Macrophage Activation Syndrome (MAS): September 2008

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I. Sentinel and Historically Defining Papers

1. Tristano AG. Macrophage Activation Syndrome: a Frequent but Under-Diagnosed Complication Associated with Rheumatic Diseases. *Medical Science Monitor* 2008;14:RA27-36.

   ⇨ *This article is the most recent and most comprehensive review of the body of literature pertaining to MAS, including a summarization of the 74 cases previously reported in the English language literature.*

2. Sawhney S, Woo P, Murray KJ. Macrophage Activation Syndrome: a Potentially Fatal Complication of Rheumatic Disorders. *Archives of Diseases of Childhood* 2001;85:421-426.

   ⇨ *This paper presents a cohort of 9 children with MAS,along with one of the first reviews of the literature.*

3. Stéphan JL, Zeller J, Hubert P, Herbelin C, Dayer JM, Prieur AM. Macrophage Activation Syndrome and Rheumatic Disease in Childhood: a Report of Four New Cases. *Clinical and Experimental Rheumatology* 1993;11:451-6.

   ⇨ *This is the first report of MAS in association with rheumatic diseases. Of note, at the time of this report the term "macrophage activation syndrome" was loosely used to describe a syndrome with functionally activated macrophages, regardless of the etiology.*

4. Hadchouel M, Prieur AM, Griscelli C. Acute Hemorrhagic, Hepatic, and Neurologic Manifestations in Juvenile Rheumatoid Arthritis: Possible Relationship to Drugs or Infection. *Journal of Pediatrics* 1985;106:561–566.

   ⇨ *This is the first reference in the literature which noted the association of this constellation of symptoms (now known as MAS) with juvenile rheumatoid arthritis.*

5. Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour HH Jr, Simmons RL, et al. Virus Associated Hemophagocytic Syndrome: a Benign Histiocytic Proliferation Distinct from Malignant Histiocytosis. *Cancer* 1979;44:993–1002.

II. Pathophysiology of Macrophage Activation Syndrome

6. Behrens EM. Macrophage Activation Syndrome in Rheumatic Disease: What Is the Role of the Antigen Presenting Cell? *Autoimmunity Reviews* 2008;7:305-8.

   ⇨ *This brief review considers the role of the antigen presenting cells in the pathogenesis of MAS in light of many of the most recent findings.*

7. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatric Blood and Cancer* 2007;48:124-31.

- ⇨ *The standard of care for diagnosing and treating primary hemophagocytic lymphohistiocytosis (HLH), which is essential knowledge in order to understand secondary HLH (of which MAS is one form.)*

8. Verbsky JW, Grossman WJ. Hemophagocytic Lymphohistiocytosis: Diagnosis, Pathophysiology, Treatment, and Future Perspectives. *Annals of Medicine* 2006;38:20-31.

- ⇨ *This article thoroughly reviews HLH, both the primary and to some extent secondary forms, with emphasis on genetic associations and their functional implications on the primary forms of HLH.*

9. Grom AA. Pathogenic Mechanisms in Macrophage Activation Syndrome. *Pediatric Rheumatology Online Journal* 2005;3:184-194.

- ⇨ *This is one of the most comprehensive review articles detailing the pathophysiology of MAS, including details from his earlier work investigating natural killer cell dysfunction and cytotoxic T lymphocytes dysfunction.*

10. Grom AA. Natural Killer Dysfunction: A Common Pathway in Systemic-Onset Juvenile Rheumatoid Arthritis, Macrophage Activation Syndrome, and Hemophagocytic Lymphohistiocytosis? *Arthritis & Rheumatism* 2004;50:689-98.

III. Diagnosis of Macrophage Activation Syndrome

11. Kelly A, Ramanan AV. Recognition and Management of Macrophage Activation Syndrome in Juvenile Arthritis. *Current Opinion in Rheumatology* 2007;19:477–481.

- ⇨ *This is an excellent general review article which contains a discussion of strategies for differentiating MAS from flaring systemic-onset juvenile idiopathic arthritis (SOJIA,) including the use of the biomarkers, sCD163 and sCD25.*

12. Avcin T, Tse SM, Schneider R, Ngan B, Silverman ED. Macrophage Activation Syndrome as the Presenting Manifestation of Rheumatic Diseases in Childhood. *Journal of Pediatrics* 2006; 148:683-6.

- ⇨ *This paper presented the notion that MAS may present at the debut of childhood rheumatic disease.*

13. Ravelli A, Magni-Manzoni S, Pistorio A, Besana C, Foti T, Ruperto N, et al. Preliminary Diagnostic Guidelines for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis. *Journal of Pediatrics* 2005;146:598–604.

