Graves' disease in a chronic hepatitis C patient not receiving interferon therapy

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A 36-year-old man with a chronic hepatitis C infection developed hyperthyroidism from a previously normal thyroid status. Laboratory tests showed both elevated serum thyroxine and anti-thyroid antibody titres. The patient's hyperthyroidism was brought into remission by the administration of anti-thyroid medication. Graves' disease is a possible autoimmune manifestation of chronic hepatitis C not associated with interferon therapy. The mechanism may be due to antigen mimicry, epitope modification, or T-cell activation by the hepatitis C virus. New treatment modalities may be more effective than interferon therapy for chronic hepatitis C patients with thyroid disorders.

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Introduction

Various forms of thyroid disease and abnormal thyroid test results have been reported in chronic hepatitis C virus (HCV) patients after starting interferon-alpha therapy. Graves' disease, a less common form of interferon-alpha-induced thyroid dysfunction, has also been well described.[1] However, there is a high prevalence of abnormal thyroid tests in patients with chronic HCV even before interferon-alpha therapy has been commenced[2] although overt hyperthyroidism is rarely reported. Reference has been made of some cases of coincidental occurrence of hyperthyroidism and viral hepatitis.[3] We present what we believe to be the first local report of Graves' disease in a patient with established chronic HCV infection not related to interferon-alpha therapy.

Case report

A 36-year-old Chinese man was followed up at a district hospital for chronic hepatitis infection four years ago. There was no history of blood product transfusion, intravenous drug abuse, or affected family members. He had remained relatively asymptomatic except for occasional attacks of nausea, anorexia, and malaise.

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Two years ago, he attended the hepatology clinic at the Princess Margaret Hospital, Kowloon, with tiredness and appetite loss of two weeks' duration. His serum bilirubin was 48 μmol/L (normal range, 2-18) and alanine aminotransferase (ALT) level was 1028 U/L (normal range, 0-35). Serum anti-HCV antibodies [Ortho HCV 2.0 enzyme immunoassay (Ortho Diagnostic, Raritan, NJ, US)] and HCV RNA [DNA polymerase, PCR (Perkin Elmer Cetus, Norwalk, Conn, US)] were both positive. The HCV RNA in the patient's serum was extracted, reverse-transcribed (reverse transcriptase from Promega, Madison, Wis, US) to cDNA, and amplified using a nested-PCR technique.[4] The PCR primer sequences were derived from a highly conserved 5' non-coding region of a cDNA clone of HCV from a Japanese isolate. The PCR technique was performed as described elsewhere.[4] Anti-nuclear factor, anti-smooth muscle antibody, and other viral hepatitis serological markers were all absent. Thyroid function was normal and thyroid antibodies were negative in the pre-treatment screening for possible interferon-alpha therapy. Liver biopsy showed the presence of some lymphoid follicles in the portal tracts, a few damaged bile ducts near these follicles, and low-grade lobular abnormalities including acidophil body formation, focal inflammatory infiltration, and fatty change. The histological diagnosis was: mild chronic hepatitis consistent with HCV infection.

At follow up four months later, he complained of palpitations, tremor, and weight loss at a clinic visit. There was no positive family history of thyroid disease. He also had mild diffuse enlargement of the thyroid gland. Blood tests showed the following results: total serum thyroxine 351 nmol/L (normal range, 51-142), free serum thyroxine 41.5 pmol/L (normal range, 10-36) and serum thyroid stimulating hormone < 0.1 mU/L (normal range, 2-11). Anti-thyroglobulin and anti-thyroid microsomal antibody titres were both 1:6400; TSH-receptor antibody was not measured. A thyroid scan showed increased radioactive iodine uptake. A fine needle biopsy was not performed. Based on these findings, the clinical diagnosis of Graves' disease was made. Standard dosages of propylthiouracil were given for 18 months. The patient went into remission in the second month of treatment. He has remained euthyroid for the past two months after stopping the propylthiouracil.

During follow up in the past 24 months, his ALT level has usually been below 100 U/L. A few episodes of exacerbation associated with symptoms have occurred when the serum bilirubin level rose to more than 70 μmol/L and ALT exceeded 1000 U/L. His latest liver function tests were normal apart from a slightly elevated ALT of 54 U/L.

Discussion

The occurrence of Graves' disease in our patient against a background of known chronic HCV is either due to coincidence alone or related to an extrahepatic autoimmune response to the HCV infection. Judging from the low prevalence (0.6%) of anti-HCV positivity in the Hong Kong population found in a local study[5] and the less common occurrence of Graves' disease in the male sex, chance association between chronic HCV and Graves' disease in our patient is not very likely. An autoimmune relationship linking the two diseases is a plausible explanation. Chronic HCV infections are commonly associated with extrahepatic autoimmune diseases such as thyroiditis, thrombocytopenic purpura, Sjögren's syndrome and haemolytic anaemia. Graves' disease is considered with Hashimoto's thyroiditis and primary myxoedema as closely related thyroid diseases which are known autoimmune phenomena of chronic HCV.[6] Autoimmune abnormalities occur more frequently in chronic HCV patients than they do in chronic HBV patients.[7] However, some extrahepatic immune manifestations of chronic HBV, such as glomerulonephritis and generalised vasculitis, are more common. These diseases are associated with circulating immune complexes containing HBsAg and are not related to autoimmunity.

