Japanese Journal of Gastroenterology and Hepatology

Case Report

ISSN: 2435-1210 | Volume 10

Two Cases with Germline Pathogenic Variants in Biliary Tract Cancer

Ryu KH[1], Joung JY[2], Park SY[3], Chun JW[4], Woo SM[4,5] and Kong SY[5,6,7*]

[1]Center for Cancer Prevention and Detection, Hospital, National Cancer Center, Goyang, Korea

[2]Center for Urologic Cancer, Hospital, National Cancer Center, Goyang, Korea

[3]Department of Pathology, Hospital, National Cancer Center, Goyang, Korea

[4]Center for Liver and Pancreatobiliary Cancer, Hospital, National Cancer Center, Goyang, Korea

[5]Department of Cancer Biomedical Science, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Korea

[6]Department of Laboratory Medicine, Hospital, National Cancer Center Korea, Goyang, Korea

[7]Targeted Therapy Branch, Research Institute, National Cancer Center, Goyang, Korea

[*]Corresponding author:

Sun-Young Kong,
Department of Laboratory Medicine, Hospital, National Cancer Center, 323 Ilsan-ro,Ilsandong-gu, Goyang, 10408, Korea

Received: 09 Nov 2023
Accepted: 01 Dec 2023
Published: 05 Dec 2023
J Short Name: JJGH

Keywords:

Biliary tract cancer; Germline; Pathogenic varia

Citation:

Kong SY. Two Cases with Germline Pathogenic Variants in Biliary Tract Cancer. J Gastro Hepato. 2023; V10(6): 1-3

1. Abstract

The prevalence of germline mutation in patients with biliary tract cancer has not been well described. Here we report Two biliary tract cancer cases with ATM pathogenic variant and BRCA2 pathogenic variant.

2. Introduction

Biliary Tract Cancers (BTCs) are invasive adenocarcinomas including cholangiocarcinoma and gallbladder cancer. Cholangiocarcinoma is the second most common primary liver cancer next to hepatocellular carcinoma, accounting for 10%-15% of all primary liver cancer and gallbladder cancers account for 0.6% of all cancers [1]. Risk factors for the BTCs include liver flukes, metabolic conditions (including obesity, diabetes and nonalcoholic fatty liver disease), alcohol consumption, hepatitis B and C infection, primary sclerosing cholangitis, Caroli's disease and hepatolithiasis [2].

The prevalence of germline mutation in patients with biliary tract cancer remains unclear. The frequency of germline pathogenic variants of biliary tract cancer patients also has not been well described in Korea. Here we report two biliary tract cancer cases with germline pathogenic variants.

3. Case Report

3.1. Case 1

A 61-year-old female patient was diagnosed with gallbladder cancer. As a result of computed tomography, gallbladder mass with periductal spreading to common bile duct and lymph node metastasis at porta hepatis, common hepatic artery and periportal space were observed and intrahepatic metastasis was observed (Figure 1). Pathologic finding was poorly differentiated adenocarcinoma. One of her brothers was diagnosed with gastric cancer at the age of 59 and one of her sisters was diagnosed with thyroid cancer at the age of 54 (Figure 2). She was tested with the Next Generation Sequencing (NGS) hereditary cancer gene panel including 28 genes (Table 1). Pathogenic variant was detected in ATM c.5288_5289insGA. The ATM c.5288_5289insGA is a very rare mutation that has not been reported in the general population (gnomAD KRGDB) and is classified as Lively pathogenic in Clinvar.

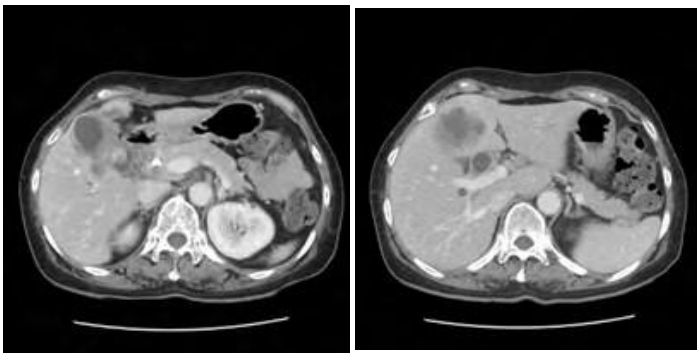

Figure 1: CT scan of case 1. A gallbladder mass with intrahepatic metastasis was observed.

