

The Impact of the Pandemic on the Progression and Delayed Diagnosis of Hepatocellular Carcinoma with Associated Infection: A Case Report.

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Abstract

Objective: To present a case of late diagnosis of hepatocellular carcinoma complicated by cutaneous focus infection due to uncontrolled diabetes mellitus. Additionally, to discuss treatment options, risk factors, relevant literature, and the impacts of the Covid-19 pandemic on diagnostic delays. Case report: A patient diagnosed with alcoholic liver disease since 2019 lost ambulatory follow-up due to the Covid-19 pandemic. However, in 2023, he presented with generalized 4+/4 jaundice, ascites, anorexia, unquantified weight loss, and night sweats more than twice a week, as well as constipation. He denied fever, bleeding, and vomiting. He was admitted to Hospital Universitário Getúlio Vargas and also required significant surgical intervention. Imaging exams revealed multiple nodular lesions in the liver, raising suspicion for hepatocellular carcinoma. After stabilizing the patient and establishing the diagnosis, he was referred to the Fundação Centro de Controle de Oncologia do Estado do Amazonas (FCECON) for abscess drainage and to the Hepatology outpatient clinic for further management. **Discussion:** The Covid-19 pandemic led to the suspension of many outpatient activities in order to avoid virus transmission, resulting in many patients losing follow-up for various comorbidities. The patient's disease progression in the subsequent years was intense both in laboratory and clinical aspects. Previous imaging exams from 2020 did not show any expansive lesions, whereas recent exams showed suggestive nodules and signs of fibrosis.

Keywords: Hepatocellular carcinoma, Cutaneous infection, Cirrhosis, Covid-19

1. Introduction

Hepatocellular carcinoma (HCC) is the most prevalent primary hepatic neoplasm and the leading cause of mortality among patients diagnosed with liver cirrhosis¹. Currently, it ranks sixth globally in terms of incidence and is the third leading cause of death from neoplasms. It typically arises in patients with advanced liver cirrhosis, with a higher prevalence in males who are overweight and around 60 years of age². The main etiologies associated with liver cirrhosis, along with viral hepatitis, include excessive alcohol consumption and non-alcoholic fatty liver disease (NAFLD). Other etiologies stemming from excessive medication use, autoimmune disease, and metabolic causes also contribute to the progression of chronic liver diseases that may eventually evolve into hepatocellular carcinoma³. Therefore, risk factors associated with the development of HCC include hepatitis B and C virus infections, liver cirrhosis, excessive alcohol consumption, exposure to hepatotoxic toxins, NAFLD, type 2 diabetes mellitus, and HIV infection³. Additionally, delayed diagnosis is considered one of the main reasons for increased mortality in patients with HCC.

HCC rarely occurs in non-cirrhotic livers, with its hepatocarcinogenesis divided into several stages involving the progression from cirrhosis to regenerative nodules, which then transform into dysplastic nodules and later into fibrotic lesions. Among the various methods to estimate the severity of hepatic parenchymal fibrosis, the FIB-4 score is the most indicated score in a clinical setting.

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Regarding the symptoms presented by the patient, they may be asymptomatic, especially in the initial phase, when diagnosis is made through laboratory tests combined with imaging studies. Typically, at this stage, the patient may experience nonspecific symptoms such as asthenia associated or not with dyspeptic symptoms⁸. As the disease progresses, the individual develops debilitating asthenia, nausea, vomiting, anorexia or hyporexia, diffuse and/or scleral jaundice, ascites, cholangitis, fatty stools, and often present with upper gastrointestinal bleeding. In addition, it is important to notice that the symptomatology may not include fever.

As the disease progresses, late manifestations that are typically associated to malignancy become more evident: dehydration, malnutrition, sarcopenia, weight loss (>10% of body weight in 6 months), hepatosplenomegaly, and bacterial peritonitis. Additionally, signs of blood dyscrasia (hematomas, ecchymoses, etc.) and decreased urinary output are also observed. In the diagnostic investigation, it is important to consider not only the patient's medical history and physical examination but also to perform laboratory and imaging tests¹⁰. Regarding laboratory evaluation, we may observe slightly elevation of transaminases; altered coagulation studies, such as increased PT/INR associated with thrombocytopenia; elevated canalicular enzymes; increased levels of bilirubin; anemia possibly associated with leukocytosis and neutrophilia in cases of bacterial coinfection; and elevated tumor markers, especially alpha-fetoprotein (AFP).

