Clinics of Surgery

Case Report ISSN: 2638-1451 | Volume 9

BRCA1 Mutation of the Ampulla of Vater Cancer: A Case Report and Literature Review

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Received: 15 Apr 2023
Accepted: 20 May 2023
Published: 30 May 2023
J Short Name: COS

Keywords:

Periampullary; Ampullary; Pancreaticoduodenectomy

Citation:

Amonkar A. Acute Necrotizing Pancreatitis-Current Concepts and Latest Treatment Strategies: A Surgeon's Perspective. Clin Surg. 2023; 9(5): 1-5

1. Abstract

Ampulla of Vater cancer typically has a better prognosis than other periampullary cancers, and common mutations found in ampullary cancer are TP53, KRAS, and APC. We report on a case of ampullary cancer with unusually rapid progression, which led to the patient's death just 5 months after diagnosis. Our analysis of the patient's tumor using NGS revealed BRCA1 and PIK3CA mutations, which are infrequent in ampullary cancers. We speculate that these rare mutations may have contributed to the patient's rapid deterioration and insensitivity to chemotherapy.

2. Introduction

Ampullary cancers are rare malignancies accounting for only 0.2% of all gastrointestinal cancers [1]. They usually have high curable resection rate and relatively better prognosis compared to other periampullary cancers [1], with a 5-year survival rate ranging from 33% to 68% [2]. Ampullary cancers can be classified into 3 distinct histological subtypes based on their epithelium of origin: intestinal (INT), pancreatobiliary (PB), and mixed type [3]. Whether there is a statistical association between histological types and the overall survival of patients with ampullary cancer is controversial. According to Chang et al., patients with PB phenotype had a much worse prognosis compared with non-PB (INT, mixed) phenotype (median overall survival of 16.1 vs 115.5 months; $p < 0.001$ in Sydney cohort, median overall survival of 11.9 vs 67.0 month; $p < 0.001$ in Glasgow cohort) [5]. On the other hand, Kwon et al. observed no statistically significant association between histologic types and overall survival of patients with ampullary cancer ($p= .378$) [1]. In our case, the patient expired 5 months after receiving pylorus-preserving pancreaticoduodenectomy, which is a much shorter period than median overall survival of ampullary cancer of either histologic status.

3. Case Presentation

A 60-year-old man was diagnosed with Ampulla of vater (AoV) cancer and referred to the surgery department of our hospital. The patient had no symptoms; however, esophagogastroduodenoscopy showed an ampullary lesion which was biopsied and diagnosed as adenocarcinoma during his regular medical checkup. He had a history of hypertension, dyslipidemia, and gout, and no familial history of cancer. Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) were performed, and a 2cm fungating mass at AoV with a 3cm heterogeneous mass between the superior mesenteric artery (SMA) and the 3rd portion of duodenum were discovered with no evidence of liver metastasis (Figure 1). Pylorus-preserving pancreaticoduodenectomy with

standard lymph node dissection was performed. Postoperative histopathology reported poorly-differentiated adenocarcinoma, 1.7cm in diameter, which invades the peri-sphincter and duodenal submucosa, and 2 out of 7 regional lymph nodes were involved. Lymphovascular invasion was present but resection margins were clear. It was confirmed to be a pancreatobiliary type on histologic examination (Figure 2). The final stage was diagnosed as stage pT1bN1, stage IIIA, according to 8th edition of American Joint Committee on Cancer (AJCC) staging system. Computed tomography (CT) showed no recurrence taken 1 month after the surgery. The patient received fluorouracil/leucovorin every 3 weeks for adjuvant chemotherapy, but after two cycles of adjuvant chemotherapy, the patient visited the outpatient clinic for abdominal pain, general weakness and poor oral intake. Large mass was palpated in the right upper abdomen, and the patient complained of severe abdominal tenderness on physical examination. The patient admitted to the hospital, laboratory examination revealed an aspartate aminotransferase (GOT) level of 159 IU/L, an alanine aminotransferase (GPT) level of 65 IU/L, a serum total bilirubin level of 0.4 mg/dL, an alkaline phosphatase of 1292 U/L. Serum tumor marker levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were still within normal range but had risen than before, 3.48 and 27.2 respectively. CT of the chest and abdomen revealed extensive liver metastasis in both hemiliver and multiple small and tiny nodules were newly seen in both lungs (Figure 3). The patient was transferred to the oncology department and started 1st cycle of capecitabine, oxaplitain (XELOX) for palliative intent. The abdominal pain was relieved and serum liver function tests were decreased after the 1st cycle of chemotherapy. After 10 days of resting period, the 2nd cycle of chemotherapy was initiated. However, abdominal pain worsened and palpable mass in the right abdomen had been enlarged. Moreover, serum GOT, GPT and bilirubin levels were increased rapidly. Chest CT revealed markedly increased size and number of metastatic nodules in both lungs, and abdominal CT showed an increase in the number and size of extensive hepatic metastasis, causing obliteration the right portal vein (Figure 4). Chemotherapy was discontinued and patient deceased due to liver failure. We had requested for next generation sequencing (NGS) analysis with the postoperative tumor specimen, and the four genomic alterations were identified. A frameshift mutation in BRCA1, nonsense mutations in TP53 and APC, and a missense mutation in PIK3CA were discovered (Table 1).

