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CASE REPORT

Systemic lupus erythematosus-like autoimmune abnormalities induced by bacterial infection

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ABSTRACT

Recent evidence has revealed that bacterial DNA can promote several of the autoimmune abnormalities observed in systemic lupus erythematosus (SLE), and a possible pathogenic role in the induction of SLE has been highlighted. We have recently encountered patients in whom bacterial infection (septicemia) triggered the production of several autoantibodies. This seems to be interesting with respect to the consideration of the relationship between SLE and bacterial infection.

Introduction

The contribution of several infections to the onset and/or exacerbation of SLE has been repeatedly suggested, although the precise pathogenesis of this disease still remains unclear (1, 2). Recent evidence has indicated that retroviruses (especially human endogenous retroviruses; HERV) may be a plausible causative agent of SLE, and HERV appear to be involved in a genetic predisposition to its development (3). On the other hand, viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19 seem to play a role as environmental factors that may trigger the development of SLE (1, 2). Furthermore, a possible important role of bacterial infection in the induction of SLE has been reported (4, 5). In relation to this issue, we report a recent patient who showed some of the immune abnormalities that are observed in SLE after a bacterial infection. This patient is of interest given the possibility that autoimmunity in SLE may be related to bacterial infection.

Case report

A 26-year-old man was admitted to our hospital with the chief complaints of spiking fever and a severe eruption (mainly on the face) for one week (Fig. 1). For approximately three months before admission, he had been suffering from Raynaud's phenomenon and had attended another hospital, but serum anti-DNA antibody and lupus erythematosus (LE) factor were negative, although other autoantibodies (including anti-RNP antibody) were not examined at that time. He had not been treated with steroids and/or immunosuppressants at the other hospital.

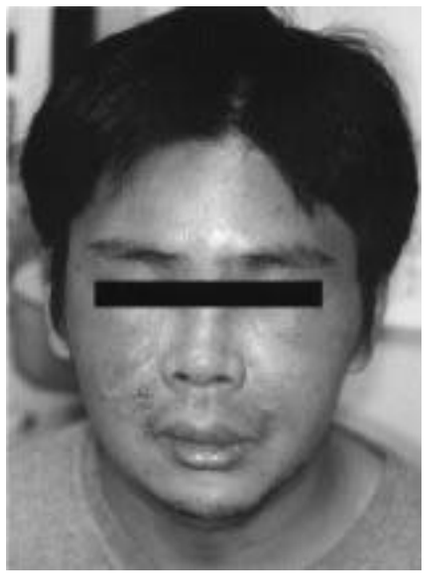

Fig. 1. Facial eruption of the patient.

On admission to our hospital, the main laboratory findings were as follows: white blood cell count 7.1 x 10^3 cells/mm^3 (neutrophils 82%, lymphocytes 10%, and eosinophils 0%), the red cell count was 408 x 10^4 cells/mm^3, and the platelet count was 25.2 x 10^4 cells/mm^3. The ESR was 64 mm/h (normal range (n) < 20) and CRP was 24.3 mg/dl (n < 0.3). The levels of GOT, GPT, and LDH were 45 IU/l (n = 10-40),22 IU/l (n = 5-40), and 1096 IL/l (n = 200-450), respectively. Transient proteinuria was observed (1.5 g/day), which disappeared after a few weeks. BUN and creatinine were within the normal range. The main immunological findings were: anti-nuclear antibody (ANA) x 2560 (n<40); anti-DNA antibody 15 IU/ml (n < 6); anti-RNP antibody 7530 U/ml (n < 10); anti-Sm antibody 934 U/ml (n < 10); anti-SSA and SSB antibodies 7.0 and 10.3 U/ml, respectively (n < 10); anti-cardiolipin antibody negative; lupus anticoagulant (LAC, phospholipid neutralization procedure) 11.1 sec (n < 6.3); CH50 (hemolytic complement activity) 31.3 U/ml (n = 30-40); IgG 1959 mg/dl (n = 800-1800); IgA 371 mg/dl (n = 90-400); and IgM 83 mg/dl (n = 60-250). Blood culture yielded gram-positive

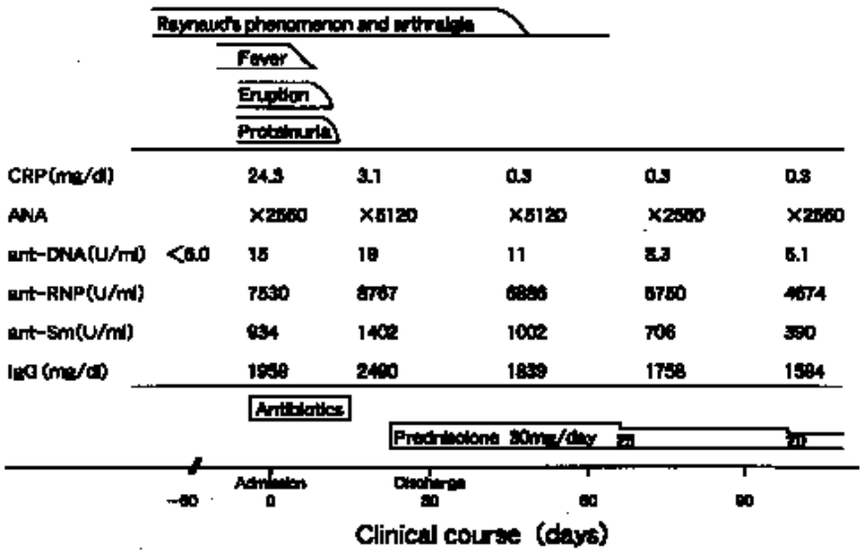

Fig. 2. Clinical course and immunological findings of the patient.

