

## CASE REPORT

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# The development of systemic lupus erythematosus following interferon- $\alpha$ therapy for hepatitis C infection

S-Abdul Wahid FADILAH,<sup>1,2</sup> Kong-Chiew-Tong NORELLA,<sup>2</sup> Mohd-Said SHAHRIL,<sup>2</sup> Raja-Sabudin AZMA,<sup>3</sup> Chooi-Fun LEONG<sup>1,3</sup> and Soon-Keng CHEONG<sup>1</sup>

<sup>1</sup>Clinical Haematology and Stem Cell Transplantation Services, MAKNA-HUKM Cancer Institute, Hospital Universiti Kebangsaan Malaysia (HUKM), <sup>2</sup>Department of Medicine and <sup>3</sup>Department of Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia (UKM), Kuala Lumpur, Malaysia

### Abstract

Interferon-alpha (IFN- $\alpha$ ) therapy has been associated with de novo development of systemic lupus erythematosus (SLE), and discontinuation of IFN- $\alpha$  resulted in disease resolution in most patients. Recurrence of SLE in the absence of concomitant IFN- $\alpha$  therapy has not been reported. We present here a woman who developed overt clinical manifestations of SLE one year after withdrawal of IFN- $\alpha$  therapy for hepatitis C virus (HCV) infection. This report highlights the importance of long-term follow-up for the belated development of SLE in patients who have experienced IFN- $\alpha$  induced autoimmune phenomena.

**Key words:** autoimmune, hepatitis C virus (HCV), interferon- $\alpha$  (IFN- $\alpha$ ), side-effects, systemic lupus erythematosus (SLE).

### INTRODUCTION

The development and the exacerbation of pre-existing autoimmune phenomena including systemic lupus erythematosus (SLE), rheumatoid arthritis, autoimmune hepatitis, idiopathic thrombocytopenic purpura, thyroid disease, and others have been reported in patients receiving interferon- $\alpha$  (IFN- $\alpha$ ) for a variety of indications<sup>1</sup> which include chronic myeloid leukaemia<sup>2,3</sup> and hepatitis C virus (HCV) infection.<sup>4-6</sup> In such patients, an unexpectedly high incidence (20%) of autoantibodies was observed, including antinuclear antibodies (ANA), thyroid microsomal antigens, thyroglobulin and parietal cell antibodies.<sup>1</sup> The duration of IFN- $\alpha$  therapy before the onset of SLE ranged from 2 weeks to 7 years.<sup>2-6</sup>

The development of SLE following treatment with IFN- $\alpha$  suggests a pathogenic role for IFN- $\alpha$  in SLE. IFN- $\alpha$  may directly trigger production of autoantibodies, enhance B cell function and facilitate presentation of self-antigens by dendritic cells, which in turn could initiate autoimmunity. IFN- $\alpha$ -induced SLE typically developed during IFN- $\alpha$  therapy and resolved upon discontinuation of the drug. Recurrence of SLE in the absence of concomitant IFN- $\alpha$  therapy has not been reported. We present here the first report of the development of full-blown SLE long after discontinuation of IFN- $\alpha$ . Given the increasing use of IFN- $\alpha$  for a variety of indications, clinicians should be aware of the potential of delayed autoimmune side-effects of IFN- $\alpha$  therapy. Specifically, close clinical and laboratory monitoring for the development of SLE is advocated among high-risk patients.

*Correspondence:* Associate Professor Dr Fadilah S. Abdul Wahid, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia (UKM), Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia.  
E-mail: sfadilah@mail.hukm.ukm.my

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A 37-year-old Indian female doctor presented with jaundice and malaise in late 2003. She had received

