting non-genomic mechanisms of treatment failure (18).

While our patient responded briefly to anti-HER2 therapy in combination with chemotherapy, her disease eventually progressed, and the *HER2* amplification was no longer detectable by ctDNA. Since ctDNA shedding remained high—as evidenced by the high MAFs for *TP53* and *KRAS*—it is unlikely that loss of *HER2* amplification was related to assay sensitivity. The more probable explanation is that her disease lost *HER2* amplification to escape HER2 inhibition, as has been observed in up to half of all patients with metastatic HER2<sup>+</sup> gastric cancer (19). Given that her relapse occurred in the CNS with leptomeningeal disease where directed penetration of systemic therapy is poor, we pursued treatment with intrathecal (IT) trastuzumab based on evidence from a phase 1 clinical trial (20). It is possible that the disease in the CNS also lacked *HER2* amplification which contributed to poor response in this setting. We were unable to perform HER2 IHC or ctDNA analysis on

the cerebrospinal fluid (CSF), and the patient's illness and quality of life considerations prevented repeat biopsies, all of which represent diagnostic limitations in this case.

In summary, we present a unique case of *HER2* amplified, MSI-H pancreatic adenocarcinoma which progressed to the CNS with leptomeningeal involvement after responses to multiple targeted treatments. This underlines the importance of up-front molecular profiling and multidisciplinary involvement in advanced pancreatic cancer. Other important points to derive from this case include having early suspicions of CNS disease in patients with *HER2* amplified and/or MSI-H pancreatic cancer and to anticipate the development of disease resistance in sequentially treating patients with pancreatic cancer harboring targetable mutations. Our patient's case provides a humbling window into the insufficient understanding of therapeutic resistance mechanisms in pancreatic cancer, clearly illustrating that dedicated collaborative and translational efforts will be necessary to overcome these hurdles and improve clinical outcomes in this disease.

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### Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/acr-20-154>

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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