Secondary hemophagocytic syndrome (HLS) or macrophage activation syndrome (MAS) complicating presentation of systemic lupus in an elderly woman

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Abstract

Secondary hemophagocytic syndrome or macrophage activation syndrome is a well-recognized complication of systemic onset juvenile arthritis (SJIA) and juvenile systemic lupus and has been termed "cytokine storm syndrome". Less frequently it may be seen in adults. Primary forms (hemophagocytic lymphohistiocytosis) are characterized by familial predominance related to genetic mutations and usually present in childhood. We observed an 72 year old Filipino woman present with fever, waxing waning mental status, pleuropericardial effusions, arthritis, cytopenias, high ferritin (7202 mg/dl (nl< 29)) and rising ANA titer. Work-up demonstrated serial low C3s, trace cryoglobulins, elevated AST/ALT and EEG evidence for encephalopathy. Lumber puncture revealed increase in cells and total protein including IgG. Electrophoresis of the CSF fluid did not demonstrate oligoclonal bands suggesting an impairment of the blood-brain barrier and/or increased IgG synthesis. Treatment with high dose steroids transiently improved her hematologic picture, which then deteriorated (WBC 1,600/ml, hgb 7.6 gm/dl, platelets 38,000/ml). One-day premortem bone marrow evaluation demonstrated a hypercellular marrow with decreased granulopoiesis and increase in histiocytic cells including engulfment of erythrocytes and neutrophils.

This patient fulfilled the preliminary diagnostic criteria for MAS complicating SJIA. We believe early institution of definitive therapy was delayed by 3 factors:

1. Cytokine storm syndromes mimic systemic inflammatory response syndromes (i.e. systemic infection),
2. this patient's age and
3. the absence of a prior rheumatic disease diagnosis.

The dropping complement levels and trace cryoglobulins suggest immune complex formation may have been etiologic. Definitive diagnosis requires a high index of suspicion and early bone marrow evaluation.

Preliminary diagnostic criteria for MAS complicating SJIA

Laboratory Criteria
1. Low platelets
2. Increase aspartate aminotransferase
3. Decreased white blood count (WBC)
4. Hypofibrinogenemia

Clinical criteria
1. Central nervous system dysfunction
2. Hemorrhages
3. Hepatomegaly

Histopathologic criteria
1. Evidence of macrophage hemophagocytosis in the bone marrow

Diagnosis: 2 or more laboratory or clinical criteria or bone marrow findings as noted above

American College of Rheumatology Criteria for diagnosis of SLE seen in this patient

1. **Arthritis**
2. **Serositis (pleuritis/pericarditis)**
3. **Neurological disorder (seizures or psychosis)**
4. **Hematologic disorder (hemolytic anemia, leukopenia or lymphopenia on two or more occasions, thrombocytopenia)**
5. **An abnormal antinuclear antibody titer (ANA)***

Imaging and laboratory evaluation

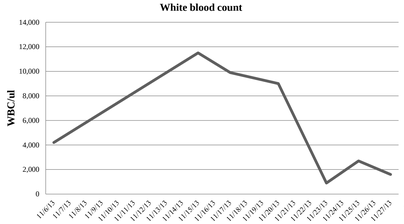
Prior to this hospitalization, there was no established diagnosis of a collagen-vascular disease or systemic lupus

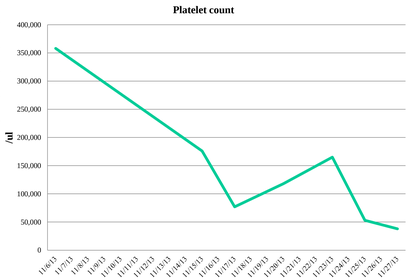
Serologic testing revealed repeated rising ANA titer to 1/640 (homogeneous and nucleolar pattern); serial low complements* with detectable cryoglobulins (Complete blood counts are reported below)

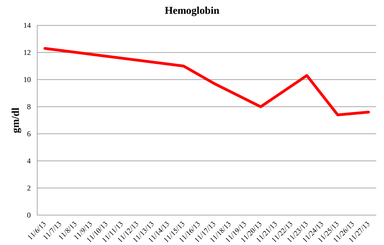
Work-up for CNS deterioration:

- MRI: Moderate generalized atrophy and numerous subcortical and central foci of of high signal on the FLAIR sequence consistent with small vessel disease
- EEG: Diffuse slowing and disorganization consistent with a diffuse encephalopathic process
- Lumbar puncture: WBCs 19 cells/ul, protein 950 gm/dl Electrophoresis IgG 13.5 gm/dl (no oligoclonal bands with identical bands in serum and CSF)

*Complement measurements are an indirect method to survey for immune complex deposition.







Treatment

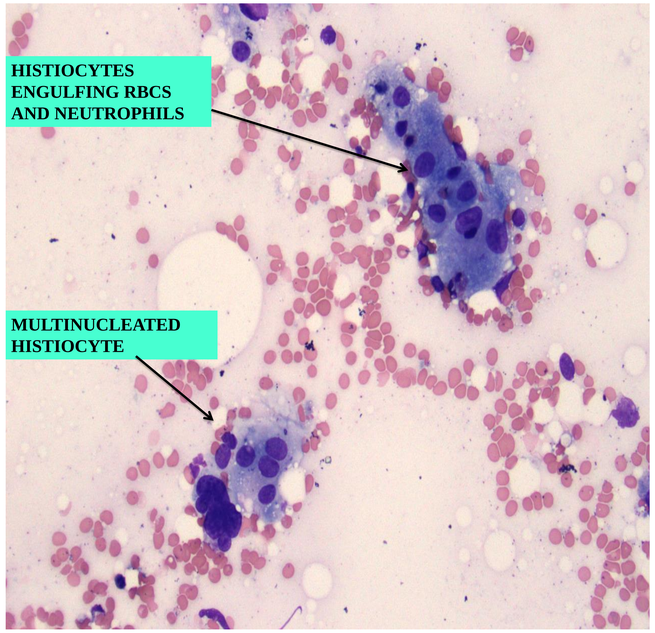
Glucocorticoids at varying doses up to 1 gram daily were administered from 11/11/13

Hydroxychloroquine 600 mg /day to 400 mg /day was instituted on 11/19/13

Rituximab 375 mg/m^2 was administered on 11/20/13

BONE MARROW ASPIRATE, CLOT AND CORE BIOPSY FINDINGS:

- Moderately hypercellular marrow with decreased granulopoiesis, dyspoiesis, with left shift (i.e. absence or diminished number of mature forms).
- Megakaryocyte dyspoiesis
- Markedly decreased erythroid series
- Increase in benign histiocytes (tissue based macrophages)



CONCLUSION

- Macrophage activation syndrome (MAS) may occur in adults and the elderly.
  - Clinical and laboratory findings suggest massive inflammation, progressing to multiple organ dysfunction syndrome and eventual death.
- MAS represents one of many causes (including infection) for cytokine storm syndrome (CSS).
- Immune complex disease (i.e. small vessel vasculitis) was likely etiologic.
- Establishing the diagnosis early warrants early bone marrow evaluation to differentiate this condition from other causes of immune cytopenias in adults.
- Early diagnosis should permit the early institution of appropriate immunosuppressive therapies (i.e. interleukin 1 inhibition and / or alkylating agents).

References

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- Jordan MB et al. How I treat hemophagocytic lymphohistiocytosis. Blood (2011) 118: 4041-4052 doi: 10.1182/blood-2011-03-278127