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**ASSOCIATION OF HEPATITIS-C WITH LIVER CIRRHOSIS AND HEPATOCELLULAR
 CARCINOMA - A CASE STUDY**

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**C ჰეპატიტთან ასოცირებული ღვიძლის ციროზი და ჰეპატოცელულარული კარცინომა -
 კლინიკური შემთხვევა**

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 სამეცნიერო-პრაქტიკული ცენტრი

რეზიუმე

ჩვენს მიერ წარმოდგენილ კვლევაში ჩართულია 57 წლის მამაკაცი, დიაგნოზით ქრონიკული C ჰეპატიტი, ღვიძლის ციროზი, გართულებული ჰეპატოცელულური კარცინოზით. პაციენტს ჩაუტარდა ანტივირუსული მკურნალობა პეგილირებული ინტერფერონით და რიბავირინით, მკურნალობის ხანგრძლივობა 24 კვირა. მკურნალობის დამთავრების შემდეგ აღინიშნა რეციდივი (HCV რნმ-ი დადებითი).

2015 წელს პაციენტი ჩაერთო C ვირუსის სანინააღმდეგო ელიმინაციის პროგრამაში. განმეორებით ჩაუტარდა მკურნალობა სქემით - პეგილირებული ინტერფერონი, სოფოსბუვირი, რიბავირინი. მკურნალობის ხანგრძლივობა 12 კვირა, რის შემდეგ მიღწეული იქნა მყარი ვირუსული პასუხი (HCV რნმ-ი უარყოფითი). პაციენტი იმყოფებოდა მეთვალყურეობის ქვეშ. დინამიკაში გამოვლინდა ჰეპატოცელულური კარცინომა (HCC 2019 წელს), რაც წარმოადგენს ღვიძლის ციროზის ერთ-ერთ გართულებას.

პაციენტს წარმატებით ჩაუტარდა ლობექტომია ქართულ-ისრაელის კლინიკა „ჰელსიკორში“. დღემდე პაციენტის მდგომარეობა არის სტაბილური, გართულების გარეშე.

INTRODUCTION: A principal element named chronic hepatitis C virus (HCV) infection is representative for the occurrence of liver cirrhosis and hepatocellular carcinoma. The majority of cases have identified with chronic infection after transmission of virus. Due to lack of symptoms and progression of disease towards chronic stage large number of cases have been investigated in later stage of disease. In the beginning stage of screening in chronic Hepatitis C-infection HCV antibodies is considered satisfactory and for differentiating continuing infection or past infection sensitive assay is important in positive HCV antibodies [4]. An estimated yearly incidence of 2,59,000 of Hepatocellular carcinoma has been estimated worldwide. Carcinoma has not been detected from hepatitis-C whereas hepatitis-B without cirrhosis was linked to hepatocellular carcinoma with higher frequency according to previous studies. Exact mechanism behind causing carcinoma is unknown since reverse transcriptase activity is seen to be associated with hepatitis-B rather than HCV virus. Some studies disclosed the information regarding prevention by directly suppressing the IFN of cell division and leading to the activation of proto-oncogenes and inhibition of tumour suppressor gene [1].

Research performed in many centres of France have proved that there is higher association of hepatocellular carcinoma in HCV patients with cirrhosis who had received DAA (direct acting antivirals) rather than patients with sustained viral response who acquired this after interferon therapy and the most cases of carcinoma had certain characteristic's like older age, severely impaired function of liver and increase blood pressure in the portal veins [8]. Decision about prognosis and management of hepatitis is based on degree of fibrosis or liver cirrhosis. For identification of liver cirrhosis or related complications transient elastography or fibro scan can be performed which is non-invasive and most appropriate according to studies since liver biopsy is invasive and painful rather worsen the condition of severe patients [2].

Japanese hospitals and clinics have treated near about 8000 patients of hepatitis-C with interferon and investigated them for 1 year between July and August after withdrawing interferon treatment. 33% of patients had confirmed with sustained viral response after 6 months of abolition of treatment and 0.4 % had developed hepatocellular carcinoma [3]. If the patient fulfils the criteria of having tumour size of less than 2 cm then liver resection is possible in 90% of cases which is created by BCLC Staging System as it is the primary treatment option for hepatocellular carcinoma but still not the best choice or suitable for all the patients although other options like liver transplantation can also be chosen according to patient comfort [5].