Regarding imaging studies such as ultrasound, findings may include: a tumor capsule perceived as a hypoechoic ring; a mosaic pattern; invasion of the portal vein, hepatic vein, or bile duct along with nodules of different sizes. Computed tomography (CT) reveals a hypodense lesion with hypervascular characteristics in the arterial phase, as well as demonstrating a mosaic pattern. Magnetic resonance imaging (MRI) intensity of the tumor depends on the size of the lesion and histological differentiation; however, it typically presents as hyperintense on T2 with hypervascularization in the vast majority of cases. Finally, as a diagnostic complement, magnetic resonance cholangiopancreatography (MRCP) and angiography can be performed in order to evaluate the bile ducts and celiac trunk, respectively. In assessing the prognosis of the individual, tumor staging, degree of liver damage, clinical condition, and responsiveness to treatment are considered^{8,13}. Among the tools for evaluating these parameters, there are a few classification tools: Okuda Classification⁸, which evaluates tumor dimensions along with clinical-laboratory manifestations such as ascites, albumin levels, and bilirubin; BCLC^{8,13} (Barcelona Clinic Liver Cancer), that assesses disease progression by combining other scores and classifications (Performance status, Okuda, and Child-Pugh) with tumor staging and bilirubin levels; and finally, the TNM staging system whose parameters include size, lymph node involvement, and distant metastases.

Often patient treatment will be of palliative nature given the aggressiveness of the HCC¹³. Among the treatment approaches that offer potential cure we have surgical resection, transplantation, and percutaneous ablation. Therapies that have positive impacts on patient recovery but may not have curative potential include systemic chemotherapy and transarterial chemoembolization¹⁴. It is important to notice that the high immunosuppression predisposes infections, with the most common focus sites being abdominal, respiratory, urinary, and cutaneous. Cutaneous involvement is the most prevalent. Bacterial skin infections exhibit a diverse array of presentations, etiology, and severity levels, often categorized as either low-risk or high-severity conditions¹⁶. Among the most common microorganisms behind these infections are *Beta-Hemolytic Streptococcus*, *Enterococcus spp.*, or *methicillin-resistant Staphylococcus aureus* (MRSA)^{16,17}. These infections typically manifest with inflammatory signs, which may or may not be accompanied by additional symptoms such as fever, blisters or ulcers¹⁸. Importantly, these signs and symptoms are not exclusively suppurative, as they sometimes are present in vasculitis or hypersensitivity responses. It is important to recognize that these manifestations are often absent in immunocompromised patients due to the pathophysiological nature of their condition.

Abscesses and furunculosis are the most common presentation of immunocompromised patients¹⁸. Cutaneous abscesses are collections of pus within the dermis and hypodermis, delineated by erythematous-edematous borders. Conversely, furuncles are infections of the hair follicle where purulent content extends through the dermis into the subcutaneous tissue, forming a small localized accumulation in the hypodermis^{16,18}. Carbuncle (or anthrax) is the convergence of several inflamed follicles that merge into one single inflammatory mass filled with purulent content. In the initial and deeper stages, these conditions may not always show signs of fluctuation. Moreover, in severe cases, they can progress into cellulitis^{16,18}. *Staphylococcus aureus*, particularly *Methicillin-resistant Staphylococcus aureus* (MRSA), predominates as the primary etiological agent in non-complicated cutaneous abscesses¹⁷. Risk factors include contact with individuals who have these lesions, immunosuppression, diabetes mellitus, and breaches in the skin barrier. The most affected regions include the cervical, facial, axillary, and gluteal areas, although they may also manifest in other areas of the body.

