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Case Report

Internal Medicine Section

Diagnosis of Hepatocellular Carcinoma through Telehealth: A Unique Case Report

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ABSTRACT

Hepatocellular Carcinoma (HCC) is common among individuals with cirrhosis, regardless of the cause, but rare in those without cirrhosis. While HCC typically spreads to lymph nodes in the abdomen, lungs, and bones, metastasis to the cardiac region is relatively uncommon. Early screening and diagnosis are crucial for determining the feasibility and prognosis of HCC treatment. In addition to well-known causes such as alcohol consumption and viral hepatitis B and C, Non alcoholic Fatty Liver Disease (NAFLD) is emerging as a significant risk factor for cirrhosis, steatosis, and advanced liver fibrosis, contributing to the rise in HCC cases due to the increasing prevalence of metabolic syndrome. The present case report highlights a 71-year-old patient with HCC who was able to receive a timely diagnosis through telemedicine and initiate treatment with an oncologist. The patient underwent Intensity Modified Stereotactic Radiotherapy (IMSR) followed by bridge therapy with chemotherapy drugs. The treatment plan was implemented in July 2022, and the patient tolerated it well, remaining haemodynamically stable with no complaints.

Keywords: Chemotherapy drug, Cirrhosis, eHealth, Liver cell, Telemedicine

CASE REPORT

A 71-year-old male patient consulted a general medicine expert through teleconsultation in June 2022, and all of his demographic information was collected. An electronic medical record with a Universal Healthcare Identifier (UHID) was established. The patient presented with gradual onset moderate generalised asthenia and fatigue, decreased appetite, nausea, abdominal discomfort, bloating, and acute bodyaches for the past 10 days. Further history revealed that the patient had co-morbidities of diabetes mellitus for 16 years, managed with glimipride 1 mg twice and metformin 500 mg twice per day, and hypertension for 12 years, controlled with cilnidipine 10 mg once per day. The patient had a significant past history of an unknown liver ailment 35 years ago, for which he received treatment, but no documentation was available. The patient reported no alcohol consumption.

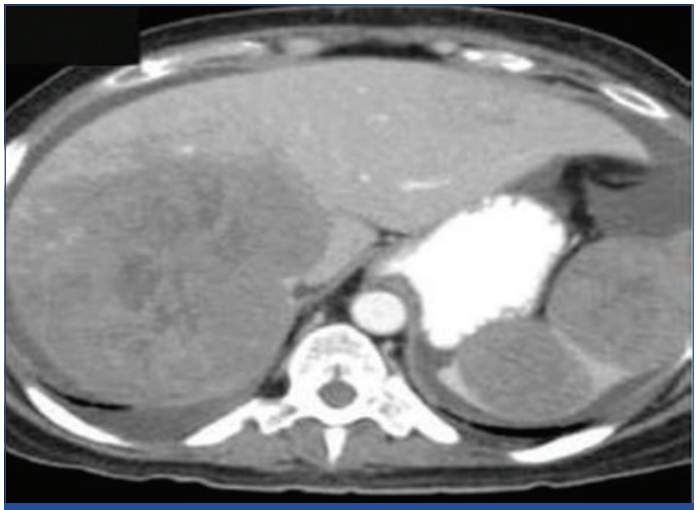
Vital signs were recorded, showing a height of 176 cm, weight of 83 kg, body temperature of 97°F, pulse rate of 88 beats per minute with a regular rhythm, respiratory rate of 17 cycles per minute, and blood pressure of 135/80 mmHg. General and systemic examinations were conducted virtually with the assistance and coordination of the centre's duty doctor and paramedic under the guidance of specialists. No clubbing, cyanosis, pallor, lymphadenopathy, or severe pedal edema was observed during the general examination. However, icterus (jaundice) was present. No abnormal findings were detected during the cardiac examination, with no heaves, thrills, murmurs, or adventitious sounds. Tracheal examination revealed normal findings with vesicular breath sounds. No rhonchi or crackles were heard. Abdominal examination showed distension with mild tenderness over the right hypochondriac and umbilical areas, guarding, rigidity, and no palpable mass. Moderate hepatomegaly (enlarged liver) was observed, while no splenomegaly (enlarged spleen) was noted. Auscultation revealed normal bowel sounds. The central nervous system examination showed normal motor and sensory systems, with normal deep tendon reflexes, plantar reflexes, gait, and coordination.