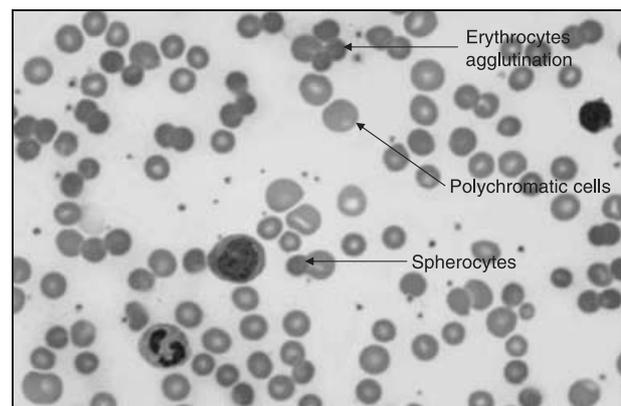
500 mL red cell transfusion one year earlier during a dental procedure for fractured teeth following a minor motor vehicle injury. At that time, the platelet count and coagulation profile were normal, and ANA was negative, hence a bleeding disorder of autoimmune origin was unlikely. There was relevant past medical history. There was no family history suggestive of autoimmune diseases. The HCV serology was positive and the serum transaminases and bilirubin level were raised. The HCV RNA level was elevated (48,000 copies) and of genotype 1B variety. Serum complement 3 and 4 (C3, C4), ANA and antidouble stranded DNA (antidsDNA) tests were unremarkable. Liver biopsy was consistent with grade 2 stage 1 chronic active hepatitis. She received subcutaneous pegylated IFN- $\alpha$  injections at a dose of 1.5  $\mu\text{g}/\text{kg}$  (80  $\mu\text{g}$ ) weekly and ribavirin (800 mg) twice daily resulting in normalization of the serum transaminases and bilirubin and undetectable levels of HCV RNA 5 months after starting IFN- $\alpha$ . Six months after commencing IFN- $\alpha$  therapy, she developed easy bruising and gingival bleeding associated with isolated thrombocytopenia (platelet count  $9 \times 10^9/\text{L}$ ) and giant platelets in the peripheral blood suggestive of immune thrombocytopenic purpura (ITP). There was also marked weight loss (more than 10 kg over 1 month) associated with hyperglycaemia (fasting blood sugar 12.5 mmol/L) that was attributed to insulinitis associated with IFN- $\alpha$  therapy. Serum C4 level was 4 mg/dL (normal range [NR]: 20–59), C3 90 mg/dL (NR: 86–184), ANA titre was elevated at 1 : 160 with a speckled pattern and antidsDNA (by enzyme-linked immunosorbent assay) was repeatedly positive. IFN- $\alpha$  was discontinued and the patient was given one unit of apheresis platelet resulting in cessation of the bleeding and increment of the platelet count ( $25 \times 10^9/\text{L}$ ) within a few weeks. The patient refused prednisolone therapy owing to the concern of flare-up of HCV infection. Several months after discontinuing IFN- $\alpha$ , both the ITP and hyperglycaemia resolved completely. However, serum C4 levels remained low and ANA was persistently positive (1 : 40 to 1 : 80).

She presented again in early 2005 with a 2-week history of fever (38°C), pallor, jaundice and multiple oral ulcers. There was no malar rash, discoid rash, photosensitivity, alopecia or arthritis. The haemoglobin was 6.4 g/dL, reticulocytes 11%, mean cell volume 133 fL (NR: 77–91), white cell count  $13.6 \times 10^9/\text{L}$  (neutrophils  $9.1 \times 10^9/\text{L}$ , lymphocytes  $3.1 \times 10^9/\text{L}$ ) and platelets  $561 \times 10^9/\text{L}$ . Peripheral blood film revealed numerous spherocytes, marked polychromasia and erythrocyte agglutination (Fig. 1). Direct antiglobulin test was positive for IgG, IgM and complements. The autoantibodies demonstrated

a wide thermal range and showed no specificity to tested red cell antigens. The patient's serum did not contain cryoglobulin. Serum unconjugated bilirubin, lactate dehydrogenase and ESR levels were markedly elevated. Serum ANA was positive and serum C4 was markedly reduced (12.9 mg/dL). Serology for *Mycoplasma pneumoniae* and infectious mononucleosis were unremarkable and HCV RNA remained undetectable. Liver and renal profiles were normal. A diagnosis of SLE complicated by autoimmune haemolytic anaemia (AIHA) was made. The patient received IV immunoglobulin and least incompatible red cells infusion resulting in resolution of the clinical symptoms. She subsequently developed breathlessness, productive cough and pleuritic pain associated with pleural rub and coarse crackles over the lung bases. High resolution CT scan showed ground glass opacities and consolidation at the lower lobes suggestive of pneumonitis and fibrosing alveolitis. The patient was treated with IV minipulse methylprednisolone, azathioprine and later rituximab resulting in resolution of her symptoms. She remained in remission four months later.