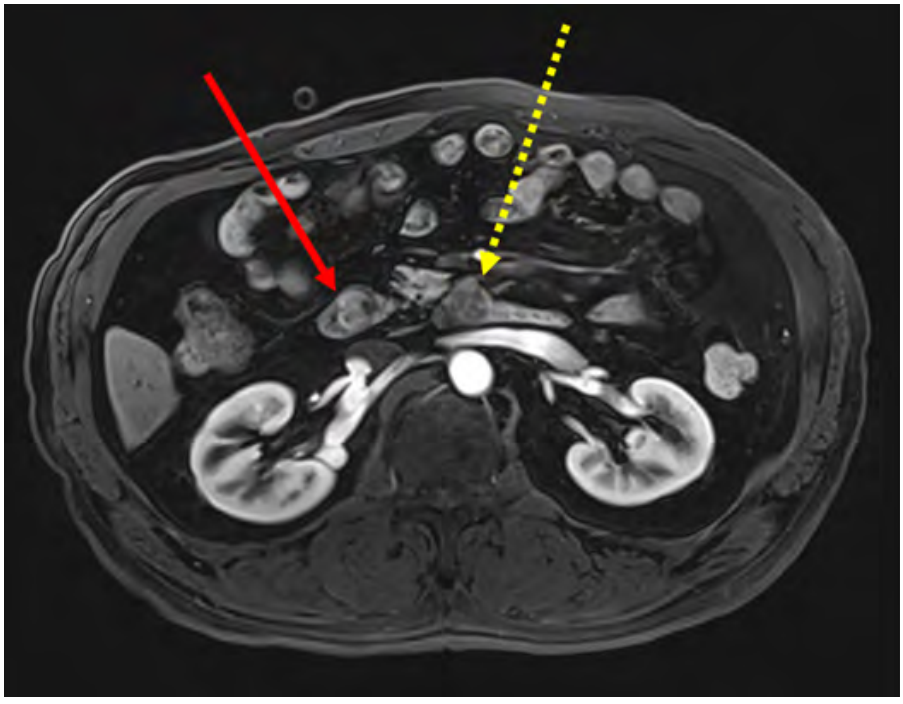

Figure 1: Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) demonstrated an ampullary mass (solid red arrow) with a heterogeneous mass between superior mesenteric artery and duodenal third portion (dotted yellow arrow).

