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Severe Autoimmune Hepatitis in a Chronic Myeloid Leukemia Patient Treated With Interferon Alpha and With Complete Genetic Response

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A patient with chronic myeloid leukemia (CML) treated with interferon alpha (IFN alpha) and who developed autoimmune hepatitis (AIH) is described. The patient was treated with IFN alpha 2a, a complete cytogenetic response was achieved 5 months later, and this response has lasted now more than 7 years. Autoimmune hypothyroidism appeared at 18 months of treatment, and 1 year later severe type I autoimmune hepatitis developed. To our knowledge this is the first report of such complication in an IFN alpha-treated CML patient. Am. J. Hematol. 59:95–97, 1998. © 1998 Wiley-Liss, Inc.

Key words: chronic myeloid leukemia; interferon alpha; autoimmune hepatitis; autoantibodies

INTRODUCTION

Treatment with IFN alpha has been related to autoimmune phenomena in patients treated with this cytokine for hepatitis and malignancies [1]. Several mechanisms may be involved: Increment in autoantibody production, increase in B and cytotoxic T cells, functional inhibition of suppressor T cells, and induction of class I and II HLA antigens expression [2].

Here we report the case of a woman diagnosed with CML who developed a severe autoimmune hepatitis on IFN alpha treatment.

CASE REPORT

A 51-year-old woman was diagnosed with CML in December 1985. Treatment with Busulfan was complicated by aplastic anemia. The recovery was associated with restoration of Ph1 negative metaphases, which comprised 80% of the total. In that moment (December 1988), the patient was referred to our institution. She was started on IFN alpha 2a therapy on August 1989. The cytogenetic exam done prior to therapy showed 20% of Philadelphia-positive metaphases, and normal diploid metaphases were observed in the rest. M-BCR rearrangement was detected in leukocyte ADN obtained at that time. At 5 months of therapy a complete cytogenetic response (CGR) was achieved and this remission has been kept since then, as proved in 6 occasions by karyotyping and/or M-BCR-rearrangement analysis by Southern blot. Absence of bcr-abl RNA by reverse transcriptase polymerase chain reaction (RT-PCR) was documented 41 months after CGR was obtained (sensitivity: $1/10^5$ cells).

Values for liver enzymes were normal, and autoantibodies were negative, at diagnosis and at the moment of starting IFN (Table I). A mild elevation of ALT (86 U/l) was observed after 1 month of treatment. Mild liver toxicity secondary to IFN was assumed; IFN alpha was continued at 9MU/d. During the first 2 years, transaminases levels stayed always in the range between 1.26 and 2.5

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TABLE I. Clinical and Analytical Evolution of the Patient*

	Date				
Variable[a]	July 1989	March 1991	Sept 1993	Feb 1996	Oct 1997[a]
Symptoms or signs	No	No	No	No	No
IFN (MU/D)	No (pretreatment)	9	5,4	2,5	0
AST (U/l)	40	42	161	89	26
ALT (U/l)	40	46	228	141	31
ALK, Ph (U/l)			205	181	220
Gamma globulin (g/dl)	1	1,3	1,6		N.D.
IgG (mg/dl)	1.170	—	2.490	1.690	
ANA	1/10	1/80	1/40	1/20	Neg
Anti-dsDNA	—	1/40	Neg	Neg	
T4/TSH (μg/dl/U/ml)	—	2.9/43	1.4/0.4		1,3/0,66
TGA	—	1/25,600	1/25,600	1/25,600	1/6,400
TMA	—	1/25,600	1/25,600	1/25,600	1/6,400

*IFN, interferon; MU/d, megaunits/day; AST, aspartateaminotransferase; ALT, alanine aminotransferase; ALK, Ph, alkaline phosphatase; ANA, antinuclear antibodies; Anti-dsDNa, anti-double-stranded DNA; TGA, thyroglobulin antibodies; TMA, thyroid microsomal antigen antibodies.
[a]Sixteen months after stopping IFN.

times the normal value (WHO toxicity grade I). At 18 months of IFN therapy, subclinical hypothyroidism and autoimmune thyroiditis were diagnosed. One year later, 30 months after the start of IFN, 3 times normal transaminase levels were reached and hepatomegaly was found.