The diagnosis of cutaneous infections predominantly relies on clinical assessment. However, when there is doubt about their nature, complementary exams such as soft tissue ultrasound (USG), blood culture, and antibiogram analysis serve to confirm the diagnosis definitively¹⁹. These diagnostic tools alongside with clinical assessment are invaluable in guiding healthcare professionals toward selecting the most effective antibiotic

therapy. Treatment of isolated furuncles of lesser expression can be done with application of topical antibiotics for 7 to 10 days. Surgical drainage of the lesion should be performed in the fluctuation phase, avoiding it in the initial phase of the disease. However, in the majority of cases, antibiotic therapy complements drainage procedures^{17,19}. In larger abscesses, systemic antibiotic therapy is indicated, especially if there is erythematous area greater than 2 centimeters surrounding the lesion. In cases of anthrax, systemic antibiotic therapy should be combined with surgical drainage¹⁹. The antibiotics are usually Beta-Lactams or Lincosamides. For lesions colonized with MRSA treatment options include Sulfamethoxazole combined with Trimethoprim, isolated Lincosamides, or isolated Glycopeptides.

Finally, the aim of this study is to describe the case of a male patient who was hospitalized in the Gastroenterology and Hepatology ward at the Hospital Universitário Getúlio Vargas (HUGV) in Manaus, Amazonas, Brazil. A case in which the Covid-19 pandemic and its consequences were fundamental to the delayed diagnosis and in worsening the prognosis of the patient. The patient was diagnosed with hepatocellular carcinoma with bacterial coinfection due to a cutaneous abscess aggravated by uncontrolled diabetes mellitus (DM).

2. Methodology

This study was conducted as a clinical case report, in which no identifiable data were disclosed that could reveal patient's identity to readers. This study adhered to strict confidentiality protocols to safeguard the patient's privacy. All information collected was obtained exclusively through review of medical record, conducting in-person interviews within outpatient clinics and hospital wards. Additionally, proper documentation was completed to obtain the patient's explicit consent for the use of the gathered information in this study, ensuring anonymity. This consent was obtained through the completion of a Free and Informed Consent Form (FICF), with the patient's agreement and full understanding of the utilization of their data in this report.

3. Case Report

Patient E.A.L., 56 years old, male, comes to the Gastroenterology and Hepatology outpatient clinic at the Hospital Universitário Getúlio Vargas (HUGV) on January 10th, 2024. He disclosed discontinuation of treatment for alcoholic cirrhosis, attributing it to the pause in outpatient public health services during the Covid-19 pandemic in 2020. During the consultation, the patient reported lower limb edema of progressive nature for the past 6 months, 4+/4 jaundice, ascites, anorexia, unquantified weight loss, and night sweats more than twice a week, as well as constipation. He denied other symptoms such as fever, bleeding, and vomiting. He denied family history of malignancies and also denied smoking. The patient is a former alcoholic, having maintained abstinence for 16 years.

The patient was diagnosed with cirrhosis in 2019 when he was hospitalized due to symptoms similar to those currently presented, subsequently he was referred for outpatient follow-up post-discharge. Notably, he reports a positive maternal family history for liver cirrhosis. Accompanied by his wife, she reports that the patient has undergone six elastic band ligations, with the last procedure in August 2022. However, opted against further sessions due to the lack of infrastructure offered at the institution where the procedures were performed. Furthermore, he discloses a history of uncontrolled type 2 diabetes mellitus diagnosed in 2012, during which he was prescribed Gliclazide 60 mg twice daily; also, systemic arterial hypertension diagnosed in 2023, to which he was prescribed Losartan 50 mg once daily and Carvedilol 3.125 mg every 12 hours.

After thorough investigation, hospitalization was requested to stabilize the patient's condition and conduct further diagnostic investigation. After 9 days from the first consult, on January 19th, 2024, he was admitted to the HUGV ward. During hospitalization he developed a progressively enlarging abscess in the interscapular dorsal region, characterized with local inflammatory signs and significant edema. Concurrently he manifested innumerable symptoms such as: generalized weakness, chills, night sweats, hematemesis, and febrile episodes ranging from 37.8°C to 38.2°C. Upon physical examination, the patient presented with 1+/4+ pallor, diffuse jaundice 3+/4+, non-cyanotic appearance, eupneic in ambient air, and normohydrated. Head and neck examination, cardiac and pulmonary auscultation yielded unremarkable findings. He also presented an ascitic abdomen with a circumference of 120 cm, displaying slight distention without palpable hepatosplenomegaly. The Traube space was unobstructed with audible bowel sounds, while upper abdomen was tympanitic, and lower abdomen was dull to percussion. Furthermore, the patient presented positive Puddle sign.

