CASE REPORT

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Persistent Fever in an Advanced Hepatocellular Carcinoma Case

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Abstract

Fever of unknown origin (FUO) presents a diagnostic challenge due to its wide range of possible causes, necessitating comprehensive evaluation. This case report describes the complexities in a 77-year-old male admitted to the intensive care unit (ICU) with persistent fever. Despite thorough investigations and treatment for identified infections, the fever persisted, leading to an uncommon and challenging diagnostic journey. Further evaluation revealed hepatocellular carcinoma (HCC) with unusual presentations, highlighting the complexities of fever management in oncology settings. This case underscores the need for heightened awareness of malignancy-associated FUO and calls for further exploration into atypical manifestations, offering insights into early diagnosis and management strategies.

Keywords: Cancer; critical care; fever of unknown origin; hepatocellular carcinoma; intensive care.

Introduction

Fever is a common symptom associated with various diseases and has a wide range of possible causes. Fever of unknown origin (FUO) is defined as a temperature exceeding 38.3°C, persisting for at least three weeks, and remaining undiagnosed after one week of thorough medical evaluation [1].

It remains a difficult diagnostic entity, encompassing over 200 possible causes, including infectious, rheumatologic, and malignant conditions [2,3]. A methodological approach, with comprehensive clinical evaluation and value-based investigative work-up, can help establish the diagnosis.

Hepatocellular carcinoma (HCC) is a primary liver tumor that typically develops in the context of chronic liver disease, especially in patients with cirrhosis resulting from alcohol use, chronic viral hepatitis, or nonalcoholic fatty liver disease [4,5]. Diagnosis often occurs late in the disease course due to the absence of symptoms in the early stages. While distant organ metastases are uncommon in HCC, they can occur, particularly in advanced stages. Persistent fever related to the disease itself is not a typical presentation of HCC, but it may arise secondarily due to complications or concurrent conditions.

This report describes the case of a 77-year-old critically ill male diagnosed with FUO, with a focus on his intensive care unit (ICU) follow-up.

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Case Report

A 77-year-old male patient presented to the internal medicine outpatient clinic with concerns of weight loss and fatigue, and had a documented fever above 38.5°C on the days it was measured for approximately ten days. During history-taking, it was noted that he had been Hepatitis C Virus-positive for more than ten years and had received no prior antiviral treatment. Follow-up examinations at the outpatient clinic revealed no pathological findings on physical examination, routine blood tests, urinalysis, or chest X-ray. Despite the absence of abnormalities on these tests, the patient was scheduled for abdominal imaging. He was admitted to the Gastroenterology clinic four days after the outpatient clinic visit due to the onset of hematemesis. During this period, the patient had a daily fever ranging from 38.5°C to 39.1°C and received neither antipyretic treatment nor empirical antibiotics. In addition to hematemesis, he experienced abdominal pain, altered bowel habits, nausea, and vomiting upon admission to the clinic. Notably, jaundice has not yet been reported. Laboratory investigations revealed elevated acute-phase reactants (C-reactive protein [CRP]: 75 mg/L; procalcitonin: 0.85 ng/mL). On upper gastrointestinal endoscopy, no distinct bleeding foci were identified. Grade 1 esophageal varices were observed in the distal esophagus, and antral gastritis was also noted. Due to the detection of suspicious mass lesions and parenchymal heterogeneity in the liver on abdominal ultrasonography, liver magnetic resonance imaging (MRI) was performed. Hepatic MRI indicated chronic parenchymal liver disease, suspected diffuse infiltrative hepatocellular carcinoma, thrombus in the right branch of the portal vein, and ascites (Figs. 1-2). During clinical follow-up, urine and blood cultures showed no bacterial growth. An attempt at paracentesis for ascitic fluid sampling was made but was unsuccessful. Following empirical treatment with ceftriaxone for five days during hospitalization, the patient was discharged, and further investigations were planned to be conducted at the outpatient clinic upon stabilization of his clinical condition, resolution of fever, and absence of any identifiable infection focus. Prior to discharge, a biopsy was obtained from the liver lesion for further evaluation.

Approximately 3-4 days after the liver biopsy, the patient returned to the emergency room (ER) with nausea, vomiting, and shortness of breath. He exhibited tachypnea, paradoxical abdominal breathing, and hypoxemia despite receiving oxygen therapy at 15 L/min. Consequently, the patient was electively intubated and admitted to the medical ICU.

