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BRIEF REPORT

# Management of Multiple Myeloma Complicated by Hepatitis C Virus Reactivation: The Role of New Antiviral Therapy

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Reactivation of chronic hepatitis C virus (HCV) infection has been reported in cancer patients receiving chemotherapy. In this study, we report the first case, to our knowledge, of thalidomide-induced acute exacerbation and reactivation of chronic HCV infection complicating management of multiple myeloma. Sofosbuvir-based antiviral therapy helped achieve viral clearance and normalization of liver enzymes, thus allowing access to future potentially life-saving chemotherapy agents.

**Keywords.** hepatitis C virus; multiple myeloma; thalidomide; viral reactivation.

Acute exacerbation (defined as increase in serum alanine aminotransferase [ALT] levels ≥3 times upper limit of normal) and reactivation of chronic hepatitis C virus (HCV) infection (defined as elevation of HCV RNA by ≥1 $\log_{10}$ IU/mL from baseline) have been reported in cancer patients receiving chemotherapy [1]. These conditions may lead to dose-reduction or discontinuation of chemotherapy and interfere with cancer care [1]. In this study, we report the first case, to our knowledge, of thalidomide-induced HCV reactivation complicating management of multiple myeloma.

## CASE REPORT

A 74-year-old white woman was diagnosed with stage II (International Staging System) multiple myeloma and genotype 2b chronic HCV infection in June 2006 and initiated on thalidomide (100 mg daily) and dexamethasone (40 mg pulse). Alanine aminotransferase and HCV RNA levels increased within 28 days after chemotherapy initiation (Table 1, Figure 1). Alanine aminotransferase levels normalized 61 days after the peak. Thalidomide was discontinued after 116 days, and the patient underwent autologous hematopoietic cell transplant (HCT) with melphalan as a conditioning regimen. Serum paraprotein, checked monthly, disappeared between 5 and 6 months after HCT.

The myeloma remained in remission until October 2012, when relapse was detected. Thalidomide was resumed at 50 mg nightly and increased to 100 mg nightly after 28 days. Four months after thalidomide initiation, acute exacerbation along with HCV reactivation was noted (Table 1, Figure 1). Thalidomide was discontinued after 92 days; ALT and HCV RNA declined substantially and reached near prethalidomide levels. Tests for hepatitis B core antibody, surface antigen, and human immunodeficiency virus 1/2 antibody were negative, with IL28B genotype CC. Liver ultrasound showed normal echogenicity, no evidence of cirrhosis, or focal liver lesions, ruling out liver involvement by myeloma [2]. The portal and hepatic veins were patent with normal directional flow, suggesting absence of thalidomide-induced thromboembolism. To prevent further episodes of acute exacerbation and HCV reactivation allowing access to other chemotherapeutic agents, the patient was started on the interferon-free combination therapy of sofosbuvir and weight-based ribavirin for 12 weeks. She achieved sustained virological response (undetectable HCV RNA at 24 weeks after treatment completion) [3]. Hepatitis C virus RNA became undetectable, and ALT levels normalized with no additional ALT peaks during or after HCV treatment. At 34 months after thalidomide discontinuation, multiple myeloma was in near-complete remission, and the patient is currently under oncologic observation.

## DISCUSSION

Thalidomide is an immunomodulatory agent approved for treatment of multiple myeloma and erythema nodosum leprosum [4]. It has also been used to treat chronic graft-versus-host disease after HCT, acquired immune deficiency syndrome-related aphthous stomatitis, Waldenström macroglobulinemia, and systemic light-chain amyloidosis [4].

Thalidomide inhibits secretion of tumor necrosis factor-α, a key cytokine that facilitates immune response to viral infections [5]. Reactivation of hepatitis B virus infection after thalidomide therapy for renal light chain amyloidosis has been observed in the past [6]. Some, but not all, authors have documented hepatotoxic effects after thalidomide administration, but only 1 case was reported in a patient with chronic HCV infection [7]. Unfortunately, HCV RNA level before thalidomide initiation was

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**Table 1. Laboratory Characteristics of a Patient With HCV Reactivation After Thalidomide Treatment**

| | | Episode 1 | | | | Episode 2 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Peak/Nadir[a] After Thalidomide Initiation | | | | Peak/Nadir[a] After Thalidomide Initiation | | |
| Laboratory Parameters | Normal Values | Baseline: Before Thalidomide Initiation | Values | Days After Initiation | Time to Return to Baseline (Days) | Baseline: Before Thalidomide Initiation | Values | Days After Initiation | Time to Return to Baseline (Days) |
| HCV RNA | 0 $\log_{10}$ IU/mL | 5.58 | 7.7 | 28 | 1175 | 3.97 | 6.83 | 169 | 306 |
| ALT | 7–56 IU/L | 86 | 140 | 21 | 91 | 88 | 241 | 121 | 92 |
| AST | 15–46 IU/L | 89 | 109 | 21 | 107 | 83 | 292 | 92 | 426 |
| Total Bilirubin | 0–1.0 g/dL | 0.6 | 0.7 | 130 | 3 | 0.3 | 1.0 | 61 | 29 |
| Total WBC count[a] | 4–11 (×1000 cells/μL) | 7.1 | 2.6 | 21 | 63 | 4.8 | 3.9 | 90 | 27 |
| ALC[a] | 1–4.8 (×1000 cells/μL) | 2.28 | 0.5 | 127 | 2 | 1.67 | 1.33 | 90 | – |

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; IU, international units; WBC, white blood cell.

