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Interferon Alpha-Induced Lupus *Proof of Principle*

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In this month's issue of *Journal of Clinical Rheumatology*, Ho et al¹ present a case of severe systemic lupus erythematosus (SLE) which developed during interferon alpha (IFN- α) therapy for chronic hepatitis C. This case of life-threatening SLE adds to a growing body of literature suggesting that exogenous IFN- α can induce severe systemic autoimmune disease in some individuals. IFN- α is a type I interferon that plays an important role in viral defense. Some of the physiologic functions of IFN- α include activation of dendritic cells and increased expression of major histocompatibility complex class I and II molecules, leading to increased antigen presentation.² This suggests that IFN- α can bridge the innate and adaptive immune systems, and thus could play an important role in immunologic self-tolerance in both health and disease. High levels of circulating IFN- α have been described in SLE patients,^{3,4} and IFN- α present in SLE patient serum is capable of inducing differentiation and activation of antigen presenting cells in vitro.⁵ While these in vitro data suggest that IFN- α could play a role in SLE pathogenesis, cases of IFN- α -induced SLE such as the one presented in this issue of the journal provide an in vivo "proof of principle" that IFN- α can be sufficient to induce SLE in certain individuals.

A number of other cases of IFN- α -induced SLE have been described, which reflect the diverse clinical spectrum of idiopathic SLE, including malar rash, nephritis, hypocomplementemia, and characteristic autoantibodies such as anti-dsDNA, anti-Ro, and anti-Sm.^{6,7} In many instances, SLE symptoms resolve after discontinuation of the IFN- α and a short course of immunosuppressive therapy, supporting the idea that IFN- α was causal.⁷ Some cases are not reversible, however, and the case presented in this issue of the journal demonstrates that IFN- α -induced SLE can be extremely severe and life threatening. Although clinical SLE is relatively rare during IFN- α therapy (<1% of patients treated with IFN- α),⁸ a greater number of patients develop a "lupus-like" syndrome, meeting fewer than 4 of the 11 formal criteria for SLE.⁹ Studies of patients receiving IFN- α for hepatitis C suggest that individuals with a positive antinuclear antibody test before therapy may be more likely to develop autoimmune complications while receiving IFN- α therapy.¹⁰ There are also reports of IFN- α therapy worsening pre-existing autoimmunity,¹¹ and due to these reports autoimmune disease is listed as a relative contraindication to IFN- α treatment.

In SLE patients, high levels of IFN- α are associated with particular clinical characteristics, including renal disease, low complement, double-stranded DNA antibodies, and antibodies to RNA-binding proteins such as Ro, La, Sm, and RNP.¹² High serum IFN- α activity is also associated with increased disease activity in a number of studies.^{12,13} Approximately 50% of SLE patients show evidence of high serum IFN- α activity in large cross-sectional studies,^{4,14} and these patients represent a substantial subgroup within SLE who likely share a common pathogenesis related to IFN- α . In a disease as clinically heterogeneous as SLE, subclassifying patients may be useful for both prognosis and treatment. Anti-IFN- α antibody therapies are

currently in early phase clinical trials in SLE, and eventually these therapies may be directed preferentially at the “high IFN- α ” subgroup of SLE patients.

Abnormally high levels of serum IFN- α are frequently found in healthy first degree relatives of SLE patients, and serum IFN- α activity levels in closely related individuals are well correlated, suggesting that high serum IFN- α is a heritable risk factor for SLE.¹⁴ Genetic polymorphisms in 2 genes in the IFN- α signaling pathway, IRF5 and Tyk2, have been associated with susceptibility to SLE.^{15,16} The association of IRF5 with SLE has been validated in large SLE cohorts, and risk at this locus has been mapped to a haplotype containing a number of functional variants.^{16,17} IRF5 is a transcription factor that can directly induce transcription of IFN- α . Recent work from our group has demonstrated that SLE patients carrying the IRF5 risk haplotype have higher serum IFN- α than SLE patients lacking the risk haplotype,¹⁸ supporting the idea that the IRF5 SLE-risk variant results in risk of SLE by predisposing to higher IFN- α production.