## DISCUSSION

Systemic lupus erythematosus infrequently complicates IFN- $\alpha$  therapy with 13 cases reported thus far.<sup>6</sup> The duration of IFN- $\alpha$  therapy before the onset of SLE ranged from 2 weeks to 7 years. These case reports reflect a spectrum of disease that is not characteristic of drug-induced lupus. Many common manifestations of SLE such as malar or discoid rash, oral ulcers, photosensitivity, and renal involvement are represented in these reports,



**Figure 1** (Wright stain, x40) Peripheral blood film of the patient showing numerous spherocytes with marked polychromasia, erythrocyte agglutination and thrombocytosis.

while the above-listed symptoms are rare in drug-induced lupus.<sup>7</sup> Similar to idiopathic SLE but unlike drug-induced lupus, ANA were present in all and anti-dsDNA were detectable in approximately 50% of the patients with IFN- $\alpha$ -induced SLE at diagnosis. These features suggest that SLE precipitated by IFN- $\alpha$  therapy corresponds to naturally occurring SLE.<sup>3,5,6</sup>

The absence of a family history and laboratory markers suggestive of autoimmune disease before initiation of IFN- $\alpha$  in our patient favours a possible causal link between IFN- $\alpha$  therapy and SLE. Numerous investigations have addressed the relationship of IFN- $\alpha$  with SLE. A role for IFN- $\alpha$  in the pathogenesis of SLE has been suggested previously, based on the detection of high levels of IFN- $\alpha$  in the sera of SLE patients, and positive correlation between IFN- $\alpha$  levels and disease activity.<sup>8</sup> Also, many of the typical side-effects of IFN- $\alpha$  treatment (fever, myalgia, fatigue, etc.) resemble symptoms of SLE.

The mechanisms whereby IFN- $\alpha$  might contribute to the development of SLE are not clear. In a recent report, serum from SLE patients was shown to induce differentiation of peripheral blood monocytes into functional antigen-presenting dendritic cells. This activity was neutralized by an anti-IFN- $\alpha$  antibody and was recreated by addition of IFN- $\alpha$ .<sup>9</sup> Presentation of autoantigens and activation of autoreactive lymphocytes by these dendritic cells could provide a mechanism for IFN- $\alpha$  in the pathogenesis of SLE. IFN- $\alpha$  also activates macrophages, increases major histocompatibility complex class II expression, and induces Th<sub>1</sub>-cell differentiation, which could lead to high autoantibody production.<sup>8</sup> Intriguingly, in the present case, withdrawal of IFN- $\alpha$  therapy was followed by a flare-up of SLE, which suggests that ongoing IFN- $\alpha$  therapy suppresses clinical manifestations of SLE. This possibility is supported by reports that IFN- $\alpha$  administered late during immunization of mice can suppress a cellular immune reaction such as delayed type hypersensitivity.<sup>10</sup> Thus, IFN- $\alpha$  may promote the development of the autoimmune disease, but also suppress clinical manifestations of autoimmune disease. Such an action is not surprising considering the pleiotropic effects of IFN- $\alpha$ .

Therapy for IFN- $\alpha$ -induced SLE has involved discontinuation of the IFN- $\alpha$  in 9/11 case reports.<sup>6</sup> Corticosteroids was given in seven of these cases and the use of hydroxychloroquine has been reported in one case previously. Clinical improvement was typically seen rapidly, within a few weeks to months in most reports, and recurrence of SLE in the absence of IFN- $\alpha$  has not been reported.

IFN- $\alpha$ -induced SLE typically developed during IFN- $\alpha$  therapy and resolved upon discontinuation of the drug. The case presented developed autoimmune features including ITP and probable immune-mediated insulinitis during IFN- $\alpha$  therapy that resolved after withdrawal of IFN- $\alpha$ . However, a year after discontinuation of IFN- $\alpha$ , our patient developed overt clinical and laboratory markers typical of SLE. The presence of a moderate titre of ANA and hypocomplementemia throughout the 1-year observation period, in the absence of IFN- $\alpha$  treatment, demonstrates that a self-perpetuating autoimmune response is occurring. It may be relevant that our patient was female, and she might therefore have been predisposed to develop SLE on exposure to IFN- $\alpha$ .

The observation that IFN- $\alpha$  can cause lupus-like disease indicates a role for IFN- $\alpha$  in SLE pathogenesis, and provides further evidence that IFN- $\alpha$  treatment can trigger the development of SLE. Given the increasing use of IFN- $\alpha$  for a variety of indications, clinicians should be aware of the potential of delayed autoimmune side-effects of IFN- $\alpha$  therapy. Treated patients should therefore be carefully monitored for autoimmune manifestations, especially since these may be misinterpreted as benign effects of IFN- $\alpha$ . In view of the recent development of molecular profiling in disease characterization and prognosis, it will be interesting to study the molecular genetics of patients who develop IFN- $\alpha$  induced SLE, so that high risks patients may be identified and managed more effectively.

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