The IFN dose was lowered; in spite of this, ALT levels peaked to 323 U/l at 47 months of treatment. A liver biopsy was obtained, showing venoportal septa, interstitial fibrosis, steatosis, and Mallory's hyaline, leukocytic infiltrate, and necrotic hepatocytes in perivenular areas. Ethanol ingestion was excluded. Viral serology was negative for HBV and HCV. HCV-RNA was not detected by RT-PCR (Table I).

The decrease in IFN dose was followed by a decrease of liver enzymes (Table I). Anti-nuclear and anti-DNA autoantibodies, autoimmune thyroiditis, and hypergammaglobulinemia were detected, whereas negative results were obtained when anti-smooth muscle, anti-LKM1, and anti-p-ANCA antibodies were assayed. This picture was consistent with the diagnosis of AIH. The AIH score was 12, according to the IAHG scoring system [3] (Table I). A second hepatic biopsy was obtained in May 1996, when the patient was receiving 1.5 MU/d of IFN alpha, and complete cytogenetic and molecular remission were present. The liver histology showed that the degree of leukocytic infiltrate was less prominent and the Mallory's hyaline had disappeared. Conversely, fibrosis was more conspicuous, although the picture was not diagnostic of hepatic cyrrhosis. Alpha-IFN was stopped July 1996. Transaminases returned to normal levels in 3 months. In December 1996, mobilization of Ph1 negative precursors to peripheral blood was done, using G-CSF [4], and 2.7×10^6 CD34 positive cells per kg were obtained. Cytogenetic studies disclosed 100% Ph1 negative metaphases. RT-PCR did not detect RNA bcr-abl in the apheresis product (sensitivity: 10^{-5} cells). The patient remained in CGR and with complete molecular response 9 months later.

DISCUSSION

Our case represents the optimal scenario in terms of leukemic control obtained by IFN alpha therapy: complete cytogenetic and molecular response have been maintained, and the patient has reached a survival of more than 10 years, 7 years on IFN alpha.

Nonetheless, the clinical picture suggests that IFN alpha has triggered several autoimmune phenomena. The presence of autoimmune thyroiditis requiring hormone replacement was first discovered after 18 months of IFN therapy. One year later, a more serious disorder appeared, which is compatible with autoimmune hepatitis [5].

The presence of autoimmune phenomena arising in CML patients treated with IFN alpha has been recognized. Sacchi et al. have reported an overall incidence of 5% in a large series from the MD Anderson Cancer Center [6]. The incidence may be even greater; we have detected the presence of red cell autoantibodies in 32% of our patients [7].

It is possible that IFN alpha may have triggered the latent presence of AIH in this patient. We have recently described that this could be the case in some patients with chronic hepatitis C treated with IFN alpha. It is interesting to point out that two patients studied by us also suffered from autoimmune thyroiditis [8].

Although a direct toxic effect of IFN cannot be excluded in our patient, there is no positive correlation between the dose of IFN and transaminases level and this also could support an immune effect more than a toxic effect.

IFN alpha interruption has been followed by a normalization of transaminases levels, which may reveal a halt of the autoimmune process. Although long-lasting CGR in spite of stopping IFN alpha has been described [9], it is possible for the disease to recur. For this reason, a collection and cyropreservation of Ph1 negative peripheral blood progenitors have been made. We feel that autologous blood transplantation may be used if the genetic response is lost after stopping IFN. Our report suggests that it would be of interest to find out which patients could be susceptible to immune complications on IFN therapy and to pay special attention to the appearance of these phenomena in subsequent studies.

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