[a] Indicates parameters for which nadir values are reported.

not provided in that case. In our patient, HCV reactivation occurred twice after thalidomide administration complicating management of multiple myeloma. Hepatitis C virus reactivation has been associated with several chemotherapeutic agents such as alemtuzumab, bleomycin, busulfan, cisplatin, cyclophosphamide, cyclosporine, cytarabine, dacarbazine, doxorubicin, etoposide, gemcitabine, methotrexate, vinblastine, and vincristine, but most notably rituximab [1, 8]. Most of these agents were administered in combination with corticosteroids [1]. Corticosteroids impact HCV, either directly by enhancing HCV RNA replication or indirectly by suppression of HCV-mediated immune response [9]. This may be responsible for the first episode of HCV RNA reactivation observed on this patient. The anti-inflammatory effect of dexamethasone may also be responsible for reduction in ALT levels before thalidomide was discontinued the first time. However, we observed that HCV reactivation occurred even when thalidomide was administered as monotherapy. In an in vitro study, thalidomide-induced inhibition of IκB kinase activation and nuclear factor-κB signaling led to enhanced replication of HCV RNA [10], and our clinical observation confirms this finding. Therefore, thalidomide should be considered along with other agents found to be associated with HCV reactivation.

Currently approved direct-acting antiviral (DAA) therapy with sofosbuvir-containing regimens has dramatically improved rates of sustained virological response and shortened the treatment duration [3]. In our patient, HCV infection was eliminated and ALT levels normalized with a 12-week course of sofosbuvir and ribavirin, thus allowing access to a wide range of future cancer treatment options.

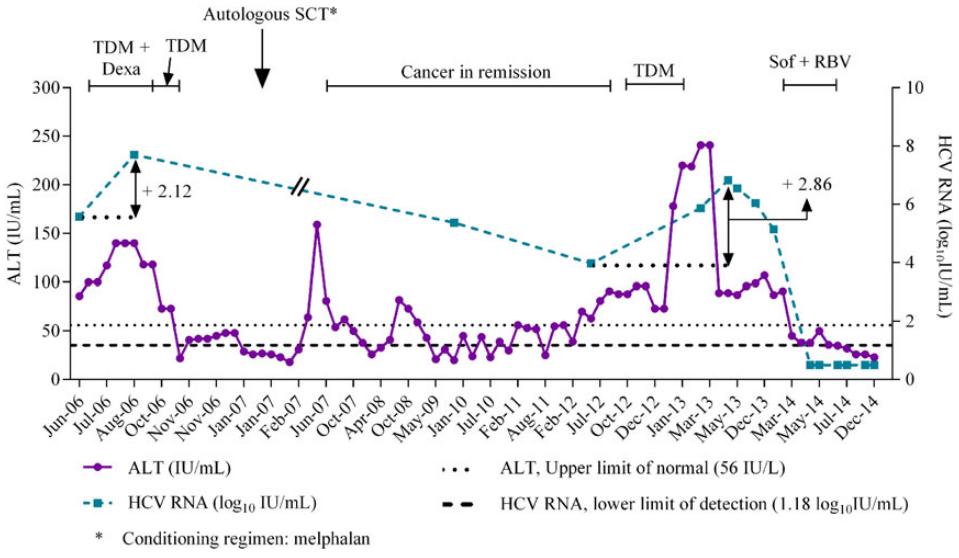


**Figure 1.** Changes in alanine aminotransferase (ALT) levels and hepatitis C virus (HCV) viral load in a patient receiving thalidomide treatment. Abbreviations: Dexa, dexamethasone; IU, international units; RBV, ribavirin; SCT, stem cell transplant; Sof, sofosbuvir; TDM, thalidomide.

Recent guidelines recommend all HCV-infected HCT candidates to be evaluated for antiviral therapy before starting conditioning regimens, and they should be treated before HCT, when possible [11]. After HCT, some experts recommend waiting for 6 months before starting antiviral treatment with DAAs to allow tapering of immunosuppressive agents [11]. Direct-acting antiviral-based treatment after HCT in HCV-infected patients with hematological malignancies, such as those with non-Hodgkin lymphoma, seems to be safe and efficacious and has been shown to improve hepatic and oncologic outcomes [12]. Preliminary data suggest that concomitant administration of DAAs is safe along with selected chemotherapeutic agents and may be used with caution in specific cases [13]. However, drug-drug interactions and overlapping toxicities must to be considered.

## CONCLUSIONS

In conclusion, acute exacerbation and reactivation of HCV may complicate cancer treatment and occur in patients receiving thalidomide. Increased awareness regarding this condition is needed among hemato-oncologists. Alanine aminotransferase and HCV RNA levels of HCV-infected patients receiving thalidomide should be monitored, and thalidomide may need to be dose-reduced or discontinued.

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