Tumour marker alpha-fetoprotein in detection of hepatocellular carcinoma or with liver cirrhosis ensures maximum sensitivity and specificity but still using alpha-fetoprotein forlorn may not give accurate results [9]. Research performed during 4 consecutive years have revealed measurement of liver stiffness together with transient elastography was successful to investigate recurrence after resection of hepatocellular carcinoma [6]. Study done in Japanese patients has revealed the development of hepatocellular carcinoma after termination of treatment with Peg IFN α -2b+ribavirin. Although cirrhosis is a self-reliant risk factor in the development of hepatocellular carcinoma, even after elimination of hepatitis requires further careful monitoring in HCV related cirrhosis whether it is compensated or decompensated [7]. Liver resection, radiofrequency ablation, arterial chemoembolization and liver transplantation are the best options if hepatocellular carcinoma is diagnosed at early stages but in later stages tyrosinase kinase inhibitors have showed a promising result since tumour was unresectable [10].

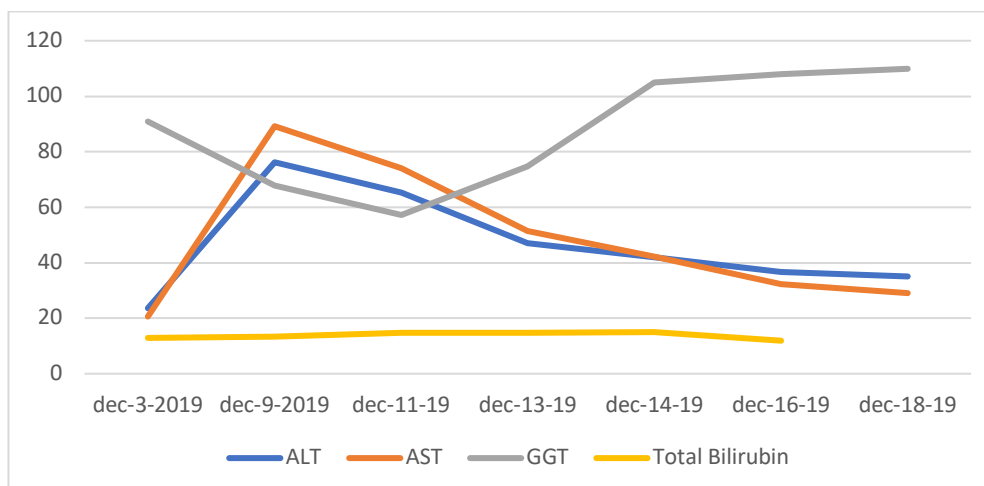
METHODS: In this case study of 57 year old male patient various tests including echocardiography, respiratory function test, ultrasound and MRI Scan, biopsy studies or histological investigations have been performed. This article includes information from various databases such as PubMed, google scholar, science direct etc. It's a case study review.

RESULTS: After performing echocardiography, respiratory function test, ultrasound and MRI Scan, biopsy study of this patient showed following results:

1. Alpha-fetoprotein was elevated to 583 μ l.
2. On assessment of respiratory function ventilation disorders were not detected and post FVC (Functional vital capacity)-94%, FEV1(forced expiratory volume)-100%, FEV1/FVC-0.81
3. On assessment of echocardiography light tricuspid valve defect, high pulmonary artery pressure PASP of 30 mmHg, IVC-1.4cm, collapsed more than 50%, longitudinal aorta-3.75cm, abdominal aorta-2.2cm (normal) was observed.
4. On the basis of histologic investigations 3rd grade hepatocellular carcinoma was identified with lymphangion-invasion and there was no spread to other structures or organs and tumour was localised in 8th segment of the liver.
5. On ultrasound hepatocellular carcinoma was not suspected.
6. MRI of 57-year-old-patient revealed localized operable hepatocellular carcinoma in the 8th segment of size 3.5/2.6 cm.
7. Biopsy: Histological investigations:
 - a) Microscopy: Samples taken from 8th segment of examined liver reveal tumour tissue represented by atypical, polymorphic, hepatocytes which was pronounced, consisting of trabeculae and solid structures. In the part of cells, a sharp polymorphism of nuclei is expressed. Lymph angioinvasion and invasion of normal liver is expressed. There was no damage noticed on the edges of resection. No tumour tissue was detected in 4th and 6th segments of the liver.
 - b) Macroscopy: Material was placed in 3 containers:
 - Tissue measuring 4*3*2 cm was revealed in 8th segment of the liver which was white in colour and dense in consistency.
 - One fragment measuring 0.4*0.1*0.1 cm was revealed 4th segment of the liver.
 - One fragment measuring 0.5*0.2*0.2 was found in 6th segment.

Below given is the chart showing laboratory values of 57-year-old male patient according to test evaluated during December 2019. In this chart varied levels of liver enzymes (alanine transaminase-ALT, aspartate transaminase-AST, Gamma glutamyl transferase-GGT) are mentioned in IU/L (international

units per litre) and total bilirubin levels which are given in $\mu\text{mol/l}$. Initially increased levels of enzymes have been observed and then it got normalized at the end of December.