Initially, symptomatic management was prescribed, including rabeprazole 20 mg once daily, ondansetron 4 mg as needed, syrup of aluminum hydroxide and milk of magnesia twice daily, paracetamol 500 mg as needed, along with a vitamin B12 supplement. The patient was asked to review after three days. However, as there was no improvement in symptoms, routine blood work was advised. The investigations revealed mild anaemia with a haemoglobin level of 10 grams/dL. The liver function profile showed elevated total and indirect bilirubin levels, as well as elevated levels of Serum Glutamic Oxaloacetic Transaminase (SGOT/AST), Serum Glutamic Pyruvic Transaminase (SGPT/ALT), Gamma Glutamyl Transferase (GGT), and Alkaline Phosphatase (ALP). Noteworthy results included a total bilirubin level of 2.4 mg/dL, an indirect bilirubin level of 1.1 mg/dL, ALP of 188 u/L, SGOT of 101 u/L, SGPT of 71 u/L, GGT of 190 u/L, globulin of 4.4 grams/dL, and an Albumin/Globulin (A/G) ratio of 0.6 [Table/Fig-1]. Based on the clinical picture and investigation parameters, an abdominal ultrasonography was advised, which revealed involvement of the right hepatic lobe with enlargement, suggesting a possible neoplastic lesion. It also indicated the presence of portal vein thrombosis and mild ascites. Subsequently, a Contrast Enhanced-CT (CECT) scan of the abdomen was performed, which revealed multiple ill-defined heterogeneous arterial phase enhancing masses in the right lobe of the liver, indicating Hepatocellular Carcinoma (HCC), along with enlarged periportal, peripancreatic, and epicardial lymph nodes, and portal vein thrombosis [Table/Fig-2].

Examination	Result	Biological reference interval	Interpretation
Liver function test			
Total bilirubin method: Dichlorophenyl diazonium tetrafluroborate	2.4	0.3-1.2 mg/dL	Above normal
Direct bilirubin	1.3	Less than 0.2 mg/dL	Above normal
Indirect bilirubin method: Calculation	1.1	0.3-1.00 mg/dL	Above normal
ALT/SGPT Method: IFCC without P-5-P	71	Male (Adult): 0-50 U/L Newborn infant: 13-45 U/L	Above high Normal
AST/SGOT Method: IFCC without P-5-P	101	Male (Adult): 0-50 U/L New born Infant: 25-75 U/L Female: 15-60 U/L	Above high Normal
Alkaline Phosphatase (ALP) method: Kinetic PNPP-AMP	188	43-115 U/L	Above high Normal

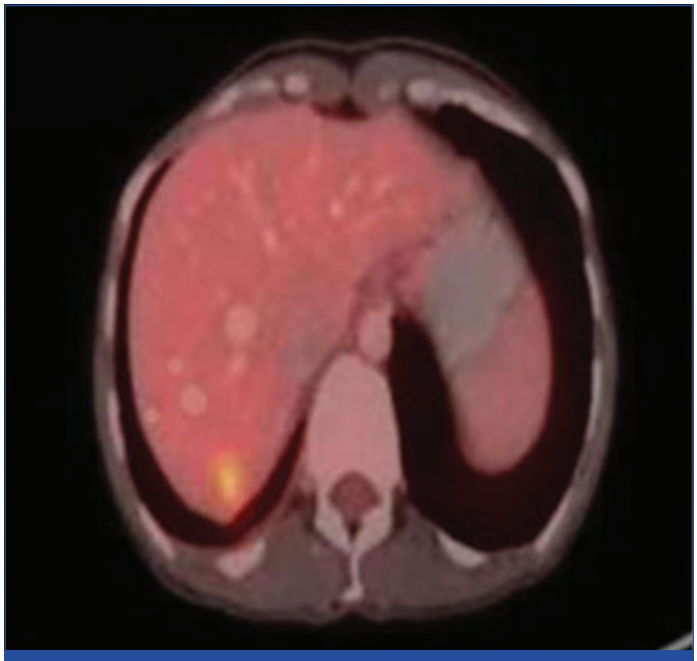
Total Protein (TP) method: Biuret	7.1	6.6-8.3 g/dL	Normal
Albumin method: Bromocresol Green (BCG)	2.7	Male (Adult): 3.5-5.2 g/dL Newborn (0-4 days): 2.8-4.4 g/dL	Normal
Globulin method: Biuret4 bromocresol green+calculation	4.4	1.8-3.6 g/dL	Above high Normal
Albumin/Globulin (AG) ratio method: Calculation	0.6	0.8-2.0	Normal
Gamma-Glutamyl transferase (GGT) method: UV Kinetic	190	0-55 U/L	Above high Normal