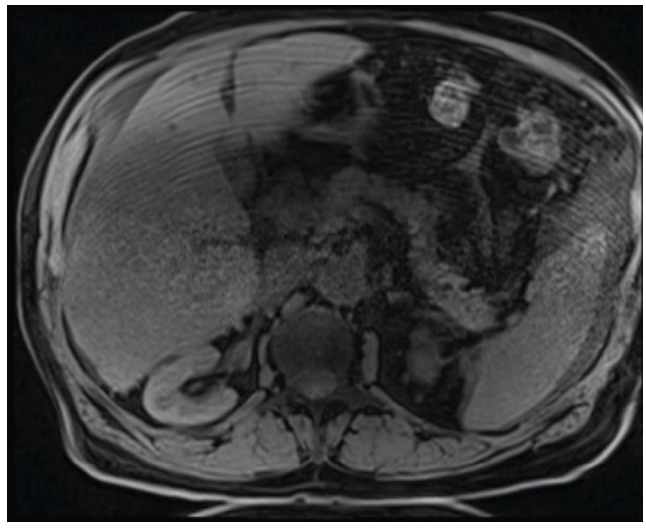

Figure 1. Magnetic resonance imaging (MRI) – Arterial phase: Potential hyperenhancement of hepatocellular carcinoma (HCC) lesions can be observed.

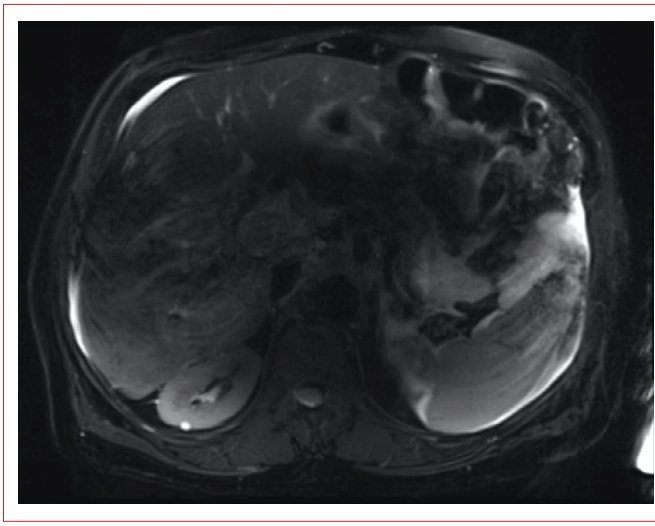

Figure 2. Magnetic resonance imaging (MRI) – Transitional phase or another delayed phase: Useful for assessing washout and capsule appearance.

Upon ICU admission, undifferentiated shock was present, and physical examination revealed abdominal distension and bilateral 1+ pretibial edema. Laboratory investigations demonstrated moderate anemia (hemoglobin: 9.5 g/dL), proteinuria, hematuria, and mild abnormalities in hepatic and renal function tests. CRP and procalcitonin levels were elevated (157 mg/L and 5.85 ng/mL, respectively).

Initially, no distinct focus of infection was detected on physical examination or microbiological testing, although the patient had purulent respiratory secretions following intubation. Empirical therapy with piperacillin-tazobactam (4 × 3.375 g/day) and clarithromycin (2 × 500 mg/day) was initiated. *Streptococcus pneumoniae* was subsequently isolated from the endotracheal aspirate and aerobic blood cultures. Piperacillin-tazobactam and clarithromycin were discontinued on the fourth day, and cefotaxime was started at 6 g/day. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test was negative, while the respiratory pathogen panel revealed rhinovirus positivity.

Due to the persistence of fever under antimicrobial therapy, vancomycin at a dose of 1600 mg/day was empirically initiated on the seventh day of ICU admission to cover suspected staphylococcal involvement. Despite the combination of vancomycin and cefotaxime, the patient's fever persisted. Therefore, after 48 hours, vancomycin was discontinued, and anidulafungin (loading dose of 200 mg, followed by 2 × 100 mg/day) was initiated empirically.

Two days after this treatment modification, *Klebsiella pneumoniae* was isolated from an endotracheal aspirate culture. As the patient had emerged from shock and acute-phase reactants had decreased (CRP: 88 mg/L; procalcitonin: 1.02 ng/mL), no further changes in empirical antibiotics were planned. However, two days later, due to acute clinical deterioration in oxygenation and the recurrence of shock, cefotaxime was discontinued, and ceftazidime-avibactam at a dose of 3 × (2 g/0.5 g) per day was initiated. Despite persistent fever, the patient recovered from shock and oxygenation improved over the following days, although he was never weaned from invasive mechanical ventilation.

During follow-up, as no microbiologically proven fungal pathogens were identified, anidulafungin was discontinued, and antimicrobial treatment was continued with ceftazidime-avibactam alone. The patient again developed circulatory shock, and despite appropriate resuscitation and interventions, he died on the 16th day of ICU stay. Fever persisted throughout the patient's ICU course, with no apparent correlation between fever patterns and any antibiotic regimen or clinical improvement. Transthoracic echocardiography and fundus examinations were performed, with neither showing findings suggestive of infective endocarditis. Two peritoneal fluid samples showed no evidence of peritonitis, and culture results were negative. No signs of infection were detected in the cerebrospinal fluid sample, and the tuberculosis PCR test was negative.

