Macrophage activation syndrome: a review of recent renal findings

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Implied for health policy/practice/research/medical education:
Macrophage activation syndrome is a life-threatening condition characterized by disproportionate stimulation and proliferation of macrophages, leading to the overproduction of inflammatory cytokines. Macrophage activation syndrome can occur in various settings, including autoimmune diseases, infections, and malignancies. The diagnosis of macrophage activation syndrome is based on clinical criteria such as fever, hyperferritinemia, hepatosplenomegaly, cytopenias, and evidence of macrophage activation on laboratory examination.

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Introduction
Macrophage activation syndrome (MAS) is a severe and potentially life-threatening complication that can occur in various rheumatic and autoimmune disorders, such as systemic juvenile idiopathic arthritis (SJIA) and systemic lupus erythematosus (SLE) (1). MAS is characterized by an uncontrolled activation and proliferation of macrophages, leading to excessive release of pro-inflammatory cytokines and subsequent multiorgan dysfunction (2). The pathogenesis of MAS involves excessive macrophage and T-cell activation, leading to the uncontrolled release of cytokines and chemokines, which can cause multi-organ dysfunction (1). The diagnostic criteria for MAS include fever, splenomegaly, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low or absent natural killer cell activity, elevated ferritin levels, and elevated soluble interleukin-2 receptor values. Hyperferritinemia is a key diagnostic criterion for MAS, and it is believed to result from the excessive activation and proliferation of macrophages (3,4).

Search strategy
In this review, a comprehensive search was conducted across multiple academic databases, including PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase. The search utilized...
Keywords such as “macrophage activation syndrome,” “glomerulonephritis,” “interleukin-2,” “splenomegaly,” “cytopenia,” “membranoproliferative glomerulonephritis,” “fever,” “macrophages,” “hypofibrinogenemia,” “proinflammatory cytokines,” “hemophagocytosis,” “mesangial proliferative glomerulonephritis,” “hypertriglyceridemia,” “crescentic glomerulonephritis,” and “interstitial nephritis.”

Etiology of MAS
Macrophage activation syndrome is a life-threatening complication of rheumatic disease that occurs much more frequently in individuals with SJIA and in those with adult-onset Still disease (5). The inflammation is caused by the uncontrolled activation of macrophages and T cells, which leads to widespread hemophagocytosis and cytokine overproduction (1). The exact incidence of MAS in childhood rheumatic disorders is unknown, but it is probably more common than previously thought (6). The known inducers of macrophage activation include toll-like receptor ligands and cytokines (7). The role of macrophages in MAS has been largely established through their mediation of hemophagocytosis and hypercytokinemia. The expansion of tissue macrophages exhibiting hemophagocytic activity in MAS is often triggered by infections or modifications in drug therapy (8,9). The reported mortality rates of MAS reach 20%-30% (5). The exact etiology of MAS is multifactorial and involves genetic, environmental, and immunological factors (10). MAS can affect different organs, including the kidneys. Recent studies have characterized MAS as a complex pathology consisting of three syndromes of hemorrhagic, neurologic, and hepatocitolyis (2).

Renal biopsy findings in MAS
The MAS is known to cause multi-organ dysfunction, including renal disturbance, which manifests as proteinuria, hematuria, and acute kidney injury (AKI) (9,11).

The current challenge in diagnosing renal pathology in MAS is the limited research on the renal pathology of MAS. Additionally, the symptoms of MAS are non-specific and can be similar to those of other conditions, making it challenging to diagnose renal pathology in MAS. Moreover, the diagnostic criteria for MAS can overlap with those of other conditions, making it difficult to establish a diagnosis of MAS. Meanwhile, there are currently no specific biomarkers for MAS, and the diagnosis is based on clinical and laboratory criteria. This can make diagnosing renal pathology in MAS challenging, as there are no specific tests to identify renal involvement. Finally, MAS is a rare condition that is often underdiagnosed, and this can lead to delayed diagnosis and treatment. This is particularly true for renal involvement, which may not be recognized until later stages of the disease.

Kidney pathologic lesions in MAS are generally a result of immune-mediated inflammation. This condition refers to inflammation and damage of the glomeruli. MAS-associated glomerulonephritis can be mesangial proliferative, membranoproliferative, or crescentic glomerulonephritis—the intensity of glomerular involvement associated with the degree of systemic inflammation and organ dysfunction (2,12).

Accordingly, there is interstitial nephritis, which refers to inflammation and damage of the tubules and interstitium. MAS-associated interstitial nephritis can present as acute, chronic, or tubulointerstitial nephritis with granulomas (13,14). Likewise, inflammation and damage of the blood vessels in the kidneys, including arteritis, vasculitis, thrombotic microangiopathy, and fibrinoid necrosis. MAS-associated vascular nephritis can lead to renal infarction, thrombosis, or hemorrhage (15,16). Besides, depending on the underlying disease, MAS-associated amyloidosis can present as primary or secondary (17). Notably, tubular injury is a common manifestation of kidney involvement in MAS. The excessive release of proinflammatory cytokines can lead to direct tubular damage. The tubular injury may manifest as tubular cell necrosis, epithelial cell apoptosis, and loss of brush border integrity. This can impair the tubules’ reabsorption and secretion functions (13,18-22).

