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Rare disease

Pegylated interferon de novo-induce autoimmune haemolytic anaemia in chronic hepatitis C patient

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Summary

A 55-year-old Egyptian woman with chronic hepatitis C undergoing treatment with pegylated interferon (Peg-IFN) alfa-2a plus ribavirin was referred to our hospital on November 2010 with prolonged easy fatigability and an attack of syncope; she had no prior history of autoimmune disorders or allergy. Laboratory investigations documented the presence of Peg-IFN induced autoimmune haemolytic anaemia and autoimmune thyroiditis. Intravenous γ globulin (IVGG) failed to correct the autoimmune process; on the other hand steroid therapy dramatically corrected both haematological and thyroid values, and step down the immune process. Our report indicated that Peg-IFN de novo-induce autoimmune haemolysis, documenting a previous report. IVGG failed to step down the immune process in our case.

BACKGROUND

Interferons are a family of natural cytokines that share a common ability to interfere with viral replication, and immunoregulation.[1] Various side effects have been reported in chronic hepatitis C virus (HCV) patients treated with pegylated interferon (Peg-IFN) -alfa-2a, including immunological disorders. Interferon may aggravate or de novo-induce autoimmune disorders seen in hepatitis C-treated patients.[2 3] We report a female patient with chronic HCV, who developed de novo autoimmune haemolytic anaemia during Peg-IFN plus ribavirin (RBV) therapy.

CASE PRESENTATION

A 55-year-old Egyptian woman with chronic HCV (metavir score A2, F2) was started on Peg-IFN alfa-2a, 180 μg/week subcutaneously, plus RBV, 1000 mg/day orally, in February 2010. The baseline HCV-RNA viral load, haemoglobin (Hb) concentration and thyroid stimulating hormone (TSH) were 202048 IU/ml, 14 g/dl and 3.46 μU/ml, respectively, at the same time antinuclear antibody (ANA) was negative. After 8 weeks of combination therapy, the patient developed haemolytic anaemia (table 1). Twelve weeks after starting treatment, serum HCV-RNA became negative. Sixteen weeks after treatment and because of Hb reduction to 9 g/dl, treatment with erythropoietin (10 000 U three times weekly) was started without improvement of haematological values. Although it is an unusual way, gradual withdrawal of RBV started at that time, which failed to stop progression of anaemia. Indeed the progression of anaemia continues despite complete withdrawal of RBV at 28th week. Levothyroxine (150 μg/day) was added at week 28th due to overt hypothyroidism (TSH 38.5 μIU/ml).At week 35th, the patient presented to our hospital with prolonged easy fatigability and syncope, where the aetiology of haemolysis was revised. Direct Coombs test was positive, at the same time bone marrow examination showed hypercellular erythroid series. The serum level of thyroid antibodies, namely, thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) were (60.8/40 IU/ml) and (48.9/34 IU/ml), respectively. Other autoantibodies including ANA, DNA double stranded antibody, antimitochondrial antibody and smooth muscle antibody were negative. The temporal association between Peg-IFN-alfa-2a and the development of anaemia, progression of anaemia despite RBV withdrawal and the exclusion of other causes of immune process, such as tumours, infectious diseases, immunodeficiency, lymphoproliferative and autoimmune disorders, led us to a

Table 1 Indices of haemolysis, and thyroid functions through out the course

	Hb	Indirect bilirubin	Reticulocytic count	Haptoglobin (30–200 mg/ml)	TSH (0.5–4.67 μIU/ml)	Free T4 (1.4–4.4 Pg/ml)
Baseline value	14	0.6	ND	ND	3.46	ND
8 weeks	10.6	2.5	4.7	ND	ND	ND
16 weeks	9	5.2	5.2	ND	ND	ND
28 weeks	5.2	2.77	4	ND	38.5	0.45
35 weeks	4.4	3.4	4	16.9	40	0.47
2 weeks after stoppage of Peg-IFN	2.9	2.04	1.9	ND	51	0.55
1 week after induction of steroid	8	0.5	1.5	ND	ND	ND
2 weeks after induction of steroid	10.8	1.1	1.2	ND	ND	ND
6 weeks after induction of steroid	13.6	0.3	1.3	ND	3.61	ND

Table 2 Patient's autoantibodies before and after steroid therapy

	ANA	TOPAb (34 IU/ml)	TgAb (40 IU/ml)	Direct Coomb's test	DNA ds Ab	ASMA	AMA
Baseline value	Negative	ND	ND	ND	ND	ND	ND
35 weeks	Negative	48.9	60.8	Positive	Negative	Negative	Negative
6 weeks after induction of steroid	ND	Negative	Negative	Negative	ND	ND	ND

AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA; antismooth muscle antibody; DNA ds Ab, DNA double stranded antibody; ND, not done; TgAb, thyroglobulin antibody; TOPAb, thyroid peroxidase antibody.

more precious diagnosis of Peg-IFN-induced autoimmune haemolysis.