Following 2015 every month patient has been assessed for liver function tests, ALT, AST, GGT, total bilirubin direct and indirect, complete blood count, alpha-fetoprotein and ultrasound investigation that's why this case is really interesting because more than 80% patient don't visit clinic for follow up and as a result suffers from complications later. According to study of this male patient lobectomy has been performed at GEORGIAN-ISRAEL CLINIC HELSICOR in Tbilisi, Georgia since other costly treatments like liver transplant was not suitable for this patient.

DISCUSSION: According to the recent studies done from the patient at Infectious Disease AIDS and clinical immunology scientific research centre showed chronic infection with HCV and cirrhosis in 57-year-old male patient, the virus is directly linked to the development of hepatocellular carcinoma. This patient referred to this hospital 7 years ago in 2013 and he was diagnosed as chronic hepatitis-c and liver cirrhosis (genotype 3a). Treatment with pegylated interferon (pegasys-180mcg) once a week, ribavirin - 200 ng-daily dose of 1200 ng for 6 months and 24 weeks was continued. Treatment finished without any side effects but after 6 months (24 weeks) HCV RNA was detectable or patient relapsed. After two years in 2015 the patient was switched in elimination programme and antiviral treatment combined with interferon (DAA-direct acting antiviral-sofosbuvir or sofosbuvir 400mg+ pegylated interferon alfa-2a 180 mcg+ ribavirin 200ng, 6tablets during day for 12 months) was started. Sustained viral response developed after continuing all these medications. Liver fibro scan or transient elastography had performed to investigate cirrhosis or other complications. laboratory data showed significantly increased levels of AFP (alpha-fetoprotein) of $475.80\mu\text{l}$. Later abdominal ultrasound was done but could not reveal any lesion. Based on performed diagnostic tests MRI SCAN of abdomen with IV contrast was recommended. For evaluation of heart functions echocardiography was performed. For excluding any lung pathology chest X-ray was performed. Biopsy was taken from 8th, 6th and 4th segment and as a result 3rd grade hepatocellular carcinoma was identified.

CONCLUSION: Based on investigation from 57-year-old male and previous studies hepatocellular carcinoma is investigated due to hepatitis-C with cirrhosis in most cases however it is a rare incidence which arises due to chronic liver disease.

Patient admitted in 2013 and even after elimination of hepatitis-C hepatocellular carcinoma had detected after termination of treatment that's why it is necessary to check alpha-fetoprotein, liver enzymes (ALT, AST, GGT), total bilirubin, investigations like ultrasound every 6 months and liver function test for every patient who suffers from hepatitis-C virus or end stage liver disease to prevent morbidity and mortality because even after termination of treatment or elimination of disease later complications may arise such as hepatocellular carcinoma.

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SUMMARY

Hepatitis-C virus infection (HCV) is endemic in many countries of the world including Georgia. Georgia has a high burden of HCV infection with an estimated 5.4% of adult population (1,50,000) people have identified with HCV. According to NCDC (National Centre for Disease Control and Public Health from May 2015 national HCV programme have been launched, supported by the American company “Gi lead” and the government of Georgia. Our main goal is to investigate and manage the hepatocellular carcinoma. According to the study done from the patient at Infectious Disease AIDS and clinical immunology scientific research centre it has been found that in 57-year-old male patient who was chronically infected with HCV, cirrhosis, the virus has been directly associated with the development of hepatocellular carcinoma. He was diagnosed as chronic hepatitis-C and liver cirrhosis (genotype 3a).

Treatment with pegylated interferon and Ribavirin 1200 mg for 6 months was continued. Treatment finished without side effects but after 6 months HCV RNA was detectable or patient relapsed. In 2015, the patient was switched in elimination programme and antiviral treatment combined with interferon for 12 weeks. Sustained viral response developed 6 months after termination of therapy. The alpha-fetoprotein is important tumour marker and was elevated around 583 µ/l. Ultrasound didn't reveal any lesion but after MRI scan 3rd grade hepatocellular carcinoma was confirmed. Following 2015 every month patient has been assessed for liver function tests, total bilirubin, complete blood count, alpha-fetoprotein and ultrasound investigation and as a result liver enzyme found to be elevated. It's crucial for every patient (end stage of liver disease) to undergo ultrasound investigations, liver function test for further follow up.

Keywords: DAA (direct acting antiviral), HCV RNA, INF (Interferon), Hepatitis C, Hepatocellular carcinoma.