4. RESULTS And DISCUSSION

During the current hospitalization, laboratory assessments revealed significant abnormalities from the outset. These included anemia, elevated PT/INR indicative of coagulation factor dysfunction due to hepatopathy, elevated C-reactive protein attributed to the ongoing infection, and fluctuating hyperglycemia managed with regular insulin, thus justifying capillary blood glucose monitoring every 6 hours. Furthermore, elevated levels of creatinine (3.0), transaminases up to 5 times the reference value, canalicular enzymes up to 5 times the reference

value, hypoalbuminemia, and increased total bilirubin due to conjugated bilirubin. In order to address the exacerbated hyperglycemic peaks potentially induced by the infectious condition, NPH Insulin 0.4 IU/kg/day was initiated, administered as 30 units before breakfast and 11 units before dinner.

Following daily laboratory tests highlighted a worsening anemic state, persistent alteration in PT/INR being treated with Phytonadione (vitamin K) 10 mg once daily, and persistent elevation of C-reactive protein, transaminases, canalicular enzymes, and direct bilirubin. Additionally, hypoalbuminemia persisted, prompting the initiation of 3 ampoules of albumin every 8 hours on January 22nd. During the hospitalization period, the patient experienced multiple asymptomatic episodes of hyperkalemia, which were promptly corrected with Glucose-Insulin therapy. Additionally, the initial laboratory evaluation, facilitated the calculation of scores such as Child-Pugh and MELD to quantify the severity of liver disease and assess the need for liver transplantation. For this patient, Child score was determined as 11C and MELD score was as 29, indicating moderate severity of liver disease with a high mortality risk (100% mortality within 1 year and 76% mortality within 3 months). Notably, the alpha-fetoprotein level recorded on August 8th, 2023 was 512.16.

Upon admission, the patient was prescribed antibiotic therapy with Ceftriaxone 1 g every 12 hours associated with Clindamycin 600 mg every 6 hours for a 7-day regimen. This treatment protocol was initiated due to a deep cutaneous abscess in the dorsal region, measuring approximately 7.5 cm in length, characterized by well-defined edges, significant edema, erythema around the lesion, and purulent drainage, alongside a persistent fever of 37.8°C. It is worth noting that prior to admission, the patient was on the 4th day of ciprofloxacin which was discontinued upon admission.

Upon completion of the antibiotic course on January 24th, 2024, a blood culture with antibiogram was requested, revealing no further pathogen growth. Subsequently, a consultation with the Hospital Infection Control Committee (HICC) was sought. It was suggested to transition the antibiotic regimen to Zosyn 4.5g every 6 hours for the first 48 hours, followed by renal clearance adjustment. Additionally, it was advised to substitute Clindamycin with Vancomycin 500 mg IV every 6 hours, with each dose administered over a 3-hour period for an additional 7 days, also adjusted for renal function after 48 hours. Both antibiotic courses were completed on February 8th.

Furthermore, on January 23rd, 2024, a consultation with the General Surgery Department was requested to address the abscess drainage. It was recommended to maintain the ongoing antibiotic therapy and then schedule resection of the lesion. The procedure was performed on January 28th, involving an incision with open wound for spontaneous drainage, aiming for healing by secondary intention. Following completion of antibiotic therapy, the patient presented a cavitory operative wound characterized by regular and well-defined edges. There was signs of infection or active bleeding, with minimal serous exudate drainage. Finally, granulation tissue and fibrin were evident, signifying an ongoing healing process.



Figure 1: Personal Archive



Figure 2: Personal Archive

Due to a significant decrease in renal function, a 24-hour proteinuria test was requested on January 24th, 2024, alongside a urinary tract ultrasound. The results showed a significant increase in proteinuria (1100 mg), as well as signs of bilateral nephropathy, thickened bladder and moderate ascites on ultrasonography. Subsequently, on February 29th, 2024, a consultation with the Nephrology department was requested to explore the possibility of chronic kidney disease (CKD) due to decompensated diabetes mellitus associated with a creatinine clearance of 79 ml/min, indicative of stage 2 CKD.

