Case report

The adjuvant role of thyroxine in the treatment of chronic hepatitis C infection

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Introduction

Thyroid disease (TD) is the commonest extra-hepatic complication in patients with chronic hepatitis C undergoing combination interferon-α and ribavirin treatment. About 5–10% develops TD of various aetiologies during the course of treatment.¹,² It had been suggested that patients who developed thyroid diseases tend to achieve sustained virological response more readily³ although a meta-analysis did not support this contention.⁴ Furthermore, the underlying pathogenetic mechanisms are poorly understood. The following 2 cases are presented to support this observation. In both cases, initial therapies were unsuccessful with normal thyroid function, whereas re-treatment with interferon-α (and ribavirin) in the presence of overt TD resulted in successful sustained viral clearance. Although anecdotal, these cases lend further evidence to the potential synergistic effect of thyroid hormone and interferon therapy. Further research is required to support this hypothesis.

Case presentation

Case 1

A 48-year-old woman presented for ongoing management of her TD after her first course of interferon therapy. She had chronic hepatitis C of genotype 1 with cirrhosis. She underwent a first course of treatment with combination interferon-α (IFN-α) and ribavirin (RBV) for 48 weeks and did not achieve sustained virological response (SVR) at the end of treatment despite good compliance. She had regular monthly thyroid function tests throughout and they were entirely normal. Four weeks after completion, she developed Graves’ disease (GD) with hyperdynamic cardiovascular activity in the presence of a confirmed diffuse goitre. Her thyrotropin (TSH) was undetectable [reference range (RR), 0.4–4.0 mU/l]; free tetra-iodothyronine (fT4) was 28.7 (RR, 10.1–24.5 pmol/l), free tri-iodothyronine (fT3) was 6.9 (RR, 3.3–5.8 pmol/l). Her anti-thyroglobulin (anti-Tg) antibody was normal at 1:64 (RR, < 1 : 400), anti-thyroperoxidase (anti-TPO) titre 1 : 640 (RR, 1: 400), and thyrotropin stimulating immunoglobulin (TSI) titre 14 (RR, <10 U/ml). The thyroid pertechnetate uptake scan showed diffuse uptake at 11%, (RR: 3–8%). The endocrinology team confirmed the diagnosis and began treatment with carbimazole. Her thyroid condition came under control within the ensuing 12 weeks. Six weeks after completion of the first course of combination interferon therapy, she commenced a second course for an additional 48 weeks. Her thyroid status remained normal during this period with a maintenance dose of carbimazole. Her antiviral therapy was otherwise uneventful. Carbimazole therapy was ceased after 18 months, coinciding with the time of SVR. Her viral load was found to be undetectable, confirming SVR. When
reviewed 24 months after Graves’ diagnosis, she remained euthyroid without any medication. Figure 1 summarizes her sequence of events diagrammatically.

Case 2

A 45-year-old female, the biological younger sister of Case 1, presented with acute thyroiditis following the completion of a course of IFN-α and RBV therapy. She had chronic hepatitis C of genotype 3 and had been treated with the combination therapy for the previous 24 weeks uneventfully. She too had regular monthly thyroid function tests during treatment without any abnormalities. She then developed diarrhoea and palpitations 2 weeks after the completion of therapy. Further clinical assessment found her to be thyrotoxic in the absence of a goitre. Her thyroid pertechnetate uptake scan was negligible at 1%. Her anti-Tg antibodies were elevated at 1 : 1280. Her anti-TPO antibody and TSI were not elevated. A diagnosis of interferon-induced thyroiditis was made. This was further supported by the natural progression of the disease when she developed hypothyroidism and required thyroxine supplement. Unfortunately, SVR was not achieved after the first course of thyroid treatment. Eighteen months further on, she underwent a second antiviral course with interferon-α and ribavirin. Thyroxine was continued throughout. However, she developed a second episode of thyroiditis 12 weeks into the second course of treatment with anti-Tg titre rising to 1 : 5120. Her TSH became suppressed with fT4 of 22.5 and fT3 6.5 pmol/l although on a stable dose of thyroxine. Her thyroid uptake scan was again at 2% but uninterpretable in the presence of thyroxine. Thyroxine was ceased and her condition improved following symptomatic treatment. However, 8 weeks later, she again became hypothyroid necessitating the resumption of her thyroxine. Her antiviral therapy continued independent of her thyroid event. She remained well through the remaining treatment and completed the interferon therapy uneventfully. SVR was achieved at 24-week follow-up. Her thyroxine was ceased at the same time. Her follow-up TSH levels at 8 and 24 weeks were normal. Please refer to Figure 1 for her sequence of events.