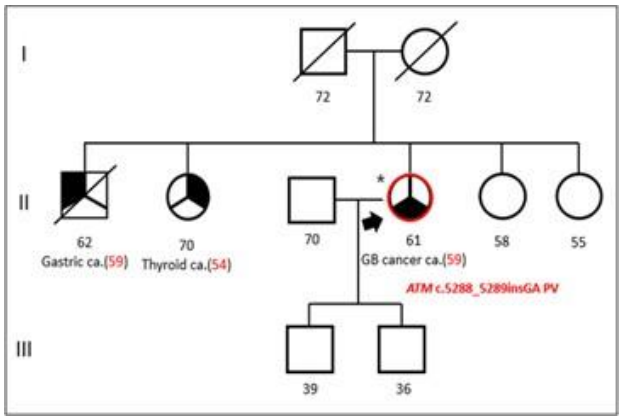

Figure 2: Pedigree of Case 1.

Table 1: Genes list in NGS hereditary cancer panel.

Classification	Gene name
NGS herediary cancer panel	*APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, RET, SMAD4, STK11, TP53*

3.2. Case 2

A 72-year-old male was initially admitted to evaluate a left neck mass and diagnosed with prostate cancer with metastasis to liver, lymph node, and bone. He was treated with chemotherapy and radiation therapy for the prostate cancer. After 6month later, elevated serum level of CA19-9 (5018u/ml) and AFP (38.9ng/ml) were noted in the laboratory examination. He was diagnosed with cholangiocarcinoma as the result of an intrahepatic mass by the computed tomography and moderately differentiated adenocarcinoma by the pathologic finding (Figure 3). His mother was diagnosed with breast cancer at the age of 94 (Figure 4). He was tested with the NGS-hereditary cancer gene panel (28 types). A genetic testing represented pathogenic variant in BRCA2 c.8991T>G. The c.8991T>G mutation in the BRCA2 gene is a mutation that has not been reported in gnomAD and has not been reported in the Korean population group (KRGDB), and is classified as Pathogenic from Clinvar. Though somatic cancer panel had not shown BRCA2 pathogenic variant at first, we found very low level of variants by re-analyzing.

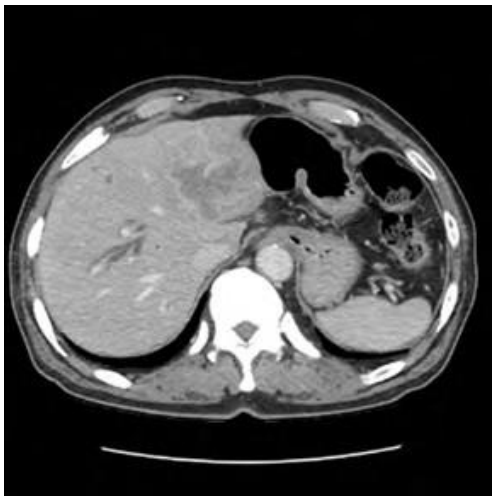

Figure 3: CT scan of case 2. An intrahepatic mass was noted.

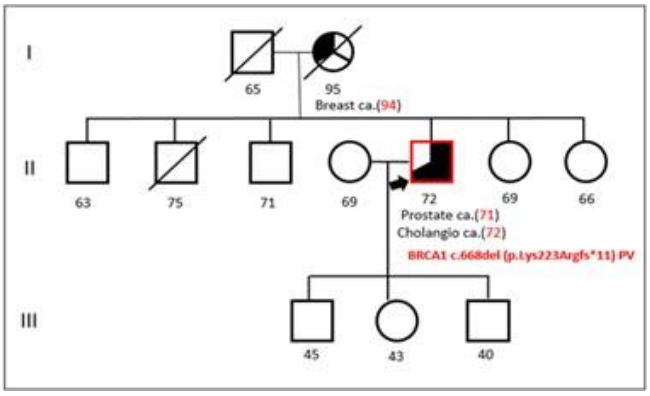

Figure 4: Pedigree of Case 2.