On January 19th, 2024, an Upper Gastrointestinal Endoscopy was requested due to hematemesis, the patient's history of elastic ligations, and underlying hepatopathy. The goal was assessing the presence of new esophageal varices and any potential pathology in the gastrointestinal tract. The endoscopic examination revealed fine-caliber esophageal. Within the distal third of the esophagus, three straight, fine blue varicose veins were noted, but without signs of active bleeding. Additionally, mild portal hypertensive gastropathy, mild erosive flat gastritis, and mild exanthematic duodenitis were observed. The patient also brought a non-contrast abdominal computed tomography scan from January 15th, 2024. The CT findings indicated absence of bile duct dilation, a dilated portal vein measuring 1.5 cm in diameter, splenic vein ectasia measuring 1.2 cm, periumbilical and perisplenic varicosities, and edema of adipose tissue planes within the abdominal wall. Furthermore, he also brought a total abdominal Doppler Ultrasound, which exhibited signs consistent with chronic hepatopathy and portal hypertension, including epigastric varices, a liver nodule displaying a regenerative pattern, and splenomegaly, with neoplasia not conclusively ruled out. Previous ultrasound examinations did not detect any expansive masses.

On February 1st, during hospitalization, a magnetic resonance imaging (MRI) of the upper abdomen was conducted. It revealed signs of chronic hepatopathy, along with heterogeneous nodular lesions in segment IV and VII, measuring 5.8 cm and 5.1 cm in diameter, respectively, suggestive of hepatocellular carcinoma (HCC); Notably, the previously pervious portal vein exhibited a normal caliber, and signs of recanalization of the umbilical vein, splenomegaly and ascitis were observed. There was no evidence of dilation of either intrahepatic or extrahepatic bile ducts. After the infection was successfully stabilized, the patient continued to show no symptoms following the initial clinical presentation. Daily occlusive compressive dressing in the abscess area was administered, and there were also notable improvements in renal function, resolution of anemia, and normalization of electrolyte levels, despite persistent alterations in TP/INR. Before discharge, the medical team conducted new laboratory tests, facilitating a reassessment of the Child-Pugh and MELD scores. These tests revealed a decrease in both scores, with the Child-Pugh score decreasing to 9B and the MELD score to 20, indicating positive progress in the patient's condition.

After careful consideration, the medical team recommended hospital discharge on February 9th, 2024, along with a comprehensive plan for ongoing care. This plan includes a referral to the Fundação Centro de Controle de Oncologia do Estado do Amazonas (FCECON) for specialized oncology support, arrangements for dressing at the stomatherapy unit within the primary care outpatient clinic, coordination for follow-up care at the Gastroenterology and Hepatology outpatient clinic of the HUGV, and a referral to the nephrology outpatient clinic to address any kidney-related concerns, and also prescriptions for Losartan 50 mg - 1 tablet daily, Gliclazide 60 mg - 2 tablets daily, and Carvedilol 3.125 mg - 1 tablet every 12 hours (with a dose adjustment planned for the next visit, increasing to 6.25 mg every 12 hours).

5. Final Consideration

As discussed in this study, hepatocellular carcinoma (HCC) stands out as one of the most aggressive neoplasms, characterized by elevated mortality rates. The Covid-19 pandemic led to the temporary suspension of numerous public outpatient activities in order to avoid transmission and overcrowding. Unfortunately, these security measures resulted in interruption of follow-up care for innumerable patients with various comorbidities, including the individual described in the study. The disease progression in subsequent years was intense, both clinically and biochemically. Notably, exams from 2020 failed to show expansive lesions, whereas recent examination showed nodules and signs of fibrosis. The diagnostic investigation encompassed a comprehensive evaluation comprising clinical manifestations, imaging studies, laboratory investigation, and tumor markers analyses. Upon returning to the specialty outpatient clinic, the patient reported no gastric complaints, with no episodes of nausea, vomiting, or bleeding, and maintained normal physiological functions while tolerating oral diet satisfactorily. Currently, undergoing follow-up for management of the hepatic nodules at the FCECON, awaiting results of new laboratory and imaging exams.

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