Laboratory assay characteristics

Third generation TSH and serum fT4 levels were determined by two-site sandwich immunoassay using an automated chemiluminescent system.
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(Diagnostic Products Corporation, Immulite 2000). The RR for TSH was 0.4–4.0 mU/l and fT4 10.5–20.6 pmol/l. The coefficients of variation (CV) were 5.0% and 5.1% at TSH concentrations of 4.0 mU/l and 10.0 mU/l, respectively. For fT4, the CV was 6.5% at 10.0 pmol/l.

Similarly, fT3 levels were performed using a two-site sandwich immunoassay using an automated chemiluminescent system (Beckman Coulter DXI). The RR was 3.5–6.0 pmol/l with 8.7% CV at 6.0 pmol/l.

Thyroid Stimulating Immunoglobulin was measured using cell culture and radio-immunoassay. This is an in-house bioassay using Chinese Hamster Ovary (CHO) cells in culture to detect the presence of thyroid stimulating activity. The CHO cells are transfected with the TSH receptor genes and thus are responsive to TSI. Thyroid-stimulating activity is measured by evaluating the intracellular release of cAMP induced by the patient’s serum immunoglobulin on the CHO cells. The results are reported as units/ml (U/ml). TSI should be absent in the normal population. A TSI level of <10 is considered negative, 10–50 as weakly, 50–100 as moderately and >100 U/ml as strongly positive.

Serum autoantibodies to thyroglobulin and thyroperoxidase were measured by agglutination (Serodia-ATG and Serodia-AMC, Fujirebio, Inc., Tokyo, Japan). Normal titres were less than 1:400 for both.

Thyroid nuclear uptake scans

These were performed using 99m-pertechnetate tracer with uptake studies taken at ~20 minutes post injection with a normal uptake ratio of 3–8:1.

Discussion

TD is the commonest extra-hepatic manifestation of interferon-based treatment in patients with chronic hepatitis C. While still preliminary, it has been our observation that patients who developed TD during treatment achieved a much higher rate of cure or SVR. This was not supported by our meta-analysis however, which was additionally compounded by inherent reporting differences in treatment, the ad hoc method of surveying for TD while having treatment and that some patients were having regular IFN rather than pegylated IFN. These two case reports, although anecdotal, mimic the natural experiment in which neither patient achieved SVR from hepatitis C treatment in the absence of TD. Conversely, both achieved the desired outcome in the presence of TD. It is also fortuitous that the two cases carry both the favourable and unfavourable genotypes in types 3 and 1, respectively. Further more, Case 1 carried the additional poor prognostic factor of cirrhosis and yet managed to achieve SVR. The second case is inherently more responsive because genotype 3 patients often have a much better response rate of ~70–80%, independent of thyroid disease. Despite this favourable factor, the patient did not clear the virus in the absence of TD following the first course of treatment but did so in the presence of TD.

