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CASE REPORT

Severe autoimmune hemolytic anemia during pegylated interferon plus ribavirin treatment for chronic hepatitis C: a case report

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Key Clinical Message

We report a rare case of severe autoimmune hemolytic anemia triggered by pegylated interferon during combination therapy for chronic HCV. This case demonstrated that interferon can de novo induce autoimmune hemolytic anemia during therapy for chronic hepatitis C in a previously healthy patient.

Keywords

autoimmune hemolytic anemia, chronic hepatitis C, pegylated interferon, ribavirin.

Introduction

Currently, combination therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV) is still a standard treatment of chronic hepatitis C (CHC). Interferons are one kind of natural cytokines that can interfere with viral replication, cell growth, differentiation, and immunoregulation [1]. Therapy with IFN in CHC patients has been associated with various side effects, such as fever, chills, cardiac insufficiency, and immune-mediated events [2]. Nevertheless, IFN-induced hemolytic anemia is uncommon [3]. We present here a case of autoimmune hemolytic anemia (AIHA) during the treatment of CHC with PEG-IFN and RBV (Table 1).

Case Report

A 57-year-old woman with chronic hepatitis C, genotype 1b, started treatment with pegylated interferon-a2b at a dose of 80 μg weekly plus 900 mg/day ribavirin in March 2015. She had no prior history of allergy or autoimmune diseases. Levothyroxine (50 g/day) was added at 8th week due to overt hypothyroidism. At 12 weeks of combination therapy, serum HCV-RNA decreased below detection limit. After 28 weeks of treatment, RBV was reduced to 600 mg/day because of anemia (hemoglobin 106 g/L) and was completely withdrawn 4 weeks later because of a further reduction in hemoglobin (Hb) levels (Hb 90 g/L). At 34 weeks of treatment, the patient has taken a slice of paracetamol three times due to a fever, 1 day later Hb was 94 g/L. At week 35th, Peg-IFN was stopped, and the patient was admitted to our hospital with fatigue and dizziness. The patient referred dark urine and backache some days before admission. Laboratory data were as follows (normal ranges in parenthesis): Hb: 48 g/L (115–150), reticulocyte percentage: 10.24% (0.59–2.07), total bilirubin: 71.2 μmol/L (6.8–30.0),indirect bilirubin: 57.4 μmol/L (5.1–21.4), aspartate aminotransferase: 62.8 U/L (13.0–35.0), alanine aminotransferase:36 U/L (7.0–40.0), thyroid-stimulating hormone: 27.960 mIU/mL (0.27–4.2), free triiodothyronine: 2.45 pmol/L (3.1–6.8), free thyroxin: 12.91 pmol/L (12.0–22.0), antithyroglobulin antibodies (TgAb): 4000.00 IU/mL (<115.0), antithyroid peroxidase antibody (TPOAb): 373.50 IU/mL (<35.0), plasma-free hemoglobin: 50.0 mg/L (<40).Urine hemosiderin, direct and indirect Coombs tests for IgG and C3d were positive, and ham test was negative. At the same time bone marrow examination showed hyperplastic

Table 1. Indices of hemoglobin, HCV virus load, and thyroid functions throughout the course

	Washed red blood cells transfusion (units)	Hb (115–150 g/L)	HCV-RNA (<500 IU/mL)	TSH (0.27–4.2 mIU/mL)	Free T4 (12.0–22.0 pmol/L)	Free T3 (3.1–6.8 pmol/L)	Substitutive levothyroxine therapy
Beginning of DAA/RBV treatment	No	138	45,100,000	ND	ND	ND	No
4 weeks during DAA/RBV treatment	No	124	3530	ND	ND	ND	No
8 weeks during DAA/RBV treatment	No	115	591	58.43	9.6	3.33	Yes
12 weeks during DAA/RBV treatment	No	109	<100	19.38	12.15	3.84	Yes
28 weeks (the time of reduction of RBV)	No	106	ND	33.82	13.57	3.34	Yes
32 weeks (the time of stoppage of RBV)	No	90	ND	ND	ND	ND	Yes
34 weeks during DAA treatment	No	94	ND	ND	ND	ND	Yes
35 weeks (the time of stoppage of PEG-IFN)	No	61	ND	ND	ND	ND	Yes
2 days after stoppage of PEG-IFN	2	48	ND	25.99	12.67	1.67	Yes
4 days after stoppage of PEG-IFN	4	78	0	ND	ND	ND	Yes
6 days after stoppage of PEG-IFN	No	70	ND	27.96	12.91	2.45	Yes
9 days after stoppage of PEG-IFN	No	54	ND	ND	ND	ND	Yes
11 days after stoppage of PEG-IFN	4	76	ND	ND	ND	ND	Yes
17 days after stoppage of PEG-IFN (the time of splenectomy therapy)	No	69	ND	ND	ND	ND	Yes
3 weeks after splenectomy therapy	No	119	ND	ND	ND	ND	Yes
12 weeks after splenectomy therapy (beginning of DAA treatment)	No	139	400,000	0.864	17.08	5.29	Yes
12 weeks after DAA treatment cessation	No	138	0	ND	ND	ND	Yes
24 weeks after DAA treatment cessation	No	144	0	ND	ND	ND	Yes

Hb, hemoglobin; TSH, thyroid-stimulating hormone; Free T4, free thyroxin; Free T3, free triiodothyronine; DAA, directing antiviral agents; ND, not done.

anemia and an increased proportion of erythroid series. In addition, abdominal CT scan revealed a chronic liver damage. Based on these findings, we concluded that the patient had AIHA.

