CELIAC DISEASE ONSET AFTER PEGYLATED INTERFERON AND RIBAVIRIN TREATMENT OF CHRONIC HEPATITIS C

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ABSTRACT - ***Aim*** - Report of a case of a woman patient who developed celiac disease after pegylated interferon γ-2a and ribavirin use for chronic hepatitis C. ***Patient and Method*** - A 34-year-old woman with chronic hepatitis C, genotype 3, receiving pegylated interferon γ-2a and ribavirin for 6 months, developed progressive malaise and anemia 6 months after the end of treatment. ***Result*** - Additional investigation revealed duodenal villous atrophy and positivity for anti-endomysium and anti-gliadin antibodies. Celiac disease diagnosis was performed and symptoms and laboratory abnormalities improved after gluten-free diet. ***Conclusion*** - Celiac disease must be ruled out in patients with malabsorption complaints in or after interferon (or pegylated interferon) therapy. Screening for celiac disease with detection of anti-endomysium antibodies would be done in susceptible patients.

HEADINGS - Celiac disease. Hepatitis C. Interferon Alfa-2a. Ribavirin. Autoantibodies.

INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy characterized by malabsorption resulting from inflammatory injury to the mucosa of the small intestine after ingestion of gluten-containing grains in susceptible individuals[7]. The gliadin fraction of wheat gluten and similar alcohol-soluble proteins in other grains are the environmental factors responsible for the development of the intestinal damage. CD results from an inappropriate T cell-mediated response against ingested gluten[8]. This process creates a situation commonly observed in other autoimmune diseases[15]. In addition, CD frequently is associated with autoimmune diseases including diabetes mellitus type I, autoimmune thyroid disease, Sjögren syndrome, Addison disease, autoimmune atrophic gastritis and autoimmune hepatitis[8, 12, 18]. Recent studies emphasize the necessity of investigating these autoimmune disorders in CD patients[3, 17].

Actually, pegylated interferon (PEG-IFN) in combination with ribavirin provides the most effective treatment for patients with chronic hepatitis C[10]. However, interferon (IFN) therapy is associated with induction or exacerbation of pre-existing autoimmune disorders and to investigate these conditions is advisable before treatment beginning and the follow-up[6].

In this report, we describe a patient with CD onset after PEG-IFN and ribavirin use for chronic hepatitis C and review the literature about this rare situation.

CASE REPORT

In March 2001, a 34-year-old woman with positive antibodies for hepatitis C, repeatedly elevated serum alanine aminotransferases concentrations for more than 6 months, hepatitis C RNA detectable by reverse transcriptase polymerase chain reaction (PCR), genotype 3, and chronic active hepatitis on liver biopsy, received PEG-IFN γ-2a 180 μg once a week plus ribavirin 1,0 g daily for 6 months according our protocol. Viral clearance was observed and the patient remained asymptomatic until April 2002, when she started progressive fatigue and involuntary weight loss. Thyroid function tests were normal and iron-deficiency anemia was detected. An upper gastrointestinal endoscopy showed a flat duodenal mucosa and distal duodenal biopsy resulted in partial villous atrophy. Dual-energy x-ray absorptiometry showed osteopenia. Positivity for IgA anti-gliadin antibodies and IgA anti-endomysium antibodies (EMA) and response to gluten-free diet enable us to make a diagnosis of CD.

DISCUSSION

Autoimmune side-effects including hyperthyroidism, hypothyroidism, diabetes mellitus, interstitial pneumonitis, autoimmune thrombocytopenic purpura, hemolytic anemia, rheumatoid arthritis and systemic lupus erythematosus have been reported to exacerbate or develop during interferon therapy[6].

Recently, the activation of CD during IFN therapy alone for chronic hepatitis C has been reported in three cases[2, 5] and, in patients receiving IFN and ribavirin in another three cases[1, 4, 5]. Screening for EMA before IFN use has been recommended[2].

IFN use has potential to exacerbate autoimmune disease either by direct effects on tissues or by interaction with the immune system, altering the link between lymphocyte populations and the profile of cytokine production. IFN acts in the differentiation

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of T helper (Th) 2 cells to Th1 cells and improves T-cell and natural Killer cell citotoxicity[5]. Ribavirin promotes a Th1 cytokine-mediate immune response, suppressing Th2 response[16]. Similarly, gluten-induced activation of lamina propria Th1 cells followed by secretion of IFN gamma is an important pathogenic mechanism in CD[15]. Thus, it is possible that the impairment of Th1/Th2 balance exerted by IFN or IFN and ribavirin might induce or activate CD in predisposed individuals. We do not known if PEG-IFN action is stronger in this setting. As far as we are concerned, this is the first report after PEG-IFN use.

In another view, FINE et al.[9] observed an increased prevalence of CD in patients with hepatitis C virus infection compared with other forms of liver disease or with controls without liver disease and hypothesized that is indeed the infection with hepatitis C virus rather than its treatment that is associated with the increased prevalence of CD in this patient population.

Although CD prevalence in Brazil (1:375-681) is lower than in the United States, and the majority of European countries (1:200-300)[11, 13, 14], we suggest that patients with hepatitis C must be screened for EMA before IFN (or PEG-IFN) and ribavirin treatment. In patients with EMA positivity, the need for therapy has to be balanced against the risk to develop an overt CD or, alternatively, treatment must be done in conjunction with a strict gluten-free diet[4, 5]. Finally, more studies are necessary to access the role of the hepatitis C virus infection in the pathogenesis of CD.

Martins Jr EV, Gaburri AK. Doença celíaca após tratamento de hepatite C crônica com interferon peguilado e ribavirina. Arq Gastroenterol 2004;41(2):132-3.

RESUMO - ***Objetivo*** - Relatar caso de doença celíaca ocorrendo após uso de interferon peguilado e ribavirina em paciente com hepatite C crônica. ***Paciente e Método*** - Mulher de 34 anos com hepatite C crônica, genótipo 3, tratada com interferon peguilado γ-2a e ribavirina durante 6 meses, desenvolveu quadro de astenia e anemia após 6 meses do término do tratamento. ***Resultado*** - Investigação complementar revelou atrofia vilositária à biopsia duodenal e detecção de anticorpos anti-endomísio e anti-gliadina, realizando-se diagnóstico de doença celíaca. Dieta isenta de glúten foi instituída, observando-se boa resposta clínica e laboratorial. ***Conclusão*** - Doença celíaca deve ser afastada em pacientes com quadro de má absorção durante ou após uso de interferon (ou interferon peguilado). Rastreamento de doença celíaca através da realização de anticorpo anti-endomísio pode ser considerado em populações susceptíveis.

DESCRITORES - Doença celíaca. Hepatite C. Interferon alfa-2a. Ribavirina. Auto-anticorpos.

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