These two natural experimental cases highlight the potential influence of thyroid involvement in achieving SVR. While the thyroid gland is clearly implicated, it remains undetermined whether it is the actual underlying inflammatory autoimmunity of TD that is the culprit or the exposure to supraphysiological concentrations of thyroid hormones (TH). Pathogenetically and pertinent to Case 1, GD is a highly immune-mediated condition which has been reported to be precipitated by interferon therapy. It is currently unclear whether the behaviour of this condition is any different from de novo GDs which may influence the final hepatic viral outcome. Thyroiditis such as that seen in the second case also shares a similar immunological mechanism, with the rising anti-Tg levels with each episode, lending strong support to this observation. While demonstration of autoantibodies is not proof of autoimmunity, the timing of these events soon after administration of an immunomodulators in a primed medium strongly implicates a causal link rather than an epiphenomenon. However recent report suggested a direct thyroid-toxic effect of IFN on thyrocytes, and alluded to in Figure 2. Because the two cases are biologically related, it is possible that in genetically predisposed individuals, IFN therapy is able to induce an unusually amplified response, successful in clearing the virus but damaging the thyroid in the process. Recent publication indicated that genetic variations in the IL-28B gene enhanced the natural spontaneous clearance of the virus. It is not known if this was the case in both our cases as haplotype studies were not available. Hepatitis C infection by itself will result in an induction of IFN-α and β production as part of the innate immune response. IFN also causes the activation of natural killer cells, maturation and proliferation of dendritic cells, proliferation of memory T cells, and prevention of T-cell apoptosis. These factors will induce a rise in thyroid auto-antibody titres, which will in turn cause the immune-related changes demonstrated in both cases. The addition of exogenous IFN-α then further inflames an already vulnerable thyroid gland. Studies have shown that in patients who developed TD, immune marker levels such as Interleukin-6 (IL-6), Tumor Necrosis...
Factor-alpha (TNF-α) and Chemokine Ligand 10 are higher and these factors may be involved in eliciting SVR.

The second potential influencing factor is the exposure to TH. Normal physiological TH levels are unlikely to be effective as all patients would otherwise have normal circulating concentrations. The first case was exposed to high doses of TH early in the second course of therapy while her GD was coming under control. The second developed thyroiditis both before and during the second course of treatment, again exposed to the same milieu. In both cases, the presence of TD in the intervening periods may have indeed primed the tissue for a favourable response. However, the presence of TH in vitro also potentiates the antiviral action of interferon in cultured human cells. In the presence of IFN, TH can also enhance the immune activation pathways such as HLA-DR antigen expression. It is therefore plausible that the favourable outcome is related to the exposure to supraphysiological concentrations of TH.

A third consideration is whether repeated treatment with interferon will confer an improved chance of SVR. Patients receiving retreatment course have ~16% of achieving SVR, usually in the absence of TD. Retreatment in non-responders is often less effective than relapers, especially with genotype 1. This is pertinent to Case 1 who, at least on the grounds of prognostic markers, is least favoured to achieve SVR. In addition, re-exposure to interferon does not appear to increase the risk of thyroid disease. Figure 2 summarizes the hypothetical mechanism of achieving SVR in these 2 cases.

Our report has a number of drawbacks. Firstly, we did not have the opportunity to study the single nucleotide polymorphisms (SNPs) near the interleukin (IL) 28B gene locus in both cases. These SNPs have been shown to play an important part in the spontaneous recovery, response to treatment and attaining SVR from HCV infection. It would be fascinating to know of the cases harbour the favourable SNPs although the clinical utility of this novel finding remains to be refined. Secondly and clearly, these are anecdotal cases and may be considered coincidental. Nevertheless, they suggest a potential existing mechanism in accentuating the SVR rate in the presence of thyroid disease. It is critical that further clinical studies are performed.

Figure 2. The proposed hypotheses for the eradication of HCV with TD and IFN-based therapy. IL-6, Interleukin-6; IFN, Interferon; MHC-II, major histocompatibility complex-II; TH, T helper.
to see if this observation can be reproduced before any definitive conclusions can be extracted. Further, demonstration that thyroxine (both in supraphysiological and physiological concentrations) can enhance the IFN-α antiviral effects in vitro would also considerably strengthen this hypothesis.

Conclusion

These two biologically-related cases illustrate the genetic tendency to develop autoimmune-mediated TD when undergoing IFN-α based treatment for chronic hepatitis C. The presence of the TD, either by way of the immune mediation or exposure to high concentrations of TH (or both), represents a favourable prognostic factor in achieving SVR for hepatitis C. Further investigation is required to confirm this potentially enhanced prognostic outcome, especially for the resistant genotype 1 patients. This is very important because patients who have sustained viral eradication can have regression of cirrhosis and a reduced risk for cirrhosis-related complications.  

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