Hemophagocytic Syndrome in Autoimmune Diseases

Hemophagocytic syndrome (HS) is a condition characterized by the activation of histiocytes and the resulting hemophagocytosis in the bone marrow. Symptoms frequently seen include high fever, lymph node swelling, consciousness disturbance, jaundice and bleeding tendency. In laboratory tests, pancytopenia, elevated ferritin and lactate dehydrogenase (LDH), may become a clue for suspecting this condition. For diagnosis, it is essential to prove the existence of hemophagocytes, usually in the bone marrow. This condition is most often seen with viral infection (virus associated hemophagocytic syndrome; VAHS) or with malignancy. In recent years, HS associated with systemic lupus erythematosus (SLE) has also drawn attention (1). In addition, there are recent reports of HS associated with other collagen diseases (2-4). The concept of autoimmune associated HS (AAHS) is gradually being known, and case reports are increasing steadily (5). This condition may not be so rare as originally considered. We have recently seen a patient with dermatomyositis, who developed HS and vasculitis. Her HS was treated successfully with methylprednisolone pulse therapy (submitted for publication). In this issue of Internal Medicine, Takahasi et al report a patient with SLE, who developed HS while taking low doses of prednisolone (6). Their case also was successfully treated with methylprednisolone pulse therapy. As well as the cases of the original report on acute lupus hemophagocytic syndrome (1), where all the patients responded well to steroid therapy, these cases and other reports suggest that large dose prednisolone or methylprednisolone pulse therapy may be the first option of treatment for patients with AAHS. In an exceptional case of HS in an SLE patient reported by Hayashi et al (7), HS was observed after 4 weeks of 60 mg/day of oral prednisolone, when the disease activity of SLE seemed to be under control. Her HS state improved after prednisolone was rapidly reduced to 20 mg/day. Although no evidence of viral infection was observed, it was considered that this patient may have had VAHS. When HS occurs in an SLE patient, the differential diagnosis between AAHS and VAHS necessitates careful consideration.

The pathogenesis of AAHS is not well known. Two major pathways for the binding and phagocytosis of hematopoietic cells by histiocytes are hypothesized. 1) Autoantibodies directed against hematopoietic cells are produced. These autoantibodies react to hematopoietic cells. Histiocytes phagocytose these cells by binding through their Fc receptors. Antibodies such as PA-IgG may be found in patients with this condition. 2) Deposition of circulating immune complexes on the hematopoietic cells results in their phagocytosis by histiocytes through interaction of complement and complement receptors. Circulating immune complexes may be elevated in these patients. AAHS may occur when antibodies against hematopoietic cells are undetectable and without increased serum immune complexes. Other mechanisms may be important in such cases, and further accumulation of cases is necessary.

In addition to the pathways described above, cytokines overproduced by activated macrophages or T cells are thought to be important in histiocyte activation. Interleukin (IL)1, TNFα, interferon (IFN)γ are among the cytokines reported to be important for histiocyte activation and the pathogenesis of HS. Ohga et al reported that IFNγ is a sensitive marker of disease activity for VAHS (8). In their study, TNFα was also elevated in 11 of their 19 VAHS patients. However, IL1β was found in only 1 of 19 patients, during severe relapse. Recently, Lay et al (9) reported that TNFα mRNA is upregulated in Epstein-Barr virus (EBV)-infected T cell lymphomas. Culture supernatants of EBV-infected T cell lymphomas enhanced phagocytosis and cytokine production of a monocytic cell line, U937. This enhancement was largely blocked by anti-TNFα, and almost completely blocked by a combination of anti-TNFα and anti-IFNγ. They concluded that TNFα production by virus-infected T cells is important for the pathogenesis of VAHS, and anti-TNFα may be effective for treatment of this often fatal disease (9). Another recent study reported the possible importance of IFNγ, IL10 and IL12 in the pathogenesis and modulation of the disease activity of HS (10).

See also p 550.

In the case reported in this issue, Takahasi et al (6) detected elevated serum IL1β in their patient. However, serum IL2, IFNγ, and TNFα levels were normal. They suggest that IL1β may have played an important role in the pathogenesis of HS in their patient. In this case report, the level of IL1β was not extremely high, and the time course was not investigated. Therefore, it is difficult to conclude that overproduction of IL1β was directly associated with the pathogenesis of HS. Nevertheless, the production of various cytokines in HS patients should be carefully examined in future HS patients.

In conclusion, AAHS is a condition which deserves more attention from rheumatologists. Close observation of factors such as cytokines, autoantibodies and immune complexes is necessary to more clearly understand the pathogenesis of HS, and to establish a standard for therapy.

Akito Tsutsumi, MD and Takao Koike, MD
The Department of Medicine II.
References