[Table/Fig-1]: Initial laboratory investigations.
PNPP: Nitrophenyl phosphate



[Table/Fig-2]: CECT axial image shows the right liver lobe with multiple fused heterogeneously developing lesions with inner necrosis.

To rule out metastasis and secondary growths, a Positron Emission Tomography Scan-Computed Tomography (PET-CT) was conducted, which confirmed multifocal HCC with low-grade metabolically active multiple enhancing lesions in the right and caudate lobes of the liver. No significant regional lymphadenopathy or other evident metabolically active disorders were observed in the rest of the scanned segment of the body [Table/Fig-3].



[Table/Fig-3]: PET fused axial image of right liver lobe with indicating metabolically active hypodense lesions.

Alpha Fetoprotein (AFP) was highly elevated at 3405 ng/dL. Hepatic serology for Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) was negative. Upper Gastrointestinal endoscopy revealed portal hypertension with low-grade esophageal varices. The diagnosis of HCC was established based on the elevated AFP level, along with the findings from the CT and ultrasound scans. The patient received counselling through telemedicine and telehealth, where the carcinoma and the planned therapy were explained in detail. Virtual palliative counselling was provided, and the patient was informed about the potential adverse effects and the tolerance to the therapy. A referral was made to a higher cancer centre, where a team of surgical oncologists, radiation oncologists, and medical oncologists evaluated the patient. Stereotactic body radiotherapy was recommended as the initial treatment, consisting of five fractions based on intensity-modulated radiation therapy. RT stimulation CT scan was performed to initiate the therapy, and the patient received 30 Gy in five fractions at 6 Gy per fraction. The initial plan was to initiate bridge therapy, so chemotherapy with sorafenib was started after radiotherapy. The patient tolerated the treatment well.

The patient has been regularly followed-up through teleconsultations for assistance and guidance, with most of his symptoms alleviated. Routine investigations such as Complete Blood Picture (CBP), liver function tests, and AFP were performed during the follow-up visits, showing a steady decline in the parameters as the treatment progressed. Expert psychologists from Apollo Telehealth conducted psychological counselling sessions through telemedicine to assess the patient's mental status and the impact of cancer on his psychological health. Counselling sessions were conducted as needed. Health coaches from ATH facilitated telemedicine sessions on lifestyle modifications, dietary guidance, and guidance related to the therapy and its adverse effects. The patient felt at ease and comfortable during these telemedicine sessions, which helped instill self-confidence and a positive attitude in dealing with cancer. Confidentiality of patient data, privacy, and security were prioritised and handled with utmost professionalism.

DISCUSSION

Primary liver cancer, commonly known as HCC, is one of the leading causes of cancer-related death worldwide [1]. Cirrhosis and chronic liver disease are the main risk factors for HCC, with viral hepatitis and excessive alcohol consumption being the top two risk factors globally. In less developed countries, HCC ranks as the second most common cause of cancer death in men [1]. About 80% of liver cancers occur in cirrhotic livers, which are at high risk for developing HCC. The management of HCC is challenging, as over 60% of patients are not eligible for surgery at the initial stage due to inadequate liver function and the aggressive nature of liver cell carcinoma. Surgery is only considered for large singular HCCs greater than 10 cm in size [2]. The diagnosis of HCC is established based on clinical findings, as there is no definitive pathological confirmation. Screening for HCC includes regular ultrasound and radiological tests, as well as serological markers such as Alpha Fetoprotein (AFP) every six months [3]. Treatment modalities are decided based on the functional status of the liver, tumour size, presence of metastases, and other factors. Due to the aggressive nature of HCC, it is often detected at an advanced stage with liver metastases [4]. Early detection of cancer is associated with better prognosis, making AFP a commonly used biomarker for HCC diagnosis. In the future, new biomarkers may become available for early lesion detection [4,5].