Staphylococcus epidermidis. Infection with viruses such as CMV and EBV was not detected by serum tests. Biopsy of skin lesions indicated the presence of perivasculitis.

He was diagnosed as having septicemia and treated with antibiotics. His symptoms such as the fever and skin eruption,as well as infection-related laboratory findings (including CRP), were dramatically improved by antibiotic therapy, but Raynaud's phenomenon and slight arthralgia of the hands remained after treatment. In contrast, serum levels of several autoantibodies gradually increased even after resolution of the septicemia (Fig. 2). Steroid therapy was started for his progressive immunological abnormalities and the levels of several autoantibodies gradually decreased during treatment. This patients is now being followed up and has had no further exacerbations of SLE-related laboratory and clinical findings, including Raynaud's phenomenon and arthralgia.

Discussion

Our patient seems to have developed prominent immunological abnormalities after the onset of bacterial infection. However, he had been suffering from Raynaud's phenomenon for several months, so we cannot exclude the possibility that he had autoimmune laboratory abnormalities (such as anti-RNP antibodies, which are related to Raynaud's phenomenon) (6), before the onset of infection. However, anti-DNA antibodies were not detected before the infection developed, as described above. He could have been diagnosed with SLE based on the usual diagnostic criteria (e.g. positivity for ANA, anti-DNA and Sm antibodies, lymphopenia, malar rash, arthralgia, and proteinuria) (7), but symptoms such as the rash and proteinuria were transient and improved by antibiotics alone. Therefore, we think that it is difficult to make a diagnosis such as an SLE or mixed connective tissue disease (MCTD).

The patient showed high levels of several autoantibodies, and their levels increased progressively even after improvement of his symptoms. Therefore, we used steroids to treat the antibody levels, which were probably due to polyclonal B cell activation (PBA) triggered by his bacterial infection. After steroid therapy, the levels of these autoantibodies gradually decreased, and there has been no evidence of further SLE-related symptoms to date. Accordingly, steroid treatment seems to inhibit bacterial infection-related PBA and the consequent development of the clinical manifestations of SLE.

Several studies have indicated a possible important role of hypomethylation of DNA, especially of the cytosines that precede guanines in DNA strands (CpG dinucleotides), in the pathogenesis of SLE (4, 5,8, 9). Bacterial DNA is rich in CpG dinucleotides and is hypomethylated; it can induce various immune changes in mice and humans both *in vivo* and *in vitro* that are like those observed in SLE, including PBA, secretion of cytokines such as interleukin (IL)-6, and production of autoantibodies including anti-DNA antibodies (4, 5).

Certain SLE patients even without infection are known to show an elevated level of circulating plasma low-molecular-weight DNA which is enriched in hypomethylated CpGs, although the precise role of DNA hypomethylation in inducing PBA is still unclear (8). Supporting these findings, several reports have indicated that the level of DNA methylation (especially in T cells) and the levels of transcription of DNA-methylation regulating enzymes (e.g., DNA methyltransferase-1; DNMT-1) are lower in SLE patients than in normal controls (9-11). Regarding this issue, we have reported that the increased transcription of HERV genes in patients with SLE is mediated by DNA hypomethylation (9, 11). The increase of several antibodies observed in our patient may have been due to PBA mediated by bacterial infection, although serum cytokine levels (such as IL-6) were not high, probably due to the rapid clearance of cytokines as we previously reported (12). Furthermore, recent evidence has indicated that toll-like receptor (TLR), which is known to be involved in mediating cell activation on stimulation with microbial constituents, acts as a signaling receptor for CpGs and/or lipopolysaccharide (LPS) (13, 14). In addition, CD5 positive B cells have been known to play an important role in the production of autoantibodies (15). The expression of TLR and CD5 on cells seem to be interesting in the pathogenesis of infection-mediated exacerbation and/or the onset of SLE. We are now investigating these points in our patients with SLE including this patient.

Our previously reported patients with autoimmune abnormalities extremely similar to SLE/MCTD who showed hyper-responsiveness to infections had

high levels of anti-RNP antibodies and Raynaud's phenomenon, as was seen in the present patient, and they showed infection-mediated hypersensitivity pneumonitis or hemophagocytic syndrome (12, 16). The presence of anti-RNP antibodies as a predisposing factor may be important with regard to hyper-responsiveness to infection and the resultant development of autoimmunity. In addition, we have previously reported that viral infection, especially CMV, can induce the onset or exacerbation of SLE in predisposed individuals, based on several reported cases (including ours) (2). Clinical studies and/or case reports describing the relationship between autoimmune diseases (such as SLE) and bacterial infection are uncommon compared with the experimental investigations in this field. Therefore, further clinical investigations (in addition to experimental studies) are required to clarify the mechanism of autoimmunity related to bacterial infection and/or hypomethylated bacterial DNA.

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