- ⇨ *This paper evaluated a cohort of 74 MAS patients, including 17 new patients and 54 patients previously presented in the literature. Through statistical analysis of the clinical features of these 74 patients, this group developed preliminary classification criteria for MAS in patients with SOJIA. These preliminary classification criteria are limited by the retrospective nature.*

IV. Macrophage Activation Syndrome and Systemic-Onset JIA

14. Zhang K, Biroschak J, Glass DN, Thompson SD, Finkel T, Passo MH, et al. Macrophage Activation Syndrome in Patients with Systemic Juvenile Idiopathic Arthritis is Associated with MUNC13-4 Polymorphisms. *Arthritis & Rheumatism* 2008;58:2892-6.

- ⇨ *After identification of subclinical MAS in children with SOJIA, genetic studies were undertaken revealing a significant increase in primary HLH-associated mutations in these children.*

15. Behrens EM, Beukelman T, Paessler M, Cron RQ. Occult Macrophage Activation Syndrome in Patients with Systemic Juvenile Idiopathic Arthritis. *Journal of Rheumatology* 2007; 34: 1133-8.

- ⇨ *This article presented the hypothesis that the disease processes of SOJIA and MAS may be related, since patients with newly diagnosed SOJIA were found to have occult MAS without the frank clinical symptoms.*

16. Bleesing J, Prada A, Siegel DM, Villanueva J, Olson J, Ilowite NT, et al. The Diagnostic Significance of Soluble CD163 and Soluble Interleukin-2 Receptor Alpha-Chain in Macrophage Activation Syndrome and Untreated New-Onset Systemic Juvenile Idiopathic Arthritis. *Arthritis & Rheumatism* 2007;56:965-71.

- ⇨ *This article presents data suggesting diagnostic utility of two biomarkers in the diagnosis of MAS in SOJIA patients.*

V. Macrophage Activation Syndrome and Other Rheumatic Diseases

17. Pringe A, Trail L, Ruperto N, Buoncompagni A, Loy A, Breda L, et al. Macrophage Activation Syndrome in Juvenile Systemic Lupus Erythematosus : An Under-Recognized Complication? *Lupus* 2007;16:587-92.

- ⇨ *This article raised awareness that juvenile systemic lupus erythematosus is, aside from SOJIA, the most common rheumatic disease associated with MAS.*

See Tristano AG. referenced in Section I.

- ⇨ *This broad review article has a very detailed reference list which includes the vast majority of references reporting MAS in association numerous rheumatic diseases, including multiple types of JIA, systemic lupus erythematosus, rheumatoid arthritis, adult-onset Still's disease, juvenile dermatomyositis, Sjögren's syndrome, scleroderma, Kawasaki disease, and mixed connective tissue disease.*

18. Rigante D, Capoluongo E, Bertoni B, Ansuini V, Chiaretti A, Piastra M, et al. First Report of Macrophage Activation Syndrome in Hyperimmunoglobulinemia D With Periodic Fever Syndrome. *Arthritis & Rheumatism* 2007;56:658-61.

- ⇨ *This article reports the first association of MAS with hyperimmunoglobulinemia D periodic fever syndrome, and it also mentions a previously reported case of a child with neonatal onset multisystem inflammatory disease and macrophage activation syndrome.*

VI. Treatment of Macrophage Activation Syndrome

See Tristano AG. referenced in Section I.

- ⇨ *This article provides a table describing the primary and secondary treatments used in all patients presented in the English language literature, a table listing the primary and secondary treatments for MAS based upon the primary rheumatic disease, and background information about potential mechanisms of action of these medications in MAS.*

See Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. referenced in Section II.

- ⇨ *This article describes the therapeutic standard of care of primary HLH, an understanding of which is significant to physicians treating MAS given that it provides much of the basis to our therapeutic approach to MAS.*

See Kelly A, Ramanan AV referenced in Section III.

- ⇨ *This article outlines the previous evidence in support of the therapeutic approach to MAS anchored by intravenous corticosteroids, followed by cyclosporine or etoposide in refractory or recurrent cases.*

19. Stéphan JL, Koné-Paut I, Galambrun C, Mouy R, Bader-Meunier B, Prieur AM. Reactive Haemophagocytic Lymphohistiocytosis in Children with Inflammatory Disorders. A Retrospective Study of 24 Patients. *Rheumatology (Oxford)* 2001; 40:1285-92.

- ⇨ *This article retrospectively reviews the course and management of a cohort of 24 children with MAS, highlighting corticosteroids as the primary therapeutic intervention, as well as the utility of cyclosporine A and other therapeutic strategies.*

20. Mouy R, Stephan JL, Pillet P, Haddad E, Hubert P, Prieur AM. Efficacy of Cyclosporine A in the Treatment of Macrophage Activation Syndrome in Juvenile Arthritis: Report of Five Cases. *Journal of Pediatrics* 1996;129:750–4.

- ⇨ *This is a report of five children with MAS treated successfully with cyclosporine A.*

21. Ravelli A, De Benedetti F, Viola S, Martini A. Macrophage activation syndrome in systemic juvenile rheumatoid arthritis successfully treated with cyclosporine. *Journal of Pediatrics* 1996; 128:275–8.

- ⇨ *This is a report of one boy with MAS and SOJIA treated successfully with cyclosporine A.*