Histologically, HCC can be well-differentiated or poorly-differentiated, with the most typical architectural pattern being trabecular. Other patterns include sarcomatoid, compact, and pseudoacinar. The histology may vary based on the degree of differentiation, with well-differentiated cells showing smaller size, less nuclear atypia, and double the nuclear density compared to normal liver cells. Moderately-differentiated cells are larger with more eosinophilic cytoplasm, pseudoglands, distinctive nucleoli, bile, and massive

tumour cells. Poorly-differentiated cells are larger with significant pleomorphism and hyperchromatic nuclei, and may contain spindle cell or small-cell regions [6].

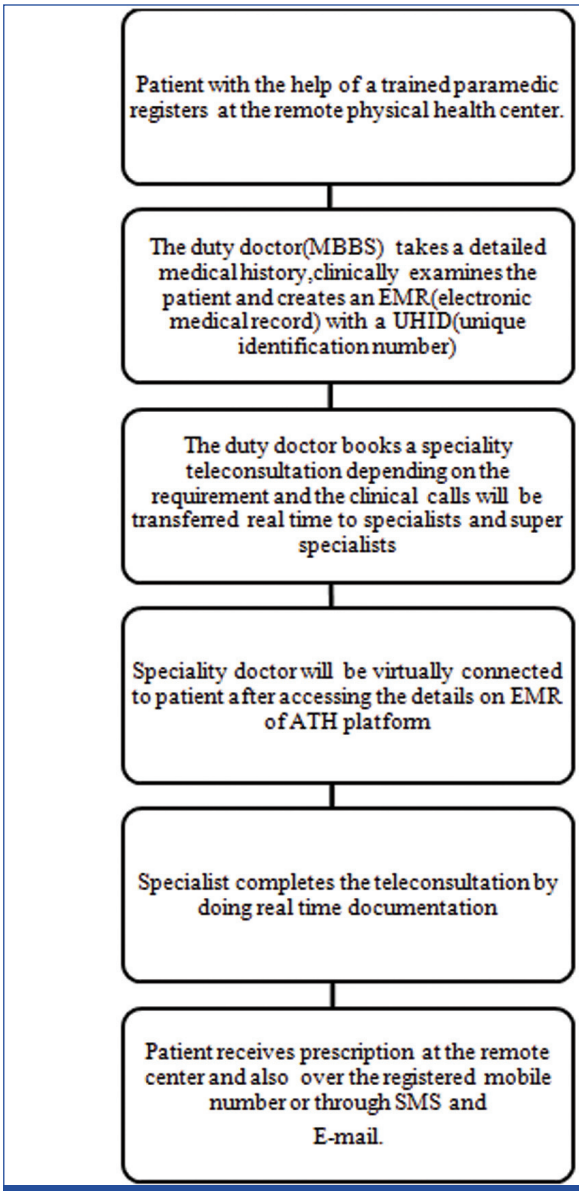
During initial assessment, liver function tests may show elevated levels of bilirubin, ALT, AST, ALP, and albumin, indicating the extent of the condition. Patients with impaired liver function or reserve may also have higher levels of INR, PT, thrombocytopenia, anaemia, hyponatraemia, or hypoglycaemia. These results are typically seen in advanced HCC, chronic hepatitis, or cirrhosis-related HCC. In patients with early, non cirrhotic HCC, liver function test results may be normal. Paraneoplastic symptoms of HCC may include hypoglycaemia, hypercalcaemia, and erythrocytosis. Additional laboratory tests, such as hepatitis B surface antigen, anti-HCV antibody, alpha antitrypsin level, copper levels, and iron saturation, may be conducted to assess the underlying causes of HCC [7].

