Author's response to reviews

Title: Takotsubo cardiomyopathy and transient thyrotoxicosis during combination therapy with Interferon-alpha and Ribavirin for chronic hepatitis C

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Dear Professor Timothy Shipley,

We are pleased to submit the revised version of our manuscript entitled “Takotsubo Cardiomyopathy and Transient Thyrotoxicosis during Combination Therapy with Interferon-alpha and Ribavirin for Chronic Hepatitis C” for consideration as a case report paper.

Authors response to the peer review:

Referee 1:

• We report a rare case of Takotsubo cardiomyopathy associated with transient thyrotoxicosis, in a female patient treated with IFN-α and Ribavirin for CHC, in order to highlight an unusual complication of thyrotoxicosis and the difficulties associated with the management of CHC.


• TCM caused by thyrotoxicosis is rare and has previously been reported in a few cases. A table with the case reports of TCM associated with thyrotoxicosis has already been published [Eliades M, El-Maouche D, Choudhary C, Zinsmeister B, Burman KD: Takotsubo Cardiomyopathy Associated with Thyrotoxicosis: A Case Report and Review of the Literature. Thyroid 2013, -Not available-, ahead of

The diagnosis of non-autoimmune destructive thyroiditis was made based on clinical history, physical examination, the absence of positive antibodies and the triphasic evolution pattern. Thyroid ultrasonography showed diffuse heterogeneity and near normal color-flow Doppler, rather than the enhanced flow characteristic of Graves' disease. In our case, RAIU could not have been helpful because contrast angiography had been recently performed. Technetium-99m (99m Tc)-pertechnetate scintigraphy was not available at that moment. Typically, thyroid scan demonstrates markedly reduced uptake in the thyroid gland during the initial stage, but this finding is not present in all patients. Serum thyroglobulin levels are usually elevated in destructive thyroiditis, yet, thyroglobulin increases in any kind of hyperthyroidism.

In our case, similar to other cases previously reported, the hyperthyroid state was indeed relatively mild and of short duration. TCM is frequently triggered by an acute medical illness or by intense emotional or physical stress. We believe that transient, mild thyrotoxicosis associated to the emotional stress could have been the cause of this TCM. The pathogenesis of this disorder is not well understood. Postulated mechanisms for TCM pathogenesis include: direct cardiotoxicity of catecholamine excess, epicardial coronary vasospasm, micro-vascular dysfunction, shifts in cardiac metabolism from fatty acids towards...
carbohydrates and left ventricular outflow tract obstruction, resulting in myocardial stunning. Thyroid hormones have cardiovascular effects that are similar to catecholamine-mediated stimulation of #-adrenergic receptors and can enhance chronotropic and contractile responses to catecholamines. Some studies have also reported an association between coronary vasospasm and hyperthyroidism.

• Informations regarding CHC treatment before and after the diagnosis were added.

• The discussion was focused to the role of thyroid disfunction on the pathogenesis of TCM.

• To the best of our knowledge, this is the first report of a TCM associated with transient destructive thyrotoxicosis resulting from combination therapy with IFN-# and Ribavirin for CHC. Although TCM is rare and has a good long term prognosis as it is usually fully reversible, physicians should be aware of this diagnosis especially in myocardial infarction patients with normal coronary arteries. We believe this case presentation is important to gastroenterologists, endocrinologists, cardiologists, primary care physicians and to those with related research interests.

• Following the recommendations we corrected the spelling/editing errors.

Referee 2

• We displayed the TSH and Free T4 values in a diagram in relation to time (Figure 5)

• We replaced the sentence "CHC and its treatment may initiate or worsen thyroid dysfunction" with “A higher prevalence of thyroid disorders has been reported in HCV-infected patients than in the general population [Antonelli A, Ferri C, Pampana A, Fallahi P, Nesti C, Pasquini M, Marchi S, Ferrannini E: Thyroid disorders in chronic hepatitis C. Am. J. Med 2004, 117(1):10-13]. Antiviral therapy of CHC possibly induces de novo or exacerbates pre-existing silent thyroid disorders. [Elena Vezali, Ioannis Elefsiniotis, Constantinos Mihas, Evangelos Konstantinou, George Saroglou. Thyroid Dysfunction in Patients with Chronic Hepatitis C: Virus- or Therapy-related? J Gastroenterol Hepatol. 2009; 24(6):1024-1029].

• We considered appropriate and we were pleased to add the reference [PMID: 23560557]

Thank you very much for your interest in our work and for your valuable suggestions,

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