Case Report

Lupus erythematosus profundus (lupus panniculitis) induced by interferon-β in a patient with multiple sclerosis

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Abstract

We report a patient with multiple sclerosis (MS) who developed subcutaneous nodules in the face, shoulders and extremities while being treated with interferon (IFN)-β-1b. These nodules fluctuated in parallel with myelopathy, and were diagnosed as lupus erythematosus profundus (LEP) based on histopathological findings. The patient showed no relapse of either neurological symptoms or subcutaneous nodules after cessation of IFN-β-1b. This agent can cause induration and necrosis in the sites of injection but also systemic skin lesions such as LEP ascribable to its immunomodulatory effects.

Keywords: interferon-β, lupus erythematosus profundus, multiple sclerosis

Introduction

Interferon (IFN)-α and β are multifunctional cytokines produced by leukocytes and fibroblasts, respectively. Both are used clinically in the treatment of viral hepatitis, immune-mediated disorders and hematological malignancies, especially multiple myeloma, and IFN-α has been reported to sometimes cause or exacerbate autoimmune inflammatory disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (1). Here, we report a patient with multiple sclerosis (MS) who developed lupus erythematosus profundus (LEP) in conjunction with frequent attacks of myelopathy while being treated with IFN-β-1b. This skin manifestation can be described also as lupus panniculitis because the subcutaneous adipose tissue is mainly affected. No relapse of either myelopathy or LEP was seen after cessation of IFN-β-1b, and we postulate that this agent might have contributed to the development of LEP with neurological exacerbations in our patient.

Case report

A 19-year-old woman showed frequent attacks of retrobulbar optic neuritis and transverse myelopathy with no significant previous or family history. She was diagnosed as having a relapse-remitting type of opticospinal MS based on elevated levels of total protein and IgG in the cerebrospinal fluid (CSF) and abnormal signals in the thoracic cord suggestive of demyelination on magnetic resonance imaging (MRI). After commencement of IFN-β-1b at a dose of 8 MIU subcutaneously every other day at age 29 the patient showed a decrease in the frequency of relapse. At age 33 she suddenly developed painful nodules in the face, both shoulders and upper limbs with no precipitating cause. This symptom persisted, and the patient was admitted to our hospital two months later because of acute-onset paraparesis with urinary incontinence. Physical examination showed multiple subcutaneous nodules with slight redness and tenderness in the above-mentioned regions (Figs. 1A and B) in addition to bilateral

hypesthesia and hypalgesia under the Th3 level and muscle weakness in both legs. The Babinski's sign was bilaterally positive. Both upper extremities did not show either muscle weakness or sensory disturbance. Laboratory tests demonstrated no abnormal findings in serum other than a slight increase in C-reactive protein (1.32 mg/dl, normal <0.1 mg/dl) and positive results for the anti-nuclear (×160) and anti-SS-A antibodies (×77). The anti-double stranded DNA antibody was negative and serum levels of complements were within normal limits. CSF showed normal levels of total protein and IgG with no oligoclonal IgG bands. MRI demonstrated abnormal intensities but no obvious enhancement effects of gadolinium in the upper thoracic cord. Skin biopsy from the subcutaneous nodule in the left shoulder showed severe infiltration of lymphocytes in the dermis and fat tissue suggestive of lobular panniculitis (Fig. 1C).

Myelopathy and skin nodules quickly improved after methylprednisolone pulse therapy at a dose of 1000 mg/day for 3 days, but one month later these symptoms simultaneously reworsened. Despite readministration of methylprednisolone followed by oral prednisolone, both neurological and skin symptoms fluctuated (Fig. 2). Soon after cessation of IFN-β-1b the subcutaneous nodules disappeared, and the patient has remained in good neurological condition without relapse of myelopathy for one year to date. The anti-nuclear and anti-SS-A antibodies are still detectable in serum.