Serological tests for *Brucella*, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV) were negative. Thoracic computed tomography (CT) was performed on the fourth day of ICU admission and revealed multiple lesions, the largest being an irregularly bordered mass measuring 63 mm in the right lung, with a radiological interpretation suggestive of a metastatic mass (Fig. 3). A liver biopsy obtained during the gastroenterology clinic stay was reported on the seventh day of ICU admission as moderately differentiated HCC.

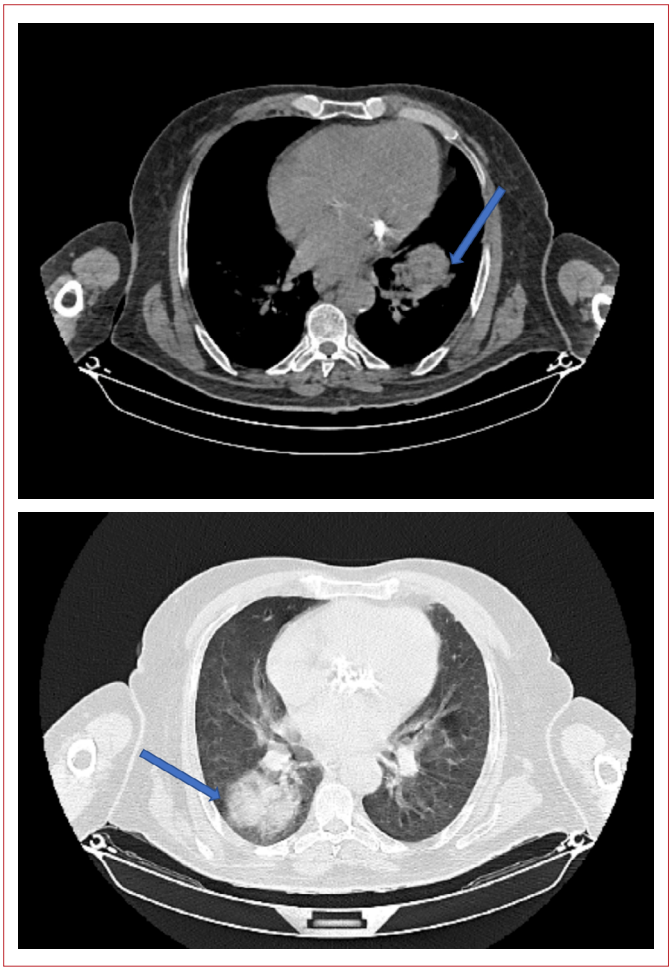

Figure 3. Thoracic computed tomography (CT) scan.

Discussion

In our investigation, we identified more than one episode of nosocomial infection and isolated specific microbiological agents. However, the onset and persistence of fever occurred before the patient's ICU admission. Moreover, the fever was not only unresponsive to various antibiotic regimens but also showed no decline in frequency despite clinical and laboratory improvement with appropriate antimicrobial therapy. The presence of a malignant etiology (with no pathological diagnosis available, but with radiological findings suggestive of HCC metastasis) and the persistence of fever despite clinical and laboratory response to infection-directed therapy, as well as its ongoing nature even after resolution of microbiologically documented infections, led us to consider that the fever in this patient may have been associated with advanced malignancy.

Tumor necrosis and pyrogenic cytokine production are the likely mechanisms of tumor-related fever [6]. Fever is not a common presenting symptom in most solid-organ malignancies but has been reported, particularly in patients with renal cell carcinoma [7]. Our case adds a layer of complexity, as the patient, despite having HCC, experienced continuous fever for more than three weeks and ultimately succumbed to septic shock. The persistence of fever in cancer patients, even with appropriate therapy for infectious causes and thorough evaluation for non-infectious etiologies, underscores the challenges of fever management in oncology.

Distinguishing between infectious and non-infectious causes of fever at onset is particularly difficult in patients with cancer. A substantial prospective study by Toussaint et al., [6] encompassing 477 episodes of fever in cancer patients, revealed that infection accounted for the majority (67%) of fever cases. Respiratory tract infections were the most common infectious causes, followed by bacteremia, urinary tract infections, and soft tissue infections. Non-infectious causes, constituting 23% of cases, included neoplastic fever attributed to the tumor, fever following surgical or invasive procedures, drug-induced fever, and FUO, which accounted for 10% of cases.

Hepatocellular carcinoma typically presents with non-specific symptoms in the early stages. As observed in our case, these symptoms may range from abdominal pain, weight loss, and a right upper quadrant mass to unexplained deterioration in later stages of the disease. However, the occurrence of HCC presenting as persistent fever is rarely reported in the medical literature [8,9].

Our case underscores the importance of recognizing that FUO can serve as a presenting symptom of malignancy and, despite treatment of concurrent infections, may persist. The limited literature on HCC presenting with FUO highlights the need for further exploration and understanding of this atypical manifestation. In clinical practice, heightened awareness of the potential association between FUO and malignancy, especially HCC, may be essential for early diagnosis and appropriate management. Future research and additional case reports are necessary to expand our knowledge and refine therapeutic approaches for such complex clinical scenarios.

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