INVESTIGATIONS

Refer tables.

DIFFERENTIAL DIAGNOSIS

Ribavirin induced haemolytic anaemia.

Peg-IFN de novo-induced haemolytic anaemia.

TREATMENT

Discontinuation of Peg-IFN-alfa-2a at week 42nd did not stop the progression of haemolysis or hypothyroidism (table 1). Similarly intravenous γ globulin (IVGG) (400 mg/kg/day for 5 days) failed to step down the autoimmune process. In contrast the addition of prednisolone (1 mg/kg/day) achieved improvement of haematological and thyroid values (table 1). Gradual withdrawal of prednisolone (10 mg each 2 weeks) started after 2 weeks of steroid induction.

OUTCOME AND FOLLOW-UP

Six weeks after steroid induction Hb and TSH levels normalised (table 1), in addition the direct Coombs test and antithyroid antibodies became negative (table 1). Six months after stoppage of Peg-IFN, serum HCV-RNA was negative and the patient achieved sustained virological response (table 2).

DISCUSSION

Autoimmune diseases could be developed or exacerbated during interferon therapy, including psoriasis, vitiligo, rheumatoid arthritis, lichen planus, sarcoidosis, dermatitis herpetiformis, type 1 diabetes mellitus, haemolytic anaemia and thyroiditis.[2 3] Lack of autoimmune or allergic diseases stigmata prior to IFN therapy, hinted that autoimmune haemolysis de novo-induced in our case.

IFN-induced haemolytic anaemia is very unusual. In a survey of adverse events occurring on IFN treatment, autoimmune haemolytic anaemia occurred in only 2 of 11 241 patients.[4] Otherwise there are only a few reported cases in the literature.[5 6] IFN can cause de novo autoimmune haemolysis as well as aggravating pre-existing disease.[7] The diagnosis of Peg-IFN-induced autoimmune haemolysis usually delayed, miss-diagnosed as RBV-induced and only suggested after progression of anaemia despite discontinuation of RBV. Severe IFN-induced haemolysis was reported and may associate with serious sequel like ischemic heart disease[6] and syncope like our case.

Flores *et al*.[8] reviewed 73 patients with autoimmune haemolysis treated with IVGG and found responses in 29 (40%). There are no available data about the use of IVGG in management of IFNN-induced haemolytic anaemia in literature. Although full dose IVGG was tried, we could not get significant improvement of haematological values. Discontinuation of IFN and induction of steroid therapy resulted in dramatic improvement and remission of haemolysis in our patient, supporting previous reports.[6 9 10]

Autoimmune haemolysis was associated with autoimmune thyroiditis in our patient. Thyroid disease is a frequent side effect of IFN-therapy for HCV. In patients treated with IFN, hypothyroidism occurs in 2.4–19.0% of the patients.[11–13] Previous study demonstrated that thyroid autoantibodies detection before treatment can predict the occurrence of thyroid dysfunction during therapy.[14] The baseline thyroid autoantibodies were not measured in our patient, consequently we could not predict the thyroid dysfunction in our patient, in addition we could not judge whether our patient was susceptible for autoimmune thyroiditis or developed de novo thyroiditis after IFN therapy. Indeed the baseline thyroid autoantibodies should be measured for a better prediction of thyroid dysfunction in those patients. As previously reported,[15–18] the presence of both TPOAbs and TgAbs associated with aggressive autoimmune destructive process of the thyroid gland (reflected by highly elevated TSH) in our case.

In patients developing hypothyroidism during IFN treatment, substitutive levothyroxine therapy is indicated without the need to withdraw IFN therapy. Overt hypothyroidism in our case not responded to usual levothyroxine dose (200 mg/day), cessation of RBV and IFN, nor IVGG. On the other hand steroid therapy induced dramatic improvement of thyroid function and antithyroid antibodies.

Learning points

- Peg-IFN can de novo-induce autoimmune haemolytic anaemia and not merely exacerbate a pre-existing one.
- The rapid deterioration of haematological values seen in our patient, suggests that careful medical supervision is necessary during treatment with Peg-IFN and RBV.
- Early diagnosis will avoid unwanted discontinuation of RBV, and serious sequel of progressive anaemia.
- Severe anaemia presenting with serious haemodynamic instability and association with other autoimmune disorders may be a clue for early diagnosis of Peg-IFN-induced autoimmune haemolytic anaemia.

Competing interests None.

Patient consent Obtained.

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