Discussion

IFN-β-1b is widely used for MS, particularly in the relapse-remitting type as in our patient, in order to prevent worsening of neurological symptoms. This agent often produces induration with or without skin ulcers in the site of injection as an adverse effect (2). Our patient showed multiple subcutaneous nodules with histopathology of lobular panniculitis irrespective of the injection site of IFN-β-1b and no involvement of visceral organs such as kidneys, leading to a clinical diagnosis of LEP, which is an autoimmune disease mainly affecting the skin. LEP is similar to SLE with regard to the

gross appearance of skin manifestations and involvement of IFN in the pathogenesis (3). Because skin symptoms quickly improved after cessation of IFN-β-1b, this agent is considered to have caused LEP in our patient. There are several recent reports showing association of autoimmune diseases, including SLE, after long-term use of IFN-β for MS (4-6). Considering that the anti-nuclear and anti-SS-A antibodies were positive at the onset of skin symptoms, IFN-β-1b may have altered the immune status and caused LEP in our patient, although this agent has not been shown to increase the frequency of autoantibodies in MS (7-9).

The most interesting point in our patient is that LEP fluctuated in parallel with upper thoracic myelopathy. This neurological manifestation was clinically indistinguishable from relapse of MS as previously seen, but our patient showed neither abnormal findings in CSF nor new obvious lesions on MRI. Although the precise etiology of myelopathy in our patient is unclear, there are two possibilities worth consideration. One is mild exacerbations of MS, which were undetectable in both the CSF study and MRI. Our patient initially showed a decrease in the frequency and severity of relapse in response to IFN-β-1b, but the therapeutic efficacy may have diminished after the long-term use of this agent. The other is involvement of autoantibodies causing neurological symptoms. It is well known that neurological manifestations as seen in MS occasionally develop also in other autoimmune disorders, especially in SLE and Sjögren's syndrome, and autoantibodies such as the anti-SS-A antibody are considered to play an important role in the pathogenesis (10-12). Considering that our patient showed myelopathy as seen before the use of IFN-β-1b in conjunction with development of LEP, the pathognomonic autoantibodies may have easily migrated into the spinal cord across the blood-brain barrier impaired by MS in the present case, resulting in frequent exacerbations of neurological symptoms (13).

In conclusion, we described LEP due to IFN-β-1b in a patient being treated for MS. This agent can cause induration and necrosis in the sites of injection

but also systemic skin lesions such as LEP ascribable to its immunomodulatory effects. When systemic skin lesions develop during treatment with IFN-β-1b, autoimmune diseases due to alteration of the immune status are possible causes, and in such a case cessation of this agent should be considered as a potent therapeutic option.

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Figure legends

Figure 1: Subcutaneous nodules with slight redness (in circles) were seen in the left shoulder (A) and the left forearm (B). Biopsy from the nodule in the left shoulder demonstrated marked infiltration of mononuclear cells in the subcutaneous fat tissue suggestive of lobular panniculitis (C, bar=100 μm).

