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New onset of multi-drug hypersensitivity reaction after successful treatment of hepatitis C with ledipasvir-sofosbuvir in CKD: A case report.

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Abstract

In recent years, multiple drug regimens are available for the safe and efficient treatment of Hepatitis C in a short period. There are case reports of drug reactions in patients treated with interferon Alfa-2b and ribavirin combination. However, there are no reports of hypersensitivity reactions to previously tolerated medication after eradication of HCV with the new regimen. Here we report a patient presenting with hypersensitivity reactions to multiple drugs, which were previously well tolerated, after the successful eradication of chronic Hepatitis C with the ledipasvir-sofosbuvir combination. The patient may have had an underlying hypersensitivity reaction to medications before his infection with Hepatitis C. Chronic Hepatitis C infection appears to exert an immunosuppressive effect which masks the hypersensitivity reaction. Complete eradication of viral load by the newly available drugs ledipasvir-sofosbuvir unmasked the immunosuppression. However, the immunomodulatory effect of the new drug cannot be excluded as a possible etiology. It is important to know that these hypersensitivity reactions can occur after the successful treatment of Hepatitis C and may cause life-threatening reactions in patients.

Keywords: Hepatitis C, HCV infection, CT scan

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Introduction

The global hepatitis C virus (HCV) prevalence was estimated at 2.5% (177.5 million) of the world population in 2013 [1]. The disease is one of the major causes of chronic liver diseases, and approximately 399 000 people die each year from hepatitis C related illnesses, mostly from cirrhosis and hepatocellular carcinoma [2]. Acute HCV infection usually is asymptomatic, and about 15-45% of infected persons spontaneously clear the virus within six months of infection without any treatment [2]. Therefore, early identification may be needed to prevent chronic infection. Various drugs have been used to treat HCV infection successfully [3-5]. The combination of two or four drugs has been recommended to provide optimal efficacy and to prevent drug resistance [5,6]. During the treatment, patients may suffer cutaneous side effects such as severe generalized nummular eczema which is secondary to interferon Alfa-2b plus ribavirin combination therapy [7,8]. Likewise, other older combinations may also cause similar reactions and are no longer considered first-line treatment for HCV infection. Ledipasvir-sofosbuvir combination is recommended as first-line antiviral therapy for Hepatitis C infection in treatment naïve patients and patients who failed therapy with Interferon-Ribavarin [9].

There are no reports about the resurgence of hypersensitivity reactions to newly available oral anti-Hepatitis C medication. Here we report a patient presenting with hypersensitivity reactions to multiple drugs after the successful treatment of chronic Hepatitis C with the ledipasvir-sofosbuvir combination. The patient had no previous allergic reactions to those drugs prior to successful eradication of Hepatitis C infection.

Case Report

A 74-year-old Caucasian male with chronic Hepatitis C infection with Chronic Kidney Disease Stage-1 was initially treated with Interferon alpha-2b, Sofosbuvir and Ribavirin in January 2015. He developed severe side effects from interferon. In February 2015, he was treated with Ledipasvir-Sofosbuvir for 12 weeks. He tolerated the treatment well and HCV RNA was undetectable 12 weeks after completing the treatment.

Before treatment, his liver function tests, complete blood count and basic metabolic panel were normal, except anemia which was attributed to rectal bleeding. The virus was identified as hepatitis C genotype 1b. Ultrasound of the abdomen and CT scan of the abdomen did not show cirrhosis of the liver. He tested negative for HIV infection.

His past medical history is significant for Resection of the lower lobe of the left lung due to Tuberculosis (1958), bleeding hemorrhoids (1987), cerebrovascular accident (2000, 2014), triple vessel disease S/P coronary artery bypass graft (2002), renal cell carcinoma S/P nephrectomy (2005), Chronic Kidney Disease Stage 1 (2005), Borderline Diabetes Mellitus (2005), Hypertension (2005), H. pylori infection (2005), varicose veins (2005) and left inguinal hernia repair (2017). He has a 150 pack-year history of cigarette smoking and quit smoking 15 years ago. He abused intravenous drugs for 15 years as an American soldier during the Vietnam War. He contracted Hepatitis C infection through intravenous drug abuse.

Table 1. *Hypersensitivity reaction to previously tolerated medications in sequential order after eradication of HCV infection.*

Drug	Type of allergy
Iodine (Radiocontrast)	Pruritic rash, angioedema
Clopidogrel	Localized superficial swelling of skin and lip swelling
Enalapril	Lip swelling and numbness of mouth
Ticagrelor	Pruritic rash, angioedema, shortness of breath
Morphine	Pruritic rash
Hydromorphone	Pruritic rash
Meperidine	Pruritic rash

He was on the following medication for comorbid illnesses for more than 15 years prior to treatment: Tamsulosin, Finasteride, Iron supplements, Enalapril, Aspirin, Metoprolol succinate, Tadalafil, Pantoprazole, Sucralfate, Simvastatin, Clopidogrel, Morphine, Hydromorphone and Meperidine. He was not allergic to any of the above medication prior to treatment. Between June 2015 and 2016 he presented with angioedema and pruritic rash in response to each of the medication in sequential order as shown in Table 1. All hypersensitivity reactions were confirmed to be due to the said medications by a rechallenge with the same medication.

Discussion

Various reactions such as pruritus, rash, and nummular eczema have been documented with Interferon-based treatment for HCV infected patients [3,4,7-11]. Our patient was treated with Ledipasvir-Sofosbuvir which is considered safer and more effective [12]. There are no case reports of new onset of hypersensitivity reactions to previously tolerated medications after the eradication of Hepatitis C virus. We found that this patient developed hypersensitivity reactions in sequential order to different medications to which he had no known allergies for more than 15 years. From our experience, not all patients treated with Ledipasvir-Sofosbuvir develop new onset of hypersensitivity reactions to medications. Other particular but yet unknown factors may be involved in the causation of this atypical reaction in this patient.

Studies show that prolonged innate immune activation by HCV impairs the development of successful adaptive immune responses [13]. It is likely that the patient may have had underlying hypersensitivity at baseline. It may also depend on the genotypes of the hepatitis C virus. The real causes of these peculiar responses were unknown. These types of reactions to many drugs may be life-threatening to the patient if not paid attention and cared. Chronic Hepatitis C infection appears to exert an immunosuppressive effect which masks the hypersensitivity. Complete eradication of viral load by Sofosbuvir-Ledipasvir unmasked the immunosuppression. However, the immunomodulatory effect of the new agents cannot be excluded as a possible etiology. The resurgence of the immune system of the HCV free patient after eradication of virus may explain multidrug hypersensitivity reactions. The etiology of this atypical hypersensitivity reaction remains unknown. These type of reactions are not commonly anticipated and can lead to life-threatening complications in the patient.

Conclusion

In any event, we recommend close monitoring of patients treated with Sofosbuvir-Ledipasvir after the eradication of HCV while prescribing previously tolerated medication. Also, the patient needs to be made aware of the possibility of developing hypersensitivity reactions to all kinds of drugs. For those with a known history of hypersensitivity reaction, we recommend carrying an EpiPen with or without oral anti-histamine and steroids at all times. New onset of multidrug hypersensitivity reactions should be anticipated and treated promptly to prevent mortality or morbidity from this uncommon but life-threatening condition.

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