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Acute Myeloid Leukemia, E-coli bacteremia, Salmonella urinary tract infection, *Clostridium Difficile* colitis, Subarachnoid hemorrhage and Gastrointestinal bleeding in an HCV Cirrhotic Patient on newly approved Anti-HCV Medications

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Introduction

Chronic HCV infection can predispose to different lymphoproliferative disorders including lymphomas (diffuse large B-cell lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma) and plasma cell disorders (monocolonalgammopathies) [1,2]. Kelaidi et al reported a case of large granular lymphocyte leukemia occurring in association with Marginal Zone Lymphoma and HCV and responding to interferon and ribavirin [3]. They have suggested an etiologic link between HCV and antigen-driven lymphoproliferative disorders [3].

A large retrospective cohort study (HCV-infected cohort = 1,46,394; HCV-non-infected cohort = 5,72,293), among US veterans showed significant association between HCV infection and non-Hodgkin's Lymphoma (NHL), Waldenstrom's Macroglobulinemia (WM) and cryoglobulinemia but failed to show any association with Hodgkin's lymphoma (HD) or multiple myeloma (MM), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) [4]. One other study from Hematology departments from ten different Italian cities, the prevalence of HCV infection was higher in patients with CLL (9.0%, 9 out of 100), ALL (7.6%, 5 out of 54), AML (7.9%, 11 out of 140), and CML (12.2%, 6 out of 49) patients. These patient groups were not, however, large enough to render statistically significant results [5]. In one study from the association between HCV infection and AML/ALL/refractory anemia with excess blast was found to be weak and statistically non-significant [6].

Recently the Ledipasvir-Sofosbuvir combination has been approved for treating chronic HCV infection, genotype 1 in both cirrhotic and non-cirrhotic patients [7]. The most common reported adverse events were fatigue, headache, insomnia, and nausea [8]. Documented life threatening complications of the combination medicine includes symptomatic bradycardia especially with concurrent use of amiodarone [9]

Case presentation

We report a 47-year-old male with EtOH/HCV cirrhosis -MELD score 17-, treatment naïve who was started on the combination Ledipasvir-Sofosbuvir on September, 1st, 2015. His baseline blood work was suggestive of pancytopenia mostly secondary to hypersplenism (Table 1). He presented to our hospital ten weeks later with coffee ground emesis, delirium, and hypoxic respiratory failure requiring intubation and mechanical ventilation. Esophagogastroduodenoscopy (EGD) showed non-bleeding gastric varix and portal hypertensive gastropathy with no obvious source of bleeding. MCi Tc-99m Ultratag RBC scan was negative as well. Blood work showed worsening pancytopenia (Table 1), metabolic acidosis and elevated ammonia level. An automated white blood cell differential was not done due to leucopenia. Manual counts showed 70% Neutrophils and 30% lymphocytes. He was given two doses of Granulocyte-Colony Stimulating Factor (G-CSF). Three days later he developed disseminated intravascular coagulation (DIC) with a coagulation panel showing a prothrombin time PT of 35, INR 3.5, fibrinogen less than 60, D-dimer more than 20 and FDP more

than 20. Blood cultures were positive for E-coli bacteremia, stool positive for Clostridiumdifficile and urine culture was positive for Salmonella infection.

Patient was treated with appropriate antimicrobial regimens and blood products. Meanwhile a computed tomographic imaging of head was done due to patient's inability to follow commands while still intubated and off sedation. It showed left frontal and temporal subarachnoid hemorrhage. His blood counts showed sudden rise in WBC, with peripheral blood smear showing 85% abnormal leucocytes with high suspicion for Acute Promyeloid Leukemia(APML). Phenotyping by flow cytometry showed peripheral blood with high population of CD117 positive, CD34 negative, HLA-DR negative myeloblasts representing approximately 93% of leucocytes consistent with Acute Myeloid Leukemia (AML). Subsequently he was started on All-TransRetinoic Acid (ATRA) and Arsenic trioxide. He initially recovered from gram-negative bacteremia, urinary tract infection and intra-cranial bleeding. He was transferred out of the intensive care unit eleven days after admission. He continued his clinical recovery till day eighteen of hospitalization when he complained of abdominal pain and developed hypotension, tachypnea and hypoxia. Acute abdominal series failed to reveal air under diaphragm and any evidence of mega colon. He was transferred back to the intensive care unit and his condition deteriorated rapidly. He had severe lactic acidosis with an arterial PH of 6.8 and eventually cardiac arrest. Resuscitation was unsuccessful and he was pronounced on day eighteen of hospitalization. Autopsy was not done per family request.

We as gastroenterologists, hepatologists and internists should not presume that pancytopenia is solely a manifestation of hypersplenism especially when there is a significant drop in blood counts compared to previous values. Most probably his leukemia and blasts were hiding in the bone marrow and G-CSF subsequently revealed it in the peripheral blood. Finally, we cannot make any conclusions or even suggestions of possible association between chronic HCV infection and leukemia -AML in this case- from one side or between new directly acting antivirals and leukemia from this case but we aim to report this unusual co-incidence.

Table 1: Laboratory results.

	6 months before HCV treatment	70 days after start of HCV treatment	10 Days after APL treatment
HGB	13.4	8.7	7.7
WBC	7.7	0.8	8.8
Platelets	92	23	40
HCV PCR	31,270	Undetectable	NR

Author Contributions

H Salameh and H Saraireh wrote the manuscript and reviewed the literature. H Salameh and S Merwat critically revised the manuscript for important intellectual content, supervised the process and approved the final draft. H Salameh is the article guarantor and the corresponding author.

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