Case reports

Intermittent high fever accompanied with adenosquamous carcinoma of the gallbladder successfully managed by complete radical resection: a case report

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Abstract

We report a case of adenosquamous carcinoma of the gallbladder with intermittent high fever and positive findings of a primary lesion and regional lymph nodes on positron emission tomography (PET-CT). The patient was a 62-year-old-man who visited a local clinic with a high fever. His white blood cell count (WBC) and serum level of C-reactive protein (CRP) were elevated. However, the origin of the fever was not identified. He was diagnosed with an unidentified fever and admitted to our hospital. Abdominal enhanced CT revealed a gallbladder tumor invading the liver and enlarged regional lymph nodes. PET-CT showed positive findings of a local lesion and regional lymph nodes. He was diagnosed with gallbladder cancer with lymph node metastases. The patient underwent hepatic resection of segments 4a+5 with radical lymph node dissection as curative surgery. Preoperative drainage of the gallbladder to improve the high fever was not performed. The post-operative course was uneventful. The severe, intermittent high fever improved immediately, and the levels of WBC and CRP levels decreased to the normal ranges after surgery. The histological findings of the resected specimen revealed that the tumor was an adenosquamous carcinoma invading the liver without any lymph node metastases or inflammatory changes. The radical and aggressive resection contributed to improving the uncontrollable fever as a paraneoplastic syndrome.

Keywords: gallbladder cancer, adenosquamous carcinoma, intermittent high fever

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Introduction

Gallbladder carcinoma generally has a poor prognosis in general. Specifically, adenosquamous carcinoma is considered to be more malignant than pure adenocarcinoma. Its nonspecific symptoms and signs, which are sometimes presented only in the advanced disease, cause its late diagnosis and poor prognosis. Despite its poor prognosis, radical resection is still the most effective treatment for the management of patients with gallbladder carcinoma. This report presents a case of an intermittent high fever accompanied with adenosquamous carcinoma of the gallbladder that was successfully managed by a complete radical resection. Preoperative positron emission tomography-computed tomography (PET-CT) was strongly positive in the gallbladder and regional lymph nodes. However, the lymph nodes were pathologically negative for cancer or inflammatory changes. The severe, intermittent high fever improved immediately after surgery.

Case report

A 62-year-old-man who had an intermittent high fever visited a local clinic. The laboratory data revealed that his white blood cell count (WBC) and serum level of C-reactive protein (CRP) were elevated (WBC: 19,800/µL and CRP: 18.35 mg/dL). However, a physical examination did not reveal any abnormal findings, and the origin of the fever was not identified. He was diagnosed with unidentified fever and was admitted to our hospital. The other laboratory data on admission revealed: red blood cells (RBC) count: 326×10^4/µL (normal range: 380 - 550), platelet (PLT): 33.2×10^4/µL (13.0 - 37.0), total bilirubin (T-bil): 0.63 mg/dL (0.30 - 1.20 mg/dl), aspartate aminotransferase (AST): 15 IU/L (13 - 33 IU/L), alanine aminotransferase (ALT): 12 IU/L (6 - 27 IU/L), alkaline phosphatase (ALP): 602 IU/L (115 - 359 IU/L), gamma-glutamyl transferase (GGT): 165 IU/L (10 - 47 IU/L), amylase (AMY): 56 IU/L (37 - 125 IU/L). Abdominal ultrasound examination revealed a solid tumor occupying the gallbladder (Fig. 1). Abdominal enhanced CT revealed a low-density area extending from the gallbladder to the gallbladder bed (segments 4a, 5) with an ir-
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Regular and unclear margin. The regional lymph nodes were enlarged, suggesting massive lymph node metastases (Fig. 2). The patient was negative for tenderness of the right hypochondrium and Murphy sign on physical examination. 18F-fluorodeoxyglucose PET-CT (18F-FDG PET-CT) showed positive findings in the gallbladder and the regional lymph nodes. The standardized uptake values (SUV) (max) were 16.1 in the gallbladder and 3.8 in the regional lymph nodes (pericholedocal and celiac artery), which were positive, and 2.0 in the paraaortic lymph nodes, which was negative (Fig. 3). We diagnosed the patient with gallbladder cancer with lymph node metastases (cT3N1M0 stageⅡB according to the Union for International Cancer Control (UICC) 7th TNM clinical classification\(^9\)). Although the severe high fever and increased levels of WBC and CRP levels suggested an acute cholecystitis, we did not perform preoperative drainage of the gallbladder to avoid dissemination of the cancer cells through puncture of the gallbladder.