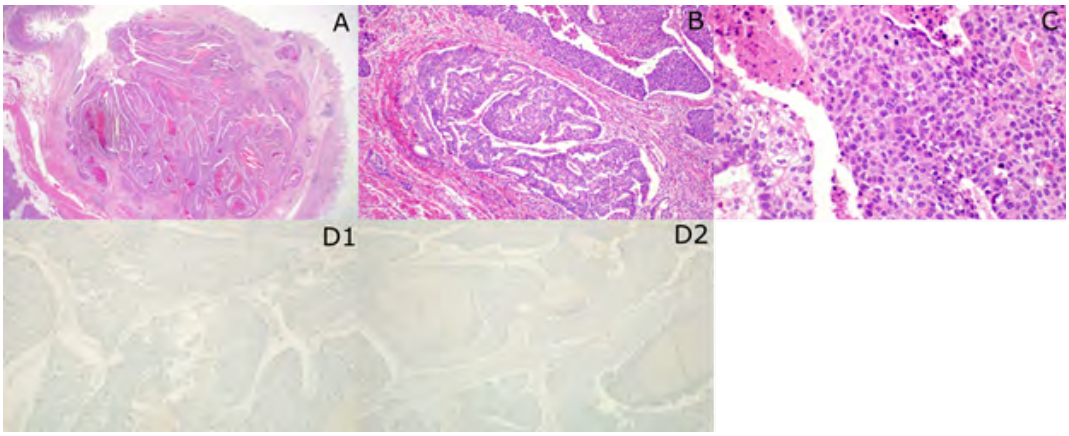

Figure 2: (A) The tumor is centered at the ampulla of Vater (B) Glandular differentiation is noted (C) Tumor cells are characterized by prominent nucleoli and high-grade atypia (D) Chromogranin A (D1) and synaptophysin (D2) are negative by immunohistochemistry.

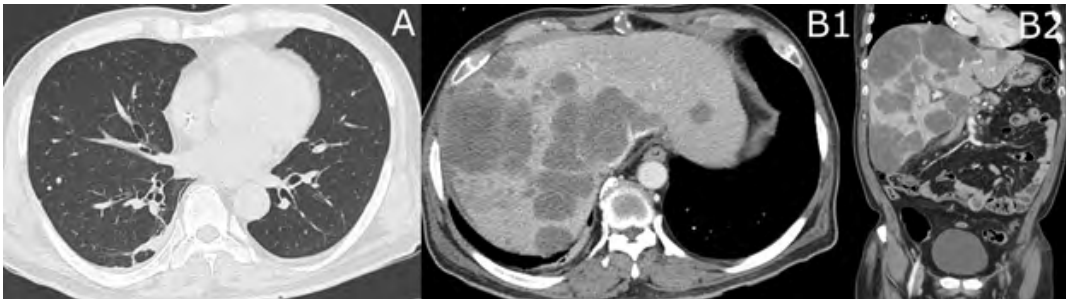

Figure 3: (A) Chest computed tomography (CT) discovered multiple metastatic nodules in both lungs (B1) Coronal and (B2) sagittal abdominal CT showed extensive liver metastasis.

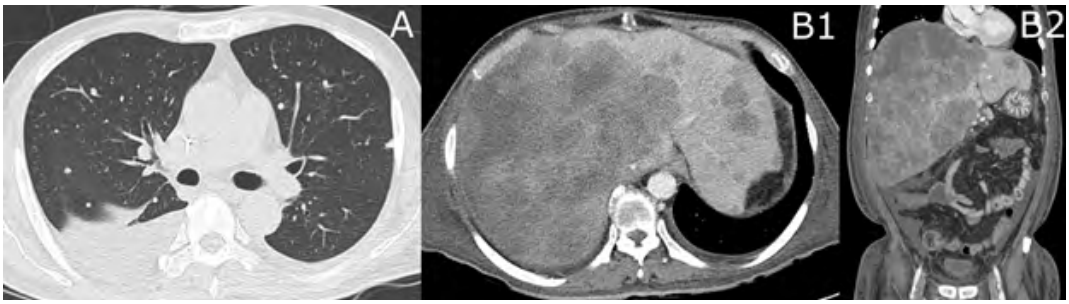

Figure 4: (A) Chest computed tomography (CT) scan discovered markedly increased size and number of metastatic nodules in both lungs with pleural effusion. (B1) Coronal and (B2) sagittal abdominal CT showed increased number and size of extensive hepatic metastasis with ascites.

Table 1: Next generation sequencing (NGS) profiling results.