4. Discussion

BTCs are not common but fatal malignancies which have 5-year survival of less than 15% with the majority of patients diagnosed at the advanced stated of disease [3]. The peak age of incidence for BTC is the seventh decade and the disease affects both genders [4]. The incidence of BTC is higher in the eastern world compared to the west due to geographical risk factors like liver fluke [5].

Many cancers have frequent familial excess ad inherited susceptibility, such as colon, breast, pancreas, ovary and prostate cancer. Related to familial risk observations, there are prevention guidelines for relatives in colon and breast cancers. The familial risk for the BTC is not well known. Samadder et al reported the population-based assessment of the risk of cancer in relatives of individuals with BTS with Utah Cancer Registry that they found no increased familial risk of BTC in relatives and concluded BTC risk occurs sporadically rather than through genetically inherited predisposition or environment shared by close relatives [6].

The prevalence of germline mutation in patients with biliary tract

cancer remains unclear. Guidelines for genetic counseling and testing are not established. There are small number of studies reporting BTC is caused by germline mutations, DNA mismatch-repair genes associated with Lynch syndrome, BRCA genes with hereditary breast and/or ovarian cancer syndrome and ATM gene [7-9]. Terashima et al reported two pathogenic variants in BRCA2 and one in BRCA1 in 269 BTC patients in Japan [8]. Maynard et al reported BRCA1/2, ATM, BAP1 gene mutations were noted in 131 patients in US [9]. Our two cases are compatible with these few studies as pathogenic BRCA2 mutation and ATM mutations though the mutations that detected in our cases are very rare.

Identification of gene mutations can be benefit for developing screening methods for BTC and for the effective treatment possibilities for BTC patients like olaparib therapy is effective treatment for some cancers with BRCA1 or BRCA2 mutations [10].

5. Conclusion

We report two cases of biliary tract cancer patients with germline pathogenic variants in ATM and BRCA2. Further study is needed to identify pathogenic variants in biliary tract cancer.

6. Acknowledgement

This study was supported by National cancer center, Korea, Grant no. 2110181.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209-49.
2. Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. Lancet. 2021; 397(10272): 428-44.
3. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol. 2014; 6: 99-109.
4. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. Liver Int. 2019; 39: 19-31.
5. Tyson GL, El-Serag B. Risk factors for cholangiocarcinoma. Hepatology. 2011; 54(1): 173-84.
6. Samadder NJ, Smith KR, Wong J, Hanson H, Boucher K, Burt RW, et al. Familial Risk of Biliary Tract Cancers: A Population-Based Study in Utah. Dig Dis Sci. 2016; 61(12): 3627-32.
7. Mecklin JP, Järvinen HJ, Virolainen M. The association between cholangiocarcinoma and hereditary nonpolyposis colorectal carcinoma. Cancer. 1992; 69(5): 1112-4.
8. Terashima T, Umemoto K, Takahashi H, Hosoi H, Takai E, Kondo S, et al. Germline mutations in cancer-predisposition genes in patients with biliary tract cancer. Oncotarget. 2019; 10(57): 5949-57.
9. Maynard H, Stadler ZK, Berger MF, Solit DB, Ly M, Lowery MA, et al. Germline alterations in patients with biliary tract cancers: A spectrum of significant and previously underappreciated findings. Cancer. 2020; 126(9): 1995-2002.
10. Ryu KH, Park S, Chun JW, Cho E, Choi J, Lee DE, et al. Prevalence and Risk Factors of Germline Pathogenic Variants in Pancreatic Ductal Adenocarcinoma. Cancer Res Treat. 2023; 55(4): 1303-12.