We performed a hepatic resection of segments 4a+5 with radical lymph node dissection as a curative surgery (Fig. 4). The post-operative course was uneventful. The severe, intermittent high fever improved immediately, and the levels of WBC and CRP levels decreased to the normal ranges (WBC: 6,900/µL and CRP: 1.01 mg/dL respectively) two weeks after surgery (Table 1). The patient was discharged on the 14th post-operative day.

The histological findings of the resected specimen revealed that the tumor was an adenosquamous carcinoma invading the liver without any lymph node metastases (pT3N0M0 stageIIA according to the UICC 7th TNM pathological classification\(^9\)). Resected lymph nodes that

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**Fig. 1** Preoperative images of the ultrasound sonography (US)

US images revealed that a bulky solid tumor occupying the gallbladder.

**Fig. 2** Preoperative computed tomography (CT) images

Multidetector-row computed tomography (MDCT) images showing that a low-density area extending from the gallbladder to the liver bed (segments 4a, 5) with an irregular and unclear margin. Swollen regional lymph nodes are also visible (arrow).
Fig. 3 Preoperative positron emission tomography (PET)-CT images
PET-CT revealed positive findings in the gallbladder and regional lymph nodes (arrow). The standardized uptake values (SUV) max were 16.11 in the gallbladder, 3.8 in the regional lymph nodes (pericholedocal and celiac artery) as positive (A) and 2.0 in the paraaortic lymph nodes as negative (B).

Fig. 4 Macroscopic findings of the resected specimen
(A) The resected specimen was a solid tumor measuring 8×7×5 cm at the gallbladder.
(B) The cut surface of the resected specimen showed that the tumor located in the gallbladder was invading the liver (segments 4a, 5).

Table 1 Perioperative clinical course of this case
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were positive by PET-CT were found to be pathologically negative both for cancer metastases and acute inflammatory changes. The gallbladder also showed no findings of acute inflammation (Fig. 5).

The patient was followed-up in the outpatient section of our hospital after surgery. A follow-up CT examination revealed multiple liver metastases seven months after surgery. He was admitted to our hospital again with a high fever 17 months after surgery. His WBC and CRP levels had increased remarkably (WBC: 53,300/µL, CRP: 27.1 mg/dL, respectively) without bacterial or viral infectious findings, and the patient died 18 months after surgery. The febrile pattern and the WBC/CRP levels were synchronized with tumor volumes before and after surgery, or disease progression after recurrence. Thus, the intermittent high fever was considered a neoplastic fever.

Discussion

Gallbladder cancer (GBC) is the fifth most frequent tumor of the digestive system and the most frequent one arising in the biliary tree. The symptoms of GBC are similar to those of the more prevalent gallstone diseases, hampering its preoperative diagnosis.

The current imaging modalities for preoperative diagnosis and staging of the disease include multidetector CT (MDCT) and magnetic resonance imaging / magnetic resonance cholangiopancreatography (MRI/MRCP). MDCT is a useful for disease staging by identifying the disease in the gallbladder and regional metastasis in the lymph nodes. However, understaging is possible because these imaging modalities may not detect distant spread.

PET, a functional imaging modality that allows for the visualization of high utilization of glucose in tumor cells, is utilized in cancer imaging. The poor anatomic localization of PET positive lesions is overcome by combining the PET and contrast-enhanced CT images (PET-CT).

