Retinal S-Antigen–Reactive Lymphocytes in a Patient with Uveitis Associated with Myelodysplastic Syndromes

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Background: Although autoimmune humoral abnormalities have been reported in patients with myelodysplastic syndromes (MDS), abnormal organ-specific cellular autoimmunity has not been demonstrated.

Methods: Peripheral blood lymphocytes (PBLs) and serum were collected from a uveitis patient with MDS. Cellular immune response against retinal S-antigen (S-Ag) was assessed by proliferation assay, and humoral immune response to S-Ag was measured by enzyme-linked immunosorbent assay.

Results: PBLs from the patient exhibited vigorous proliferation against S-Ag, while humoral immune response against S-Ag was not detectable. PBLs from controls did not proliferate against S-Ag.

Conclusion: These results provide new evidence that abnormal cellular immune responses against autoantigens may develop in MDS patients, thus leading to organ-specific autoimmune diseases such as uveitis, in addition to other systemic autoimmune disorders.


Key Words: Myelodysplastic syndromes, peripheral blood lymphocytes, S-antigen.

Introduction

Myelodysplastic syndromes (MDS) are considered to be disorders characterized by abnormal hematopoiesis and peripheral cytopenias.1 MDS often occur in elderly people, and the diagnosis is confirmed by laboratory tests including bone marrow morphology. In addition, about 20% of MDS patients develop acute leukemia, and thus MDS is referred to as preleukemia or a preleukemic state.1

Patients with MDS exhibit immunological abnormalities with autoantibodies in the serum.1 Thus, rheumatoid arthritis, systemic lupus erythematosus, and Behçet’s disease have been reported in certain cases of MDS.2 Ohno et al have reported 11 cases of Behçet’s disease with MDS and only two of them exhibited anterior uveitis.2

We describe a patient who developed bilateral uveitis during the course of MDS. Interestingly, we detected a strong proliferative response of the peripheral blood lymphocytes (PBLs) to S-Ag, which is a target antigen of autoimmune uveitis.1

Case Report

A previously healthy 72-year-old man presented with blurred vision in his left eye. He had been diagnosed as having bilateral uveitis at another clinic and was treated with topical steroid. His best-corrected visual acuity was 1.2 OD and 0.8 OS, and his intraocular pressure was normal in both eyes. The anterior chamber had a few (1+) cells in both eyes, but keratic precipitates and posterior synechiae were not present. Vitreous haze was minimal in both eyes.

Fundus examination revealed mild redness of the optic disks and multiple yellowish-white choriretinal lesions in the inferior area of both fundi. Fluorescein angiography disclosed leakage from retinal veins and macular staining (Figure 1).

Laboratory evaluation showed mild anemia (hematocrit, 36.5%; hemoglobin, 11.2 g/dL), an increase in the
white blood cell count \((10.5 \times 10^3/\mu L)\) and eosinophils \((15\%)\), and an increase of serum immunoglobulin (Ig) E \((1530 \text{IU/mL})\). In addition, morphological abnormalities were noted in the white blood cells and platelet. Lactic dehydrogenase was increased to 703 IU/L. None of these laboratory data suggested an autoimmune or infectious disease.

Hypercellularity with an increased number of megakaryocytic cells was noted in the bone marrow. This finding and his laboratory data were compatible with MDS, and he was diagnosed with MDS (refractory anemia with an excess of blasts).

To study the possible involvement of an autoimmune reaction against S-Ag for the uveitis, we performed a proliferative assay of the PBLs against S-Ag and determined the Ig titer in the serum specific to S-Ag. We found that the PBLs responded vigorously to S-Ag at a concentration of 100 \(\mu g/mL\), but no apparent response was observed at lower concentrations (Figure 2A). The strong response to S-Ag was noted at 6 and 10 weeks after the initial visit (Figure 2A). At these times, the patient was being treated only with topical steroid. In contrast, S-Ag–specific Ig was not detected in the serum (Figure 2B).

These data could be interpreted as an augmentation of the S-Ag–specific cellular immunity in this patient without affecting the S-Ag–specific humoral immunity. There have been several reports demonstrating that lymphocytes from patients who have retinal damage caused by uveitis or retinitis pigmentosa responded to S-Ag and its peptides. Thus, these findings might be related to the retinal damage induced by the uveitis, although the retinal damage evaluated by fundus examination (Figure 1) did not appear as severe as that in retinitis pigmentosa.

Yamamoto et al analyzed cellular immunity against S-Ag in eyes with uveitis at a concentration of 4 \(\mu g/mL\). In our study, a significant response was noted only at a concentration of 100 \(\mu g/mL\) of S-Ag. Because the PBLs from a normal control (S.I. = 1.3) and a uveitis patient (S.I. = 0.7) did not show any significant proliferation at 100 \(\mu g/mL\) of S-Ag, contamination of mitogens in the S-Ag was less likely. Therefore, the proliferative response detected only at a high concentration might be interpreted as a lower affinity of the S-Ag–specific lymphocytes against S-Ag.

The increase of eosinophils and IgE suggested that Th2 immunity is dominant in this patient. To confirm the Th2 dominance, it will be necessary to investigate cytokine production. Under specific conditions, a higher concentration of antigen is required to stimulate Th2 cells than Th1 cells, although contradictory results have also been demonstrated. Thus, one possible explanation for the finding that proliferative responses were detectable only at a higher concentration might be that S-Ag–specific Th2 cells were more dominant than Th1 cells in this patient. It is apparent that the experimental systems including the S-Ag used were different from those used in the previous reports, and these differences might have caused different outcome for Th1/Th2 balance determined by Ag concentration.

To the best of our knowledge, this is the first report of an S-Ag–specific cellular immunity in a uveitis patient with MDS. Furthermore, the data suggest that organ-specific cellular autoimmune disorders may develop in MDS patients in addition to humoral autoimmune diseases.
Figure 2. S-antigen (S-Ag)-specific immune responses. (A) Cellular proliferative response of peripheral blood lymphocytes (PBLs) against S-Ag. PBLs collected at two different times responded vigorously to S-Ag at a concentration of 100 µg/mL, which was comparable to the response against phytohemagglutinin (PHA) at 1 µg/mL or purified protein derivative (PPD) at 1 µg/mL. The combined mean cpm ± SE values for the unstimulated control cultures were: 937 ± 21 for the first test (black bar); and 863 ± 20 for the second test (white bar). (B) Immunoglobulin (Ig) titer in serum specific to S-Ag. S-Ag-specific Ig was not detected in the serum of this patient by direct enzyme-linked immunosorbant assay. The coated amount of S-Ag was 500 pg. For positive control, S-Ag-primed rat serum was used. Hatched bar: S-Ag-primed rat serum, black bar: serum from a healthy donor, white bar: serum from this patient.

References