Immune Pathology of Myelodysplastic Syndromes

**Key words:** MDS, autoimmune phenomenon, immune suppression, immunosuppressive therapy, prognosis

Myelodysplastic syndromes (MDS) are clinically characterized by morphological dysplasias of blood cells and cytopenias of variable combinations due to ineffective hematopoiesis (1). They often transform into acute myeloid leukemia (AML) as designated preleukemic syndromes. About 60% of cases with MDS carry a non-random chromosome abnormality such as -7, 7q-, -5, 5q-, 20q- etc and/or complex abnormalities, proving that MDS is a clonal hemopathy which originates in a multipotent hematopoietic stem cell.

**Immunological manifestation**

Patients with MDS usually manifest only a few symptoms related to anemia. However, a minor proportion of the patients suffers from a variety of symptoms suggestive of autoimmune disorders; pyoderma gangrenosum, Sweet’s syndrome, Bechet-like recurrent aptha, polyarthritis, polychondritis, vasculitis, hypothyroidism, hemolytic anemia, pure red cell anemia, immune thrombocytopenia and rare cases of pernicious anemia (2–4). All these manifestation are suggestive of some immune pathology, although the underlying abnormality of the immune system has not been precisely elucidated.

In this issue of Internal Medicine, Funato et al reported such a case of MDS with hypoadrenalism and Addison’s disease (5). See also p 1041.

Furthermore this case had some characteristics of rheumatoid arthritis and positive Coombs’ test. The pancytopenia and hypoadrenalism were successfully treated with prednisolone. Such a hypoadrenalism complicated with MDS has not been reported in the literature. Among the endocrine organ-related immune abnormalities hypothyroidism is more frequent.

Several reports indicated considerably high rates of association between MDS and immunological abnormalities of laboratory tests such as hyper-gammaglobulinemia, hypogammaglobulinemia, M-protein, positive Coombs’ tests, positive RA tests, low CD4/8 ratio, etc. These immunological abnormalities usually respond well to conventional immunosuppressive therapy such as corticosteroid therapy. However, Okamoto et al suggested that MDS patients with immunological abnormalities have a significantly shorter survival compared with those without (4).

**Clonal blood diseases and immunological disorders**

Among hematological malignancies such autoimmune disorders are most frequently seen in lymphoid malignancies such as malignant lymphomas and chronic lymphoid leukemia (CLL) and far less frequently associated with acute leukemia and chronic myeloid leukemia (CML). The high rate of association between lymphoid malignancies and autoimmune disorders suggests a role of a malignant clone in generating the autoimmune status. A typical example is the Coombs-positive autoimmune hemolytic anemia associated with B-cell CLL.

In the case of MDS, however, there is no firm evidence of involvement of lymphoid lineage in malignant MDS clones. Involvement of lymphoid lineage of either B or T has not been proved formally in MDS, except for an apparent transformation into acute lymphoid leukemia, mostly of B-cell precursor phenotypes, in rare cases of MDS (6). The rate of lymphoid transformation seems remarkably low in MDS compared with the rate of transformation into AML. This is a sharp contrast to the abundance (about 20%) of B-lymphoid transformation in CML. It is well recognized that CML usually involves B cell lineage in its chronic phase but not T-cells. There are few clonal studies of MDS; Prchal et al first indicated by clonal analysis with G-6-PD isozymes that T-cell and B-cell lineages are involved in a case with MDS (7). There are some other reports suggesting lymphoid involvement in MDS clone. However, because of the limitation of this method due to physiological skewing of X-chromosome inactivation, it is still unclear whether lymphoid lineages are regularly involved in MDS clones.

**Effects of immunosuppressive therapy**

From the therapeutic point of view, it is interesting to note that Funato et al obtained a good response with corticostroid therapy for the immune disorders as well as the pancytopenia. In spite of this relief from clinical symptoms and pancytopenia, morphological dysplasias still persisted. Although this case lacks firm evidence of clonal disorder due to the normal karyotypes of bone marrow cells, it is interesting to note that the pancytopenia responded very well to conventional immunosuppressive therapy. Such cases have been reported but sporadically.

More recently Molldrem et al reported a 60% response rate in MDS cases with anti-thymocyte globulin (ATG) (8). Others reported similar results with cyclosporin A (CSA) (9). Although these response rates are slightly less than those reported for aplastic anemia (10), such high rates of clinical effectiveness
with ATG or CSA suggest that there may be immunological suppression of MDS clones which might otherwise be able to produce more mature cells. In some cases of aplastic anemia oligoclonal cytotoxic T-cells are reportedly involved in the pathogenesis of stem cell suppression or injury (11). It is also interesting that sometimes aplastic anemia which shows a good response to immunosuppressive therapy later evolves into MDS with an apparent cytogenetic abnormality such as -7 anomaly (10). Thus, one can speculate that there is some immune-mediated pathology in both MDS and aplastic anemia. Interestingly, the autoimmune disorders reported in MDS have been far less observed in aplastic anemia. This may reflect the difference in cellularity of bone marrow between the two diseases.

**Perspectives of future study**

Theoretically, the cells of abnormal clones of MDS may either carry some abnormal antigens derived from acquired genetic abnormalities related to cellular transformation in MDS or involve lymphocytes within MDS clones which may exert abnormal functions. Normal residual lymphocytes may react to the former aberrant MDS clones or abnormal lymphocyte clones themselves may render immune disorder(s) in MDS patients.

The detection of such abnormalities at cellular and molecular levels is warranted to elucidate the immune pathology of MDS. Such studies will also clarify the similarity or dissimilarity between MDS and AA.

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**References**