Several studies have evaluated the role of PET-CT in comparison with that of conventional imaging modalities, such as MDCT or MRI, in patients with GBC. They have shown that PET-CT provides comparable sensitivity, specificity, and accuracy for the diagnosis of the primary tumor and metastases. Compared to those of MDCT and MRI, PET-CT has significantly higher accuracies for
diagnosing regional lymph node metastases and distant metastases. SW Lee et al. reported sensitivities of 87.5% for the detection of primary tumors in patients with GBC and 82.1% for the detection of lymph node metastases by PET-CT\textsuperscript{14}. They also reported maximum standardized uptake value (SUV max) of 3.65 as the best cutoff value for detecting a malignant tumor\textsuperscript{14}.

In our case, the SUV max of the primary lesion was strongly positive (16.1), while the SUV max of the regional lymph node was 3.8, above the cutoff value of 3.65\textsuperscript{14}. Therefore, clinical diagnosis was a primary lesion was associated with acute inflammatory changes, with regional lymph node metastasis.

The cause of the strongly positive value of the primary lesion was initially considered to be due to the involvement of not only tumors, but also inflammatory changes by acute cholecystitis because inflammation may cause artifacts, leading to the diagnosis of cancer on PET-CT. However, the resected specimen revealed a primary lesion and did not indicate pathological inflammatory changes. This result indicates that the origin of the high fever was not acute cholecystitis, and preoperative drainage was not needed to control the high fever. Thus, the improvement of the intermittent high fever after surgery, and the return of the high fever after the recurrence of the gallbladder cancer was likely caused by the neoplasms, a well-recognized phenomenon in patients with neoplasms\textsuperscript{10}. Interleukins, tumor necrosis factor that are induced or produced by neoplastic cells have been suggested to be mediators responsible for neoplastic fever\textsuperscript{10,13}.

In contrast, the regional lymph nodes in the present case were clinically positive in pre-operative PET-CT, but pathologically negative for cancer cells or inflammatory cells. Thus, the SUV max of the regional lymph nodes (3.8) in this case was a false-positive finding. It is difficult to explain these conflicting findings and pathways. The SUV max of the primary lesion (16.1) was remarkably different from that of the metastatic lesion (3.8). In such cases, we might consider not only the absolute values of the SUV max, which are widely used as a cutoff index, but also the relative value, i.e. the ratios of primary to metastatic lesions, to exclude the possibility of false-positive findings.

In our case report, radical and aggressive resection contributed to improving the uncontrollable fever and decreasing the WBC and CRP levels. In the Tokyo Guidelines for acute cholangitis and acute cholecystitis\textsuperscript{16}, due to the potential risks associated with preoperative percutaneous biliary drainage for fistula recurrence and carcinomatous peritonitis, one-stage radical surgery should be conducted as far as the circumstances allow. Thus, in febrile GBC patients, such as in our case, one-stage surgery would be an effective strategy, and preoperative drainage was contraindicated to avoid fistula recurrence or peritoneal dissemination of the cancer cells.

Authors’ contributions:
KH (Kiyoshi Hiramatsu), TS (Tasahi Seki), TA (Takeshi Amemiya), HG (Hidenari Goto), DK (Daiauke Kaga), HF (Hiromori Fujieda) and TA (Toshiyuki Arai) conceived the idea for the paper and helped draft the manuscript. TA (Toshiyuki Arai) proof read the paper. KH (Kiyoshi Hiramatsu) and TA (Toshiyuki Arai) participated in the clinical treatment. All of the authors read and approved the final version of the manuscript.

Competing interests:
The authors declare that they have no competing interests.

Consent for publication:
Written informed consent for publication was obtained from the patient of this case report.

Ethics approval and consent to participate:
We reported this case report in compliance with the Helsinki Declaration. We got approval of ethics committee in Anjo Kosei Hospital. The reference number in this case is C17-015. License number (Kiyoshi Hiramatsu) of clinical research is I60101.

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