Cases such as the one presented in this issue of the journal describe a highly unfortunate series of events, and remind us that serious immunologic consequences can accompany IFN- α therapy. Beyond their importance as cautionary tales, however, cases of IFN- α -induced SLE have inspired many of above referenced investigations which have shed light on the role of IFN- α in SLE pathogenesis. The finding that an exogenously administered agent can be sufficient to induce a complex systemic human autoimmune disease is striking, even when it is a rare event. Much insight has been gained regarding IFN- α as a causal factor for SLE in recent years, providing hope that we will have a better map of some of the early pathogenic events in SLE. This work could result in newer, more specific therapeutics or possibly even preventive agents targeting the IFN- α pathway in SLE.

References

1. Ho V, Mclean A, Terry S. Severe systemic lupus erythematosus induced by antiviral treatment for hepatitis C. *J Clin Rheumatol* 2008;14:166–168. [PubMed: 18525437]
2. Takaoka A, Yanai H. Interferon signalling network in innate defence. *Cell Microbiol* 2006;8:907–922. [PubMed: 16681834]
3. Hooks JJ, Moutsopoulos HM, Geis SA, et al. Immune interferon in the circulation of patients with autoimmune disease. *N Engl J Med* 1979;301:5–8. [PubMed: 449915]
4. Baechler EC, Batliwalla FM, Karypis G, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc Natl Acad Sci USA* 2003;100:2610–2615. [PubMed: 12604793]
5. Blanco P, Palucka AK, Gill M, et al. Induction of dendritic cell differentiation by IFN-alpha in systemic lupus erythematosus. *Science* 2001;294:1540–1543. [PubMed: 11711679]
6. Ronnblom LE, Alm GV, Oberg KE. Possible induction of systemic lupus erythematosus by interferon-alpha treatment in a patient with a malignant carcinoid tumour. *J Intern Med* 1990;227:207–210. [PubMed: 1690258]
7. Niewold TB, Swedler WI. Systemic lupus erythematosus arising during interferon-alpha therapy for cryoglobulinemic vasculitis associated with hepatitis C. *Clin Rheumatol* 2005;24:178–181. [PubMed: 15565395]
8. Gota C, Calabrese L. Induction of clinical autoimmune disease by therapeutic interferon-alpha. *Autoimmunity* 2003;36:511–518. [PubMed: 14984028]
9. Ioannou Y, Isenberg DA. Current evidence for the induction of autoimmune rheumatic manifestations by cytokine therapy. *Arthritis Rheum* 2000;43:1431–142. [PubMed: 10902743]
10. Bell TM, Bansal AS, Shorthouse C, et al. Low-titre auto-antibodies predict autoimmune disease during interferon-alpha treatment of chronic hepatitis C. *J Gastroenterol Hepatol* 1999;14:419–422. [PubMed: 10355504]
11. Conlon KC, Urba WJ, Smith JW 2nd, et al. Exacerbation of symptoms of autoimmune disease in patients receiving alpha-interferon therapy. *Cancer* 1990;65:2237–2242. [PubMed: 2346907]

12. Kirou KA, Lee C, George S, et al. Activation of the interferon-alpha pathway identifies a subgroup of systemic lupus erythematosus patients with distinct serologic features and active disease. *Arthritis Rheum* 2005;52:1491–1503. [PubMed: 15880830]
13. Bauer JW, Baechler EC, Petri M, et al. Elevated serum levels of interferon-regulated chemokines are biomarkers for active human systemic lupus erythematosus. *PLoS Med* 2006;3:e491. [PubMed: 17177599]
14. Niewold TB, Hua J, Lehman TJ, et al. High serum IFN-alpha activity is a heritable risk factor for systemic lupus erythematosus. *Genes Immun* 2007;8:492–502. [PubMed: 17581626]
15. Sigurdsson S, Nordmark G, Goring HH, et al. Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. *Am J Hum Genet* 2005;76:528–537. [PubMed: 15657875]
16. Graham RR, Kyogoku C, Sigurdsson S, et al. Three functional variants of IFN regulatory factor 5 (IRF5) define risk and protective haplotypes for human lupus. *Proc Natl Acad Sci USA* 2007;104:6758–6763. [PubMed: 17412832]
17. Sigurdsson S, Goring HH, Kristjansdottir G, et al. Comprehensive evaluation of the genetic variants of interferon regulatory factor 5 (IRF5) reveals a novel 5 bp length polymorphism as strong risk factor for systemic lupus erythematosus. *Hum Mol Genet* 2008;17:872–881. [PubMed: 18063667]
18. Niewold TB, Kelly JA, Crow MK, et al. IRF5 risk haplotype is associated with high serum interferon alpha activity in systemic lupus erythematosus patients. *Ann Rheum Dis* 2008;67(suppl):A44.