Gene	DNA change	Amino acid change	Type	Read depth	Variant allele frequency (%)	Interpretation
BRCA1	c.3627_3628insA	pGlu1210Argfs*9	Frameshift	1988	17	Likely oncogenic
TP53	c.859G>T	p.Glu287Ter	Nonsense	2000	60	Likely oncogenic
APC	c.1690C>T	p.Arg564Ter	Nonsense	204	53	Likely oncogenic
PIK3CA	c.1633G>A	p.Glu545Lys	Missense	1997	22	Oncogenic

Next generation sequencing (NGS) was performed with the postoperative tumor specimen.

4. Discussion

Among the mutations often found in ampullary cancer, TP53 mutation occurred the most followed by KRAS mutation, both of which were independent predictors of poor prognosis [3, 6]. APC gene was also commonly mutated, occupying the third position in frequency [7]. KRAS mutation was more prevalent in PB type, while TP53 and APC were more frequent in INT type [7]. Kurami et al. noted that INT type showed a higher rate of pathogenic germline variations than PB type [8]. It is unusual that our case carried TP53 and APC mutation despite of being PB subtype. While KRAS mutations were associated with a postoperative decrease in recurrence-free survival of ampullary cancer, the prognostic relevance of KRAS mutation was not identified in the histologic subtypes [1]. In PB type, tumor differentiation and lymph node metastasis were the prognostic factors of overall survival and recurrence-free survival, respectively, whereas no independent prognostic factors were revealed for INT type tumors [1].

Although being less frequent, PIK3CA mutations have also been demonstrated [1]. Kumari et al. analyzed the signaling pathways of ampullary cancer and discovered that the combined RAS-RAF-MAPK/PI3-AKT pathway was the most frequent alteration, occupying 70% of cases (82% in INT. 46% in PB, p=.023) [9]. The PI3-AKT pathway mutations were mainly found in INT type, whereas RAS-RAF-MAPK pathway mutations were predominant in PB type [7]. Since the mutation of PIK3CA c.1633G>A: p.Glu545Lys in our case is a known pathogenic variant, it is assumed that this mutation had been highly associated with tumor progression in our patient.

We could not find any publication about BRCA1 mutation in ampullary cancer, unlike biliary tract cancer, in which BRCA1/2 mutations have a significant role [10]. It has been known that ampullary cancer with BRCA1 mutation accounts for about 3% [11], with no data about the survival rate. Pinto et al. reported a relatively high frequency (14.3%) of germline BRCA2 mutations in ampullary cancers [12], while Wong et al. also identified pathogenic germline alteration of BRCA2 but no BRCA1 mutations in ampullary cancers [13]. BRCA1/2 alterations result in accumulation of DNA double-strand breaks, exhibiting genomic instability with an increased susceptibility to malignant transformation10. These mutations also bring about defective repair mechanisms in biliary tract cancers via homologous recombination for double-strand DNA breaks10. BRCA mutations are known to be associated with a poor prognosis in several cancers, including breast cancer and prostate cancer [14, 15]. Therefore, it is plausible that the BRCA1 mutation similarly affected cancer progression in our case.

One of the unique features of our case is that the patient's prognosis was much worse than others diagnosed with ampullary cancer in terms of survival period and disease progression rate. Furthermore, the patient carried a PIK3CA mutation, which has been rarely identified in other ampullary cancers, and to our knowledge, this is the first study to detect a BRCA1 mutation in ampullary cancer. Although TP53 mutation might have contributed to the poor prognosis, it is less likely to be the primary mechanism, as the mean survival period of TP53 mutation is 59 months, compared to 151 months for wild-type TP533. However, due to the rarity of ampullary cancer, insufficient studies have been conducted to determine the effect of each mutation on survival rates, making it difficult to conclude which mutation had the greatest impact in our case. Nevertheless, it is assumed that PIK3CA and BRCA1 mutations played significant roles in our case.

5. Conclusion

We report an ampulla of Vater cancer with unusually rapid progression, which was found to carry both BRCA1 and PIK3CA mutation that are infrequent among ampullary cancers. These mutations might have contributed to the patient's rapid deterioration and insensitivity to chemotherapy. This case report is noteworthy in that it confirms the presence of BRCA1 mutation in ampullary cancers for the first time. Identification of BRCA1 and PIK3CA mutations in ampullary cancer may have considerable implications for predicting clinical course, and further studies should be conducted to investigate the pathophysiology and explore the possibility of individualized chemotherapy.

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