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## Case report

## Herpes Zoster reactivation in patients with chronic hepatitis C under treatment with directly acting antiviral agents: A case series

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## ABSTRACT

We report a series of cutaneous Herpes Zoster (HZ) reactivation cases in patients with hepatitis C virus (HCV) infection treated with directly acting antiviral (DAA) agents. Five cases were detected among 2133 treated patients with DAAs at one of the specialized viral hepatitis treatment centers in Egypt. A control group including 2300 age and sex matched HCV patients who were previously treated with pegylated interferon and ribavirin did not show any HZ reactivation reports while on treatment. None of cases had an evidence of immunosuppression or a risk factor for HZ reactivation. The DAAs used regimens were sofosbuvir/daclatasvir in 4 cases and sofosbuvir/simeprevir in one case. HCV clearance with antiviral therapy may bring immune changes causing reactivation of other latent viral infections like HZ. A high index of clinical suspicion may be needed to guarantee early and prompt management of such cases.

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## Introduction

There is a well-known association between hepatitis C virus (HCV) infection and the occurrence of some skin disorders. The new directly acting antiviral agents (DAAs) are supposed to show less toxic adverse effects than interferon based regimens [1]. Herpes Zoster (HZ) is a viral infection that causes nerve and dorsal root ganglia latent affection. Its reactivation is usually related to decreased cell mediated immunity as in elderly and immunocompromised patients [2]. In liver transplantation settings, higher rates of HZ reactivation are reported [3].

Up to our knowledge, a single published report described the occurrence of HZ reactivation in HCV patients treated with DAAs [4]. We report here five apparently immunocompetent cases that developed HZ reactivation while on treatment for HCV by DAAs.

## Case series

## Case 1

A 59 year old female had no significant medical history except for HCV. She suffered two attacks of HZ reactivation 9 and 5 years ago. Concerning liver condition before treatment, the patient had compensated liver cirrhosis with normal albumin, bilirubin and normal INR. She started antiviral therapy with sofosbuvir/simeprevir combination. On the 3rd week of treatment, the patient complained of facial agonizing pain and described the appearance of vesicular rash that was mistaken for allergic dermatitis by her first dermatologist who prescribed an antihistaminic and topical corticosteroids. The condition was aggravated and larger vesicles started to appear and spread (small crusted red vesicles in her right side of neck, above the eye brow and hair). On the 4th day, she consulted another dermatologist who confirmed the diagnosis. She had finally achieved sustained virological response (SVR).

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Fig. 1. HZ in case 4.



Fig. 2. HZ in case 5.

wall and filled with clear fluid on an erythematous skin background that was diagnosed as HZ flare. On follow up of the virological response, the patient attained SVR.

#### Case 2

A 64 years old female patient was known to be hypertensive for 10 years. She started DAAs for her HCV infection in the form of sofosbuvir/daclatasvir combination for 12 weeks. Before treatment the patient had compensated liver condition with normal liver function tests and normal CBC (CTP; A5). Twenty-four days after treatment initiation, the patient started to complain of severe right hypochondrial pain associated with vesicular rash involving the right costal margin. The case was referred to the dermatologist who confirmed HZ infection. The patient finally achieved SVR.

#### Case 3

A 72 years old female had history of hypothyroidism which has been well controlled on levothyroxine. Before antiviral treatment the patient had compensated liver condition with normal liver function tests and CBC (CTP; A5). She started DAAs for HCV infection in the form of sofosbuvir/daclatasvir combination for 12 weeks. Two weeks after beginning therapy, she started to complain of maculopapular vesicles affecting the right side of the chest

#### Case 4

A 59 years old male patient had an irrelevant medical history apart from HCV infection. Before treatment the patient had compensated liver condition with normal liver function tests and normal CBC (CTP; A5). He began DAAs treatment using sofosbuvir/daclatasvir regimen for 12 weeks. Two weeks after treatment start, he developed vesicles on an erythematous base affecting the upper chest around nipples, infra axillary, and extending to the upper back reaching to the midline of the right side of the body. Some of these lesions ruptured leaving crusts with severe burning pain (Fig. 1). Right thoracic HZ was assumed; Tzanck test smear was performed and found to be positive for herpes virus with the presence of ballooning, multinucleated giant cells and eosinophilic inclusion bodies. He had achieved SVR on follow up.

#### Case 5

A 54 years old female patient had no medical history except for HCV infection for which she had received pegylated interferon/ribavirin therapy 4 years earlier with relapsed infection. This patient

**Table 1**

Full clinical and treatment data of the five cases.

	Case 1	Case 2	Case 3	Case 4	Case 5	Mean	SD
Age	59	64	72	59	53	61.4	7.09225
Gender	F	F	F	M	F		
DM	N	N	N	N	N		
Fib-4	0.77	1.61	2.51	1.96	7.25	2.82	2.55574
Prev. ttt for HCV	N	N	N	N	Y		
CTP Score	5	5	5	5	5	5	0
LTx	N	N	N	N	N		
ttt	SIM/SOF	SOF/DAC	SOF/DAC	SOF/DAC	SOF/DAC/RBV		
Weight	87	96	82	67	70	80.4	12.0125
Height	1.65	1.68	1.66	1.63	1.5	1.624	0.07162
BMI	31.9559	34.0136	29.7576	25.2174	31.111	30.411	3.28846
HBsAg	N	N	N	N	N		
TLC	6.1	7.7	6.1	7.3	4.3	6.3	1.32665
TSH	1.6	1.7	4.5	1.8	1.23	2.166	1.32241
PCR	252904	3000	1195418	122000	2379672	790599	1005669
Immunosupp. ttt	N	N	N	N	N		
Previous HZ	Y	N	N	N	N		
Wk of HZ	3	4	2	2	10	4.2	3.34664
Achievement of SVR 12	YES	YES	YES	YES	YES		
Post Herpetic neuralgia	N	N	N	N	N		
Ocular Complications	N	N	N	N	N		

