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Rare *ROS1-CENPW* gene in pancreatic acinar cell carcinoma and effect of crizotinib plus AG chemotherapy: A case report

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Abstract

BACKGROUND

This is the first report of an *ROS1-CENPW* fusion gene in pancreatic malignancies.

CASE SUMMARY

A 77-year-old woman with a pancreatic tumor and multiple liver metastases was admitted to our hospital. Genetic testing revealed the presence of the *ROS1-CENPW* fusion gene, a rare fusion gene that has not been previously reported in the field of pancreatic cancer. We administered crizotinib plus AG (albumin paclitaxel plus gemcitabine) chemotherapy in this patient with a rare fusion gene. After treatment, the patient's condition stabilized, and her prognosis was good.

CONCLUSION

The *ROS1-CENPW* gene treatment regimen used in this case is an excellent treatment option that provides new hope for patients with advanced pancreatic cancer and similar genetic points. To date, owing to the rarity of the *ROS1-CENPW* fusion gene, our team has encountered only a single case. Therefore, the efficacy of crizotinib plus AG chemotherapy in patients with pancreatic acinar cell carcinoma harboring the *ROS1-CENPW* fusion gene requires further validation.

INTRODUCTION

Pancreatic cancer is a highly aggressive disease with insidious onset, rapid progression, and poor prognosis[1]. Its molecular features include genomic instability and a high oncogene and tumor suppressor gene mutation rate[2]. Pancreatic cancer has a unique tumor cell microenvironment and immunosuppressive properties[3,4]; therefore, chemotherapy alone is of little benefit due to cytotoxicity and drug resistance[5]. Personalized medical treatments targeting specific genes have attracted considerable attention due to their high efficacy and unique status in pancreatic cancer treatment[6]. Unfortunately, *KRAS*, *CDKN2A*, *TP53*, and *SMAD4*, highly expressed in pancreatic cancer, have not shown satisfactory results as clinical therapeutic targets[7,8].

Pancreatic acinar cell carcinoma (PACC) is a rare pancreatic tumor that secretes various exocrine enzymes such as trypsin and lipase. Compared to pancreatic tumors arising from the ductal epithelium, PACC accounts for less than 2% of all pancreatic tumors. Metastatic PACC is generally incurable[9]. Therefore, developing personalized treatment plans for individual patients has become a priority. The discovery and reporting of the *ROS1-CENPW* locus may present a new unique approach for the targeted therapy of pancreatic cancer.

CASE PRESENTATION

Chief complaints

appetite loss, weight loss, fatigue, and abdominal pain more than 1 year

History of present illness

A 77-year-old woman presented to our hospital complaining of appetite loss, weight loss, fatigue, and abdominal pain accompanied by radiating shoulder pain. These symptoms had persisted for more than 1 year.

History of past illness

No previous history of hypertension, diabetes, cardiovascular and cerebrovascular diseases; No history of hepatitis, tuberculosis, malaria and other infectious diseases; No history of blood transfusion, trauma, surgery; No history of food and drug allergy.

Personal and family history

Born and raised in Jiaxing, Zhejiang; No history of smoking or drinking; No history of exposure to radioactive substances.No familial genetic history.

Physical examination

The physical examination revealed the following: height and weight, 150 cm and 42 kg, respectively; blood pressure, 139/69 mmHg; and pulse, 84 bpm. The abdomen was soft with tenderness in the upper part; no rebound tenderness, jaundice, or other abnormal signs were observed.

Laboratory examinations

Tumor indicators（Table 2） showed that CA19-9 233.70 u/mL, AFP 0.97 ng/mL, CEA 58.81 ng/mL, CA125 4.45 U/mL.

Imaging examinations

Imaging results (Figure 1) from Jiaxing No. 1 Hospital indicated multiple lesions in the liver (A) and a tumor in the pancreatic tail (B).

FURTHER DIAGNOSTIC WORKUP

Several additional examinations were performed to confirm this diagnosis. Positron emission tomography–computed tomography (Figure 2) revealed irregular soft-tissue density at the pancreatic tail approximately 2.49 cm × 3.24 cm with an indistinct boundary. The tumor had an uneven mass density, with a plain computed tomography (CT) value of approximately 26 Hounsfield units and no widening of the pancreatic duct. Elevated metabolism of fluorodeoxyglucose (FDG), with a standardized uptake value (SUVmax) of 2.5, was noted. Diffuse thickening and turbidity were observed in

the peritoneum, reticulum, and mesentery, with increased density and multiple nodules, the larger of which was approximately 2.17 cm. The FDG metabolism was unevenly elevated (SUVmax, 2.5). Multiple enlarged lymph nodes were detected in the retroperitoneal and pelvic mesangial area, of which the largest was about 1.87 cm × 1.38 cm; the FDG metabolism increased to an SUVmax of 3.9. Magnetic resonance imaging (MR) revealed a low signal at T1, a slightly high signal at T2, and limited diffusion on diffusion-weighted imaging. Overall, there were no obvious abnormalities in liver morphology or size, with smooth liver margins and no widening of the liver fissure. Multiple patchy low-density shadows with unclear boundaries were observed in the liver parenchyma, with a low signal on T1, a slightly high signal on T2, and a high signal on diffusion images as well as increased FDG metabolism (SUVmax, 2.6). The hilar region was well structured. No dilatation of the intra-or extrahepatic bile ducts was observed. The needle biopsy and immunohistochemistry results (Figure 3) suggested that the histological type was acinar cell carcinoma.