Alpha Fetoprotein (AFP) is a serum glycoprotein produced by the foetal yolk sac and liver during gestation. Elevated AFP levels are typical in advanced HCC and do not necessarily correlate with tumour size or vascular invasion. Approximately 40% of early HCC cases do not secrete AFP. In early non cirrhotic HCC, serum AFP levels may be within the normal range. A cut-off of 10.9 ng/mL for serum AFP provides a sensitivity of approximately 66% and a specificity of 80% (normal range is between 10 and 20 ng/mL). Serum AFP levels above 200 ng/mL are highly specific but moderately sensitive for detecting HCC. Using a cut-off point of 500 ng/mL, the specificity for detecting HCC in individuals with concurrent liver disease is over 90%. However, patients with chronic hepatitis, cirrhosis, pregnancy, and other germ line and non germ line tumours may also have high serum AFP levels. AFP is used in combination with ultrasound for monitoring HCC. Additional biomarkers such as Des-Gamma-Carboxyprothrombin (DCP) and lectin-bound Alpha fetoprotein may also be increased in HCC [8].

Despite the fact that authors did not have access to these biomarkers, they will be relevant in the future for detecting HCC at the earliest stages. Currently, the only molecular drug authorised for the treatment of advanced hepatocellular cancer is sorafenib. Sorafenib was used in this instance to bridge radiation. It targets Vascular Endothelial Growth Factor (VEGF), Radio Frequency Ablation (RFA), and platelet-derived growth factor receptors. According to data from Guo WJ et al., a combined modality approach is preferable for treating large HCCs, compared to chemoembolisation alone [9]. Sorafenib is also approved for the treatment of advanced HCC by the Food and Drug Administration (FDA) and is considered a "Fast Track" medication. It has shown promising results in Phase III trials [10]. Sorafenib is a small chemical inhibitor that targets Raf kinase, Platelet-derived Growth Factor (PGDF), VEGF receptor 2 and 3 kinases, and the stem cell factor receptor ckit. It inhibits the RAF/MEK/ERK signalling pathway, which regulates cell division and proliferation, and suppresses tumour angiogenesis by blocking VEGFR-2/PDGFR-beta signalling [11].

In the present case, early detection and initiation of therapy were made possible by the cooperative efforts of telemedicine, radiation, and chemotherapy. Early intervention has helped in stopping the progression of carcinoma, and the patient's signs and symptoms have significantly improved. Parameters such as AFP and serum bilirubin levels have shown a steady decline, indicating the effectiveness of telemedicine in early detection and treatment. Telemedicine has facilitated cancer management in the present case, providing psychological counselling, symptomatic treatment, and remote chemotherapy sessions under supervision. The benefits of telemedicine include convenience, safety, reduced healthcare costs, and improved access to care, especially for those in rural areas [12].

Apollo Hospitals, the largest and most established multi-specialty telemedicine network in South Asia, has over 20 years of extensive experience in the sector. They provide high-quality healthcare to both urban and rural communities, offering services such as teleconsultations, teleradiology, telecardiology, telecondition management, and tele-emergency services [13]. [Table/Fig-4] shows a flowchart of the teleconsultation process that authors followed.



[Table/Fig-4]: Flowchart depicting teleconsultation process.

CONCLUSION(S)

In conclusion, telemedicine has the potential to be a valuable tool in the diagnosis and management of HCC. The case study presented demonstrates how telemedicine allowed a patient with HCC to receive a diagnosis and initiate therapy without the need to travel to a large urban centre. Telemedicine also provided the patient with palliative virtual counselling sessions, guidance on therapy compliance, and emotional and mental support through virtual health coaches and telemental counselling sessions. The present report highlights the ability of telemedicine to improve access to healthcare in rural and underserved areas. The findings of the present study suggest that telemedicine can enhance access to and quality of care for HCC patients. However, further research is needed to validate these findings and determine the optimal utilisation of telemedicine for HCC diagnosis and therapy.

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