Treatment, outcome, and follow-up

Discontinuation of PEG-IFN at week 35th did not stop hemolytic anemia. Similarly intravenous immunoglobulin (IVIG) failed to step down the autoimmune process [1]. Dramatically, the patient conditions gradually improved and Hb returned to normal levels after splenectomy therapy. March 2016, the patient was given ledipasvir and sofosbuvir treatment for 12 weeks due to HCV recurrence (HCV-RNA 400,000 IU/mL), attaining sustained virological response at 24 weeks after treatment cessation. And thyroid function was maintained at normal levels with substitutive levothyroxine therapy during follow-up.

Discussion

Anemia is an important adverse reaction of the drugs used in CHC patient. The use of RBV has been considered the main drug responsible for anemia cases in hepatitis C treatment [4, 5]. RBV causes a dose-dependent reversible hemolytic anemia due to its direct toxic effect on red blood cells, or even because myelosuppression resulting from negative feedback on erythropoietin receptors [2, 3, 6]. The progression of hemolysis after RBV withdrawal indicated the anemia in our case was uncommon. In addition, paracetamol was an unlikely cause of hemolytic anemia because of its quite short course and low dose.

An autoimmune cause was suspected, as the case described an immune-mediated phenomena (hypothyroidism) during CHC treatment with PEG-IFN. Autoimmune hemolytic anemia was diagnosed in our patient (serum bilirubin, increases in reticulocytes, hypercellularity of red section in bone marrow, and positive Coombs tests). The temporal connection between antiviral therapy and disease onset, the progressive decrease in Hb levels after RBV withdrawal, and the exclusion of other causes of AIHA, such as tumors, immunodeficiency, and lymphoproliferative, implicated PEG-IFN as the cause of AIHA [7]. It is less well known that PEG-IFN can cause AIHA. In fact, several case reports and reviews were published reflecting the AIHA in relapsing remitting multiple sclerosis or hematological disorders under IFN monotherapy [8, 9]. The mechanism of IFN contributing to hemolytic anemia could be due to direct drug medullary

toxicity or autoimmunity induction, for example, the expansion of autoreactive B cells [4, 9, 10]. Although PEG-IFN was stopped, the Hb level continues to decrease probably due to its long half-life and a strong immune strike [3]. Lack of autoimmune diseases or allergy before IFN therapy in this case, hinted that Peg-IFN, as previously reported [3], can trigger an autoimmune disorder and not merely exacerbate a preexisting one.

On the other hand, as reported in the literature, AIHA and hypothyroidism may appear simultaneously, or may follow each other [11]. They may share common immunological background [11]. In our case, the positive TgAb and TPOAb indicated that hypothyroidism is a manifestation of autoimmune disorders. Our patient still needed substitutive levothyroxine therapy to maintain thyroid function without hemolysis reappearance during follow-up. Thus, hypothyroidism may play a synergistic role in the development and progression of autoimmune hemolytic anemia in our patient.

Several IFN-induced AIHA in chronic hepatitis patients have been described [1, 3, 7]. These patients all received corticosteroid treatment, and then Hb gradually returned to normal levels. Our patient refused corticosteroid treatment for fear of a relapse of hepatitis C. Surprisingly, after splenectomy therapy, within 3 weeks his anemia was corrected (Hb 119 g/L), and there was no recurrence of AIHA. These cases recommended physicians that corticosteroid or splenectomy therapy may be a choice to life-threatening AIHA induced by PEG-IFN. In addition, retreatment of our patient with ledipasvir and sofosbuvir was well tolerated and effective. Our case also suggested that direct-acting antiviral therapies may be an optimal retreatment strategy for chronic hepatitis C patients who experience virologic failure after IFN-based treatment.

Conclusions

Our report demonstrated that physicians should be aware that IFN can induce severe autoimmune hemolytic anemia in patients without a history of autoimmune abnormalities. Close monitoring of hematological and thyroid values prior to or during PEG-IFN/RBV therapy is necessary for early detection and management of medical complications.

Authorship

SW: collected the patient's data, drafted the manuscript, and monitored the patient throughout the whole follow-up period; EQ and YZ: helped to collect the patient's data and draft the manuscript; RH: edited, reviewed, and approved final version of the manuscript.

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