CTP: Child-Turcott Pough, LTx: Liver transplantation, ttt: Treatment, BMI: Body mass index, HBsAg: Hepatitis B surface antigen, TLC: Total leucocytic count, TSH: Thyroid stimulating hormone, PCR: Polymerase chain reaction, Immunosupp. Ttt: Immunosuppressive treatment, Wk: Week, N: None.

started treatment with compensated liver condition with normal liver function, CBC and INR. She received sofosbuvir/daclatasvir/ribavirin combination for 12 weeks. On week 8 of treatment, patient developed severe left lumbar and back pain followed by the appearance of maculovesicular rash on an erythematous base and the patient was diagnosed to have HZ infection (Fig. 2). The obtained smear was positive. The patient completed 12 weeks post-HCV treatment with an undetectable RNA (SVR).

Full clinical and treatment data of the five cases are shown in table 1.

## Discussion

DAA combinations are currently considered as the standard of care for HCV patients. Although very effective, DAAs have many adverse events which can be sometimes serious and life-threatening [5].

In our center; New Cairo Viral Hepatitis Treatment Center, one of the specialized viral hepatitis treatment facilities in Egypt, and among 2133 treated HCV patients with DAAs over a period of one year from January 2015 to January 2016, we reported 5 cases with cutaneous HZ reactivation during DAAs treatment. Data were also collected from a control group (2300 HCV-infected patients matched for age and sex; treated with pegylated interferon/ribavirin combination during the period from January 2011 to June 2013), and none of the control group had HZ reactivation while on interferon based treatment. Our cases included 4 females and 1 male with an age ranging from 53 to 72 years (mean age  $61.4 \pm 7.1$ ). All reported cases had compensated liver diseases, CTP score of 5, within normal CBC parameters, with good general conditions and with no other serious comorbidities. Four of our patients were treatment naïve and one had past treatment with pegylated interferon/ribavirin combination therapy. Regarding the treatment regimens, three patients received sofosbuvir/daclatasvir for 12 weeks, a single patients received sofosbuvir/simeprevir for 12 weeks and the treatment experienced patient received sofosbuvir/daclatasvir/ribavirin for 12 weeks for her condition. Four patients developed the HZ reactivation within the first four weeks, only one case (the treatment experienced who had previously received pegylated interferon based therapy) suffered this reactivation after more than 8 weeks of start of therapy. Four cases reported that this was the first incident of HZ, and one case admitted having a previous attack of HZ seven years ago. All cases showed only mild cutaneous lesions that were diagnosed as HZ reactivation either clinically or by the means of Tzanck test smear [6]. None of the patients developed post herpetic neuralgia or ocular complications.

There were none of known risk factors for HZ reactivation; no post-transplantation states, no psychological or physical stress, no concurrent infections or known immunocompromised status and none of patients were diabetic or HIV infected. All patients gave no previous history of HZ infection except for one patient. Both fibrosis stage and viral load testing showed great variability denying their contribution on the development of HZ reactivation.

The same findings of HZ reactivation were reported in a recently published series of ten cases out of 576 (2%) HCV patients treated with DAAs. The mean of age of these patients was 67 years and three of them were receiving immunosuppressive therapy following liver transplantation. This study included 6 females and 4 males and the used DAAs regimens were as follows: 7 patients

were on sofosbuvir/ledipasvir/ribavirin, 2 patients were on ombitasvir/paritaprevir/ritonavir/dasabuvir/ribavirin combination and the remaining patient was treated by sofosbuvir/simeprevir/ribavirin combination. As a sequelae of HZ reactivation, 2 out of the 10 patients, suffered from post herpetic neuralgia and only 1 patient had herpetic kerato conjunctivitis [4].

Our observation could be mismatched with the theoretically assumed restoration of the immune system that was impaired with the presence of HCV infection. Many reports described such cell mediated immunity restoration following successful antiviral therapy [7–8].

This could raise a question about the probability of present suppressive effect of HCV infection on HZ that is removed after HCV clearance by therapy, or a possible direct role of DAAs therapy in creating a pathologic inflammatory response in the setting of immune system restoration and hence HZ reactivation.

In a series of published case reports, there was a relation between HBV reactivation and HCV treatment [9–10]. The authors postulated that viral interference on HBV replication caused by HCV would be disrupted by treatment.

Another explanation would be what is called immune reconstitution inflammatory syndrome (IRIS) seen in some HIV-infected patients after highly active antiretroviral therapy (HAART). This syndrome implies a pathologic inflammatory response to previously acquired conditions in the setting of an improved immune response [11].

Though we are not sure about the relationship, yet with the temporal association and recent experience, we conclude that the incidence of HZ reactivation may be increased among patients on IFN-free regimens than in patients treated with the previous interferon based regimens. Therefore, a high index of clinical suspicion may be needed to guarantee early and prompt management of such cases.

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