Letters to the Editor

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Haemophagocytic syndrome in a systemic lupus erythematosus patient with antiphospholipid antibodies

Sir. Reactive haemophagocytic syndrome (HPS) has been found in patients with autoimmune diseases (autoimmune-associated haemophagocytic syndrome; AAHS), including SLE (acute lupus haemophagocytic syndrome; ALHS) [1, 2]. In addition, we recently encountered an antiphospholipid antibody (aPL)-positive systemic lupus erythematosus (SLE) patient who had HPS and autoimmune haemolytic anaemia (AIHA).

This patient was a 21-year-old woman who was admitted to our hospital complaining of malaise and fever for 1 week. On admission she had severe pancytopenia, with a white blood cell count of 0.9 × 10⁹/mm³, a red blood cell count of 187 × 10⁹/mm³, a haemoglobin concentration of 6.4 g/dl and a platelet count of 3.9 × 10⁹/mm³. Her lactate dehydrogenase (LDH) and total bilirubin levels were elevated to 1022 IU/l (normal range 200–450 IU/l) and 1.3 mg/dl (normal range 0.2–1.0 mg/dl) respectively. The main immunological findings were as follows: antinuclear antibody × 2560 (normally < 40); anti-DNA antibody 130 IU/ml (normally < 6.0 IU/ml); anti-Sm antibody 142.3 U/ml (normally < 10.0 IU/ml); anti-ribonucleoprotein antibody 587.0 U/ml (normally < 10.0 U/ml); haemolytic complement activity 18.0 CH50 U/ml (normal range 30–40 CH50 U/ml); direct Coombs test positive; indirect Coombs test negative; platelet-associated IgG 106.0 (normal range 9.0–25.0). Although she did not have any thrombotic symptoms, aPL antibodies were also detected [lupus anticoagulant (LAC): activated partial thromboplastin time 166.6 s (normally < 55.5 s); phospholipid neutralization procedure 72.5 s (normally < 6.3 s), anticardiolipin antibodies (aCL): IgG 3.3 (normally < 1.0); IgM 3.3 (normally < 1.0); β2-glycoprotein I (β2GP1) > 125.0 U/ml (normally < 3.5 U/ml)]. Tests for several viruses and for malignancies were negative. Serum levels of several cytokines and serum ferritin level were not elevated. Bone marrow smears showed an increased number of mature histiocytes scattered among the haematopoietic cells, and these histiocytes were involved in active phagocytosis of trilineage haematopoietic cells, including megakaryocytes, erythroblasts and granulocytes (Fig. 1a). Immunohistochemical studies revealed that the cytoplasm of the histiocytes was stained by immunoglobulins (Fig. 1b and c). This indicates that antibodies were taken up by the histiocytes in the patient’s bone marrow. She was diagnosed as having SLE and was treated with steroids (500 mg methylprednisolone per day for 3 days, followed by 40 mg prednisolone per day). Her pancytopenia was improved by this therapy. Haemophagocytosis decreased markedly when bone marrow aspiration was repeated 4 weeks after the start of steroid therapy.

Her pancytopenia was thought to be related to HPS. We previously reported a case of HPS that was probably

![Fig. 1.](image)
induced by aPL [3]. In that patient, high levels of anti-
β2GP1 antibodies but no elevation of serum cytokine
and ferritin levels were observed, as in the present
patient. Several cytokines are favoured as pathogenic
agents of HPS associated with infection or malignancy
[4, 5]; however, patients who do not show elevated
concentrations of cytokines have occasionally been
reported in AAHS [2, 3]. Although it has been suggested
that antibodies or immune complexes contribute to
the induction of haemophagocytic phenomena in
ALHS or AAHS [1, 2], our findings (Fig. 1b and c)
are thought to be the first demonstration that anti-
bodies can play an important role in haemophago-
cytosis. The specificity of immunoglobulins incorporated
by bone marrow phagocytes of the patient is unclear.
aPL may well explain the simultaneous antibody
binding to several haematopoietic cell lineages. How-
ever, we cannot rule out the possibility that other
autoantibodies (such as anti-erythrocyte antibodies)
bind to these cells in our patient. Several reports have
suggested the possibility that aCL can bind directly to
the cell membranes of erythrocytes or platelets in vivo
[6–8]. Furthermore, it has been reported that aPL can
facilitate apoptotic cell clearance by scavenger macro-
phages in SLE through opsonization, this mechanism
depending on β2GP1 [9]. It is possible that aPL may
bind to phospholipids on haematopoietic cells in certain
aPL-positive patients and that the aPL-bound cells are
then phagocytosed by histiocytes via binding between
the aPL-Fc portion and the phagocyte Fc receptor.

In our patient, autoimmune haemolytic mechanisms
also seem to play a role in her anaemia in addition
to HPS, because of the positive Coombs test and the
elevation of serum LDH and bilirubin. aPL are reported to have anti-erythrocyte autoantibody
activity that participates in the development of
AIHA in some Coombs-positive patients [6, 7]. HPS
may also contribute to the anaemia of other patients
reported as having aPL-related AIHA [6, 7], as in our
patient.

Further studies of new features associated with aPL,
such as HPS, are needed to elucidate the pathogenic role
of aPL [10].

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