TREATMENT

Chemical and immunotherapies were considered the first-choice treatments considering that the tumor had metastasized to multiple organs. To enhance treatment strategy accuracy, the patient was enrolled in a gene sequencing project, the data of which showed that her tumor mutation load was low with microsatellite stability, which enabled a genetic analysis. Based on second-generation sequencing technology, four types of mutations (including point mutation, insertion-deletion of small fragments, copy number variation, and currently known fusion genes) of 1,016 genes related to tumorigenesis and development, were detected (Table 1), including mutations in *KRAS, PIK3R2, TP53, TGFBR2,* and *CDKN2A*. *ROS1-CENPW* (intergenic) gene fusion, which has not been previously reported in the literature. The ROS1-CENPW fusion protein does not retain the intact kinase domain of ROS1, and its effect on gene function is unknown.

FINAL DIAGNOSIS

pancreatic acinar cell carcinoma

TREATMENT

To target this mutation, we selected crizotinib, a ROS inhibitor, as the drug of choice for targeted therapy. Crizotinib was administered orally at a dose of 200 mg twice daily. AG chemotherapy (gemcitabine 1000 mg/m^2 plus albumin paclitaxel 125 mg/m^2) was administered on the first and eighth days, followed by a week's rest.

OUTCOME AND FOLLOW-UP

The patient cooperated without adverse reactions or intolerance; therefore, the treatment regimen remained unchanged. Until this event, the patient received regular treatment. Laboratory examination data (Table 2) showed that the carcinoembryonic antigen (CEA) levels had declined by degrees. The carbohydrate antigen (CA19-9) levels remained stable and were not significantly elevated. Detailed data and other examination parameters are listed in Table 2. An enhanced CT scan (Figure 4) indicated that until the examination on June 21, the liver metastasis had diminished, and the pancreatic mass tended to shrink.

DISCUSSION

DISCUSSION

Herein we reported the case of a patient with pancreatic cancer harboring a specific fusion gene, the *ROS1-CENPW* mutation. *ROS1-CENPW* is a fusion gene that has not been previously used for diagnosing and treating pancreatic cancer. *ROS1* is a proto-oncogene with various physiological functions. Twenty-six genes have been found to fuse with *ROS1* and drive a variety of cancers in adult and pediatric patients when *ROS1* produces chimeric oncoproteins[10,11]. Different *N*-terminal fusion partners generate different cell signaling and oncogenic properties. ROS1 fusion oncoproteins such as SDC4-ROS1 and CD74-ROS1 regulate mitogen-activated protein kinase signaling pathways[12]. The *CENPW* locus, a novel biomarker primarily expressed in

hepatocellular and breast cancers, is closely associated with occurrence, development, and poor prognosis of cancer[13,14]. However, since the ROS1-CENPW fusion protein does not retain the complete kinase domain of ROS1, its effect on gene function remains unknown.

PACC is a rare malignant acinar-differentiated tumor with poor clinical prognosis and molecular heterogeneity[9,15]. Hypersecretion syndrome can result from the excessive release of lipases, and surgical resection remains the treatment of choice for PACC[16]. In this case, the patient missed the best time for surgical treatment because of her age and distant tumor metastasis. Fortunately, PACC often features multiple somatic gene mutations; therefore, mapping targeted treatment sites using genetic testing facilitates personalizing the treatment of locus genes[17]. Crizotinib, a specific tyrosine kinase inhibitor (TKI), is a competitive small-molecule inhibitor of ATP molecular implantation at the *ROS1* site[18]. Oral TKI resistance often develops[19]. However, it inhibits *ROS1*, *MET*, *ALK*, and other sites, is considered the gold standard for first-line treatment, and has been approved by the United States Food and Drug Administration (FDA) in the United States[20]. In addition to crizotinib, lorlatinib and entrectinib have been approved by the FDA for targeted therapy of ROS1, with an overall response rate of >60% for all four targeted drugs[21].

CONCLUSION

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In summary, *ROS1-CENPW* is a novel fusion gene locus in PACC that has not been previously reported. We searched the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Reference Citation Analysis (https://www.referencecitationanalysis.com/), and MedlinePlus (https://medlineplus.gov/) databases using ROS1-CENPW as a keyword. However, no relevant reports have been published regarding this rare fusion gene. This is a unique finding. Gene sequencing was performed in patients with PACC. Both ROS1 and CENPW have been reported only in breast cancer and hepatocellular carcinoma. However, neither has been reported for pancreatic-related cancers. However, effective

targeting sites for the treatment of PACC are lacking. Thus, discovering the *ROS1-CENPW* complex may open new avenues for targeted therapy. In this case, the treatment regimen resulted in favorable outcomes. CEA levels decreased significantly, liver metastases decreased significantly, CA19-9 Levels stabilized, and CT showed that the pancreatic mass tended to shrink. In this case, the treatment plan of crizotinib plus AG chemotherapy achieved satisfactory therapeutic effects. Therefore, it may be a good treatment option for patients with PACC harboring the *ROS1-CENPW* fusion mutation. Owing to the possible specificity in individual cases, it is worth exploring whether the treatment plan of crizotinib plus AG chemotherapy is universally applicable for treating patients with PACC who are carrying the *ROS1-CENPW* fusion gene.

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