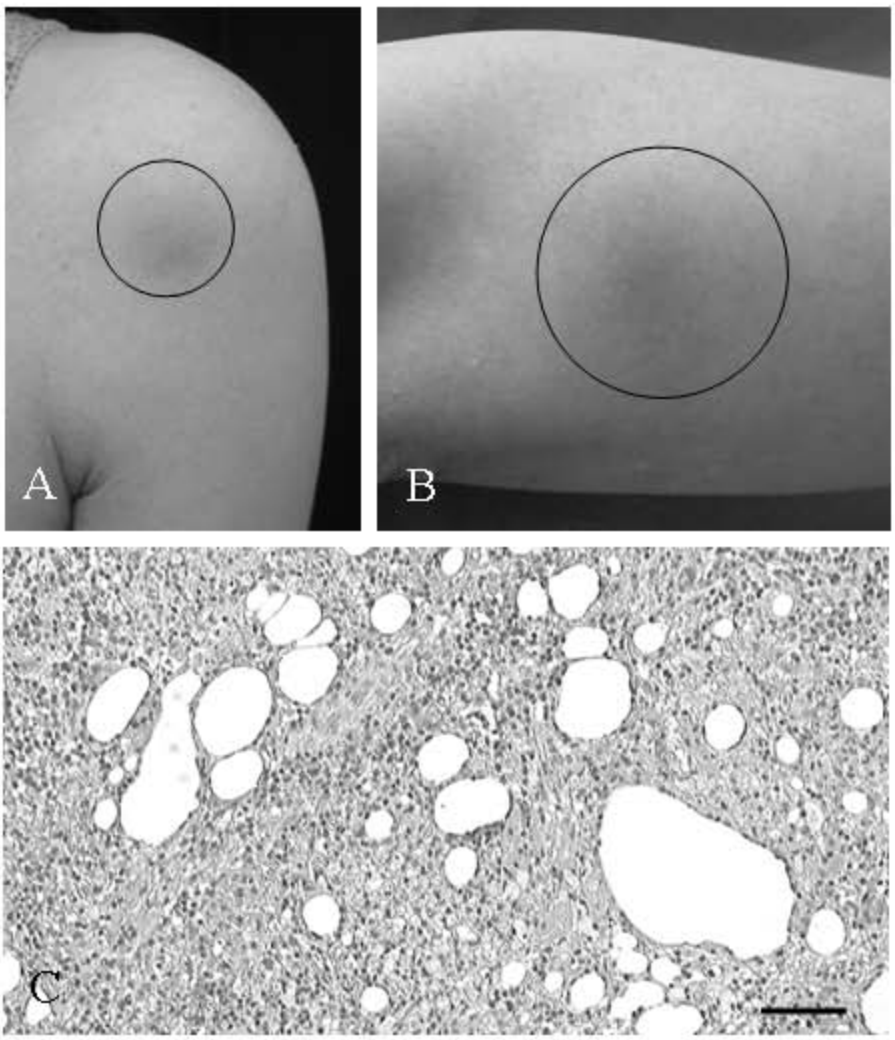

Figure 1

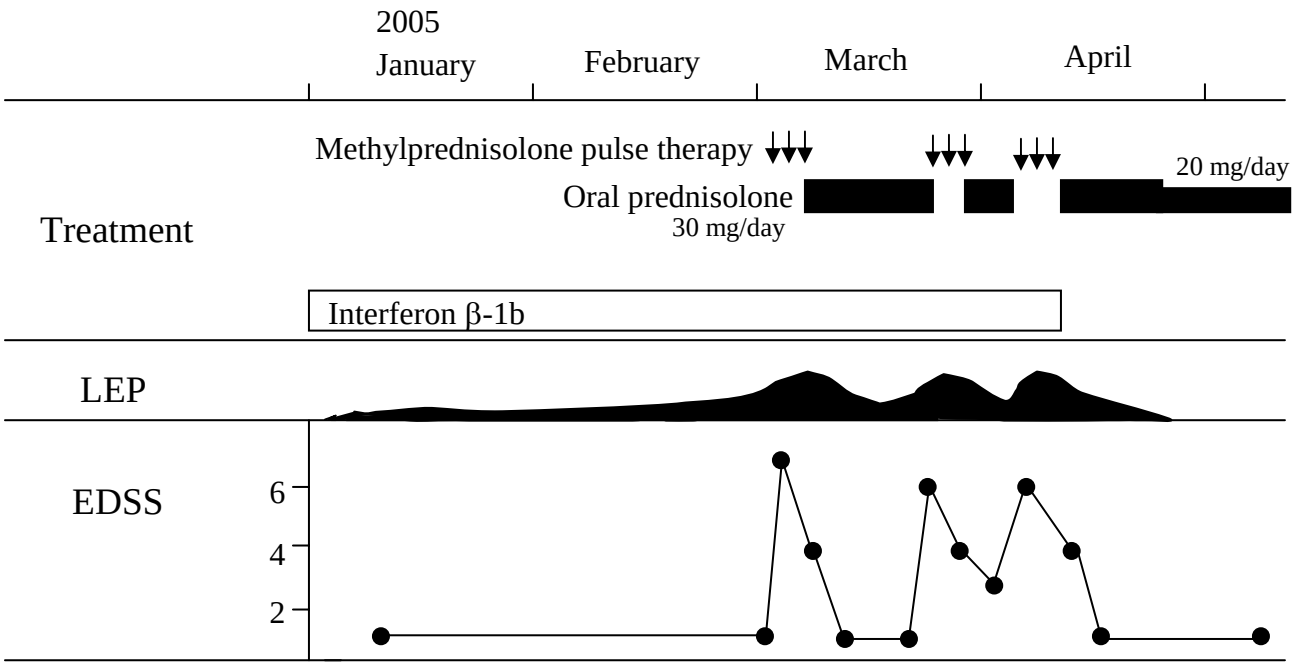
2005
January
February
March
April
Methylprednisolone pulse therapy
Oral prednisolone
30 mg/day
20 mg/day
Treatment
Interferon β-1b
LEP
EDSS
6
4
2

Figure 2