

Title: SMARCA4-deficient poorly-differentiated adenocarcinoma of the gallbladder.

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SMARCA4-deficient gallbladder adenocarcinoma

Keywords: SMARCA4, gallbladder, fluorodeoxyglucose (FDG), positron emission tomography (PET), magnetic resonance imaging (MRI)

Abstract: (99/100 words)

A 64-year-old woman presented with chest pain while eating and was referred to our hospital. Physical examination revealed abdominal distension, tenderness, and lower-extremity edema. Imaging revealed a large gallbladder tumor infiltrating the liver, with ascites and pleural effusion. A biopsy confirmed a poorly differentiated adenocarcinoma with SMARCA4 deficiency (cT3N2M1, cStage IV). Chemotherapy was ineffective and led to tumor progression. The patient died nine months later. Recently, attention has been paid to SMARCA4 deficiency which is a genetic mutation found in tumors. Here, we report on poorly differentiated adenocarcinomas of the gallbladder based on imaging findings, including fluorodeoxyglucose-positron emission tomography.

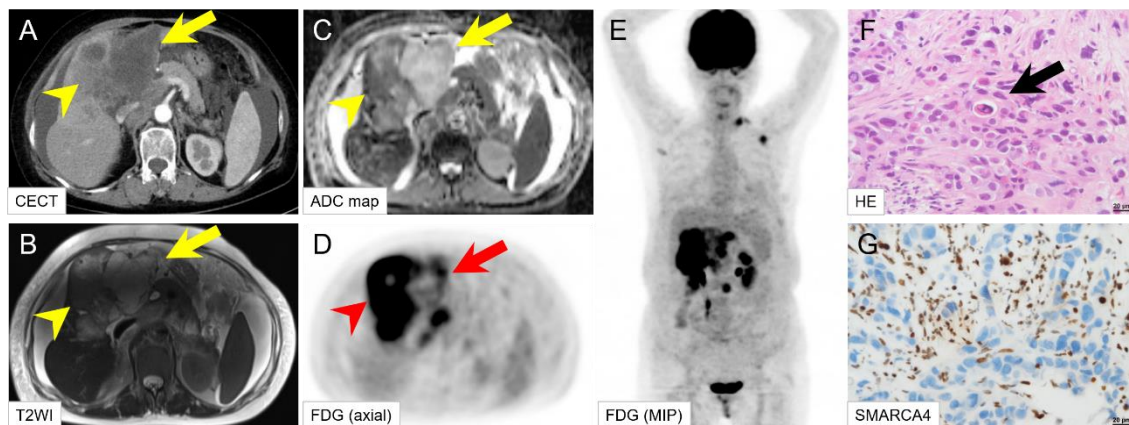
Key words: SMARCA4, gallbladder, fluorodeoxyglucose (FDG), positron emission tomography (PET), magnetic resonance imaging (MRI)

Figure: 498/500 words

A 64-year-old woman presents with chest pain on eating and is referred to our hospital after being diagnosed with pleural effusion at a local clinic. She has lost 5–6 kg of body weight in the past six months. She has no significant family or medical history. On physical examination, she has abdominal distension, spontaneous tenderness in the upper abdomen, and lower extremity edema. Multiple tumor markers are elevated: CEA 878.1 ng/mL, CA19-9 3311.0 U/mL, CA125 1983.0 U/mL, and CA15-3 373.9 U/mL. Imaging studies are performed (A-E). Contrast-enhanced CT and Gd-EOB-DTPA-enhanced MR reveal a markedly enlarged gallbladder with a necrotic tumor infiltrating the liver parenchyma. CT and MRI show ascites and pleural effusion. The tumor shows different characteristics depending on the location, consisting of a lobulated and solid mass with moderate necrosis in the center (A-C, arrowheads), a relatively high signal on T2WI, and a high ADC value suggesting severe necrosis in the tumor (A-C, arrows). The former area has marked FDG uptake (D, arrowhead), while the latter has relatively weak FDG uptake in the FDG-PET/CT (D, arrow). A PET study also reveals lymph node metastases from the para-aortic region to the left supraclavicular and axillary regions with intense uptake (E: maximum intensity projection, MIP image). An ultrasound-guided biopsy is performed on the former solid part.

Histologically, the tumor focally showed tubular structures (F, Hematoxylin-Eosin stain, arrow), suggesting the diagnosis of poorly differentiated adenocarcinoma rather than

undifferentiated carcinoma. Immunohistochemistry shows that the tumor cells have lost nuclear SMARCA4 expression, whereas infiltrating lymphocytes serve as internal positive controls (G). Comprehensive genomic profiling (FoundationOne® CDx, Foundation Medicine, Cambridge, MA, USA) also reveals *SMARCA4* loss.



The patient is diagnosed with cT3N2M1 cStage IV SMARCA4-deficient poorly differentiated adenocarcinoma of the gallbladder and receives gemcitabine, cisplatin, and S-1 (GCS) therapy. However, the tumor shows progressive disease on imaging during treatment. The tumor invades the duodenum and causes gastrointestinal bleeding and perforation, resulting in severe pain from tumor infection. The pain is refractory to non-steroidal anti-inflammatory drugs and fentanyl, and the patient develops hypotension. The patient dies nine months after the histological diagnosis.

SMARCA4-deficient tumors are characterized by low differentiation and high malignancy throughout the body [1-3]. Biliary tract adenocarcinoma with SMARCA4 deficiency is rare and limited in the literature [4]. Most studies have focused on SMARCA4-deficient

undifferentiated gallbladder carcinoma [5-7], another rare and aggressive malignancy. Recent studies have suggested that SWI/SNF mutations, including SMARCA4, are found in 43.4% of gallbladder and biliary tract cancers, 9.4% of which account for SMARCA4 deficiency [8]. Therefore, it may not be as rare as was previously thought.

Mechanistically, SMARCA4 is a chromatin-remodeling factor that regulates gene expression and DNA repair. SMARCA4 deficiency is associated with high tumor mutational burden (TMB) and microsatellite instability (MSI) [8], which are known to be associated with sensitivity to immune checkpoint inhibitors (ICIs) [9,10]. ICIs were not administered in this case; however, recently ICIs were approved for gallbladder cancer. SMARCA4 deficiency should be considered if highly aggressive tumors are suspected on imaging.

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