The patient's high titres of thyroid autoantibodies (1:6400) may reflect a genetic pattern which gives an immunological predisposition to autoimmunity. Conversely, HCV may have initiated the autoimmune thyroid disease. A French study found a high prevalence of thyroid autoantibodies in a prospective series of patients with chronic HCV infection prior to interferon therapy.[8] Our patient, by virtue of his high titres of thyroid autoantibodies, also has a strong likelihood of developing Hashimoto's thyroiditis. Nevertheless, the current belief is that the thyroid status is not directly related to the titre of these antibodies. The finding of an increased prevalence of serum HCV antibodies in patients with Hashimoto's thyroiditis suggests that HCV may have the ability to trigger Hashimoto's thyroiditis.[9] The mechanism by which this occurs could be due to HCV mimicking the structure of some components of thyroid tissue, modifying thyroid antigens to make them more immunogenic or activating T cells independently of antigen.[10]

Apart from their anti-viral and anti-proliferative effect, the interferons are also potent immunomodulatory agents. Approximately 2% of patients on interferon-alpha for chronic HCV will develop autoimmune diseases. Similarly, the induction of autoimmune reactions—especially autoimmune thyroiditis—is a recognised complication of interferon-alpha treatment of chronic HBV infection. Thyroid dysfunction, or even thyroiditis, is a significant autoimmune manifestation of interferon-alpha therapy in chronic HCV infection even though it usually resolves without treatment in most cases. It should be noted that our patient had not received interferon treatment before the onset of Graves' disease.

There are two aspects to the management of a patient's hyperthyroidism. Firstly, radioactive iodine treatment induces hypothyroidism at the rate of 3% per year; using a conventional dose, it has been reported to be as high as 70% at 10 years in some series. Secondly, interferon therapy may induce thyroid dysfunction again after a remission achieved with medical treatment.

We chose not to use radioactive iodine on our patient whose high titres of thyroid autoantibodies

signified a propensity for the development of Hashimoto's thyroiditis and hypothyroidism. He refused to undergo subtotal thyroidectomy as an alternative form of treatment. Therefore, a course of antithyroid drug was given and it succeeded in bringing about a remission of his Graves' disease. Should his hyperthyroidism recur repeatedly, we may have to consider giving him radioactive iodine and accept the high possibility of hypothyroidism and the inconvenient necessity of giving thyroxine replacement.

As for the second problem, we have managed the patient conservatively and withheld interferon-alpha treatment for the time being so as to avoid any interferon-induced thyroid dysfunction. Future treatment options will include a trial of interferon-alpha despite the inherent risks or the use of novel agents.

Graves' disease is one of the autoimmune diatheses of chronic HCV infection, independent of interferon-alpha therapy. Interferon-alpha—with its effect on the immune system—is not an ideal agent for the treatment of patients with chronic HCV who are in remission from hyperthyroidism or have high titres of thyroid autoantibodies. In these situations, proteinase inhibitors, antisense compounds and therapeutic vaccines may hold promise for future treatment of patients.

References

1. Chung YH, Shong YK. Development of Graves' disease after interferon for chronic hepatitis C. Am J Gastroenterol 1993;88:244-7.
2. Pateron D, Augier I, Doclos-Vallée JC, Jouanolle H, Hartmann DJ, Beaugrand M. High prevalence of abnormal thyroid tests in patients with chronic hepatitis C before alpha interferon (IFN) therapy: relation with IFN induced thyroid dysfunction [abstract]. Hepatology 1991;14:77A.
3. Marcini A, Demarinis L, Fiumara C, et al. The role of autoimmune mechanisms in the hyperthyroidism-viral hepatitis syndrome: a possible noncausal association. A review of the literature and the authors' own cases. Minerva Med 1990;102:2155-60.
4. Garson JA, Tedder RS, Biggs M, et al. Detection of hepatitis C viral sequences in blood donations by 'nested' polymerase chain reaction and prediction of infectivity. Lancet 1990;335:1419-22.
5. Lai JY, Tam JS, Lam LY, Leung NW. Prevalence of antibody to hepatitis C virus in HBsAg-negative chronic liver disease in Hong Kong using different assays. J Med Virol 1992;37:158-60.
6. Lunel F. Hepatitis C virus autoimmunity: a fortuitous association or reality. Gastroenterology 1994;107:1550-4.
7. Pawlotsky JM, Yahia MB, Andre C, et al. Immunological disorders in C virus chronic active hepatitis: a prospective case-controlled study. Hepatology 1994;19:841-8.
8. Tran A, Quaranta JF, Benzaken S, et al. High prevalence of thyroid autoantibodies in a prospective series of patients with chronic hepatitis C before interferon therapy. Hepatology 1993;18:253-7.
9. Duclos-Vallée JC, Johaner C, Trinchet JC, et al. High prevalence of serum antibodies to hepatitis C virus in patient with Hashimoto's thyroiditis. BMJ 1994;309:846-7.
10. Utiger RD. The pathogenesis of autoimmune thyroid disease. N Engl J Med 1991;325:278-9.