Focus on acute kidney injury in MAS
Several potential factors may contribute to the development of AKI in this disease. First, uncontrolled activation of macrophages and T cells leads to a systemic inflammatory response. This inflammation can contribute to kidney injury by causing direct damage to renal cells and disrupting normal renal function (23,24). Second, the excessive release of cytokines and chemokines in MAS, often referred to as a cytokine storm, can lead to endothelial dysfunction, increased vascular permeability, and impaired renal blood flow. These factors can contribute to the development of AKI (25-27).

Diagnostic approach to MAS
The diagnostic process for kidney involvement in MAS typically involves a combination of clinical evaluation, laboratory tests, and imaging studies. Here are some key components of the diagnostic process (2). The initial step involves a thorough clinical patient assessment, including a detailed medical history and physical examination. The clinician will look for signs and symptoms of MAS, such as persistent fever, hepatosplenomegaly (enlargement of the liver and spleen), rash, lymphadenopathy (enlarged lymph nodes), and systemic inflammation (27-29). Besides, various laboratory tests are useful in evaluating kidney involvement in MAS. Blood tests such as serum creatinine, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) are commonly performed to assess renal function. Elevated
levels of creatinine and BUN may indicate impaired kidney function (30,31). A urinalysis is also conducted to examine the urine for the presence of abnormalities such as proteinuria, hematuria (blood in the urine), and cellular casts (indicative of kidney inflammation) (32). Moreover, certain serologic markers can provide insights into the underlying autoimmune condition and its associated kidney involvement. For example, in SLE, tests for antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, and complement levels (C3 and C4) are commonly performed (33,34). Since MAS is characterized by systemic inflammation, markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated (35,36). Furthermore, MAS can lead to abnormal coagulation parameters, such as prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), as well as reduced fibrinogen levels (37,38). Likewise, imaging studies may be utilized to evaluate the kidney structure and identify any structural abnormalities. Renal ultrasound is a non-invasive imaging modality that can provide information about the size, shape, and presence of obstructive kidney lesions. In some cases, additional imaging techniques like computed tomography (CT) or magnetic resonance imaging (MRI) may be required for a more detailed assessment (39). In certain situations, a renal biopsy may be performed to obtain a definitive diagnosis and assess the specific kidney pathologic lesions. The biopsy findings can help determine the nature and extent of inflammation, immune complex deposition, glomerular involvement, and other specific kidney abnormalities (40).

**Long-term renal effects of MAS**

Prolonged or severe MAS-related inflammation and injury can result in the development of renal fibrosis. Renal fibrosis is characterized by the accumulation of excessive extracellular matrix components, leading to the progressive loss of renal function and irreversible structural changes (41,42). In some cases, also MAS-associated kidney involvement can contribute to the development or progression of chronic kidney disease. CKD is characterized by a gradual loss of renal function over time, leading to a decreased ability of the kidneys to perform their normal physiological functions (43-45).

**Control of underlying autoimmune disease**

The primary goal is to control the underlying autoimmune condition that triggers MAS. Immunosuppressive medications such as corticosteroids, disease-modifying anti-rheumatic drugs, and biologic agents may be administered to suppress the abnormal immune response and reduce inflammation (46,47). The choice of immunosuppressive agents and treatment regimens depends on the specific autoimmune condition and the severity of MAS. Treatment should be tailored to each individual’s needs and closely monitored by a rheumatologist or an appropriate specialist (48).

**Early recognition and treatment of MAS**

Early recognition and prompt treatment of MAS are crucial in minimizing renal damage and fibrosis. Close monitoring of clinical symptoms, laboratory markers of inflammation, and renal function is essential for early detection (28,49). High-dose corticosteroids, intravenous immunoglobulin, and other immunomodulatory agents may be used to suppress the overactive immune response in MAS. In severe cases, additional therapies such as interleukin-1 (IL-1) inhibitors or interleukin-6 (IL-6) inhibitors may be considered (50,51). Accordingly, aggressive supportive care measures, including hydration and monitoring of vital signs, are important in maintaining hemodynamic stability and optimizing renal perfusion (52).

**Renal protection strategies**

These modalities containing maintaining optimal blood pressure control in preventing further renal damage. Medications like angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may be prescribed to control blood pressure and reduce proteinuria (53,54). Proteinuria is associated with progressive renal damage. Management strategies for proteinuria involve dietary modifications, medication adjustments, and close monitoring of urinary protein levels (55,56). To prevent further renal injury, monitoring and correcting electrolyte imbalances and acid-base disturbances are important. This may involve administering specific medications or dietary modifications (57). In addition, individuals with MAS should avoid exposure to nephrotoxic substances, such as certain medications (e.g., non-steroidal anti-inflammatory drugs) and contrast agents, as they can worsen renal function (58,59).

**Regular monitoring and follow-up**

Regular follow-up visits with a nephrologist in managing kidney diseases are important to monitor renal function, proteinuria levels, blood pressure, and other markers of kidney health. This allows for early detection of any worsening renal function or fibrosis (60).

**Conclusion**

Significant effects on renal function and structure can be caused by MAS. The severity and duration of MAS and the underlying autoimmune condition can influence the extent of renal involvement. Treatment of MAS involves aggressive immunosuppression with corticosteroids, cyclosporine, and other immunomodulatory agents. Early recognition and prompt treatment are essential to prevent irreversible organ damage and improve outcomes in patients with MAS.
**Authors’ contribution**

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Investigation: Mansour Salesi.

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**Conflicts of interest**

The authors declare that they have no competing interests.

**Ethical issues**

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