Macrophage Activation Syndrome and Renal Involvement: A Case Report

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Abstract:
Macrophage activation syndrome (MAS) is a severe, potentially fatal condition associated with excessive activation and expansion of macrophages and T cells (mainly CD8), leading to exaggerated inflammatory response. We describe here a case of MAS causing possibly ATN and review the literature.

Keywords: *Macrophage activation syndrome, acute tubular necrosis, acute kidney injury, filgrastim.*

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Introduction:

Macrophage activation syndrome (MAS) is a severe, potentially fatal condition associated with excessive activation and expansion of macrophages and T cells (mainly CD8), leading to exaggerated inflammatory response[1]. It is characterized by bone marrow infiltration by activated macrophages and pancytopenia. Acute Kidney Injury in the settings of MAS is indicator of poor prognosis[2]. Acute tubular necrosis is the most common renal manifestation in MAS, nephrotic syndrome can also occur however little has been reported about glomerular involvement[3].

Case Report:

A 51 years old male was admitted through emergency with one week history of shortness of breath and bilateral lower limb swelling associated with mild cough, sputum, orthopnea and paroxysmal nocturnal dyspnea. There was no history of fever, abdominal and chest pain, dysuria, hematuria, loin pain, vomiting and loose motions at the time of presentation, however patient reported decreasing urine output for the last few days.

He was a chronic smoker and diabetic for last 15 years, and was taking insulin for control of diabetes. Twelve years ago he underwent percutaneous trans luminal angioplasty for coronary artery disease. Patient had pulmonary tuberculosis 8 years ago for which he took antituberculous treatment for 1 year. Three weeks ago he developed acute kidney injury (possibly due to sepsis) on chronic kidney disease (diagnosed 1 year ago) leading to three sessions of hemodialysis at another hospital for management of fluid overload. He did not require further sessions of hemodialysis, since AKI resolved.

In the emergency room patient was tachypneic with a blood pressure of 130/90 mmHg sitting, was maintaining 80% oxygen saturation while breathing room air, had bilateral pedal edema and raised jugular venous pulse. On auscultation he had end inspiratory crackles bilaterally in infrascapular regions. Rest of the systemic examination was normal. His lab investigations are shown in **Table:1**.

Table 1: laboratory investigations performed during the hospital course in the patient later diagnosed with macrophage activation syndrome.

*Filgrastim initiated $Bone Marrow Biospy.

INVESTIGATIONS	Day 0	Day 4	Day 8	Day 9	Day 11	Day 13	Day 14
Haemoglobin g/dl		7.8	10.2	10.2	9.3	8.3	8.8
WBC (/mm) ^{3}		7.9	4.5	1.96 *	0.13 $	0.07	0.21
Platelet (/mm) ^{3}		250	150	124	100	31	24
Serum Creatinine (mg/dl)	6.4	6.6	5.6	5.2	5.1	5.3	6.2
Blood Urea (mg/dl)	214	186	233	244	290	338	518
Serum Ferritin (ng/ml)		193				>2000	
Troponin I (ng/ml)		1335					
Sodium (mEq/litre)	131		128		132		
Urine C/E	Protein +++ Blood trace Pus cells many						
Stool for occult blood		Negative					
Throat swab		Klebsiella pneumoniae MRSA					
HIV					Negative		
Peripheral smear			Occasional schistocytes Acanthosis				

ECG revealed diffuse T-wave inversions and subsequent Troponin-I was found to be elevated. Antithrombotic treatment with heparin was initiated and continued for 48 hours. On the basis of examination and investigations he was treated for Acute Pulmonary Edema possibly secondary to ACS and CKD with IV diuretics. Hyperkalemia was managed medically. Patient's condition stabilized with adequate diuretic response and serum potassium normalized. Six days after admission he started developing oral ulcers. Concurrently purpuric rash on legs and ecchymosis on abdomen skin were also noted. Dermatology opinion was obtained and an initial impression of vasculitis was made. At the same time repeat labs revealed pancytopenia and worsening renal functions. A hematology review and subsequent bone marrow biopsy showed hypoplastic marrow and hemophagocytosis leading to confirmation of diagnosis of MAS, **Figure:1**. Intravenous Methylprednisolone, Filgrastim and supportive treatment (fresh frozen plasma,

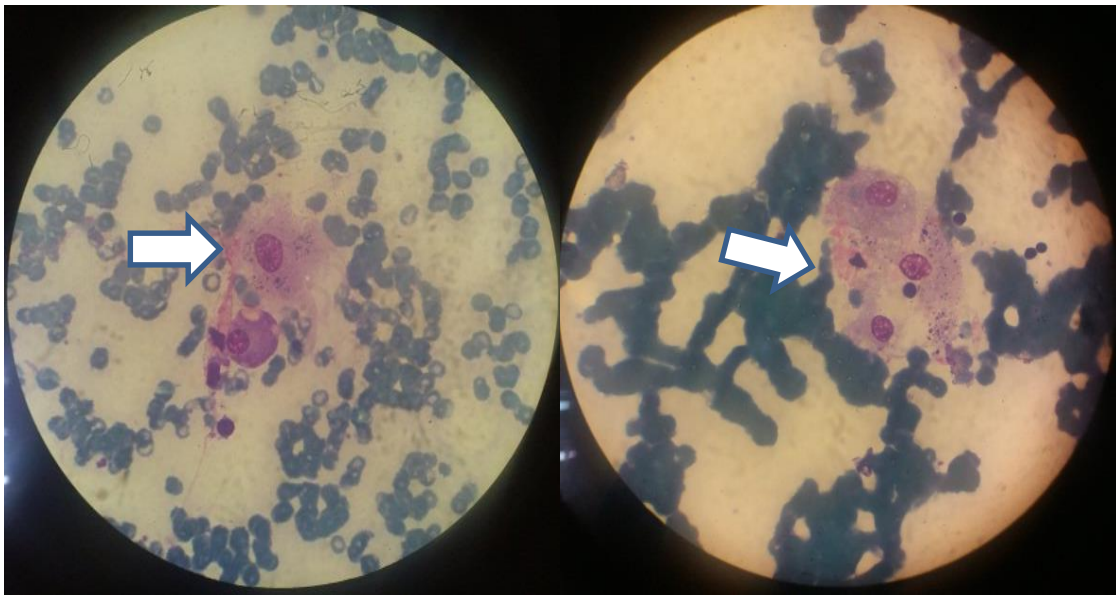

Figure 1: Macrophages engulfing the leukocytes and platelets highly suggestive of macrophage activation syndrome.

packed cell volumes) were continued but patient's condition worsened, despite the improvement in laboratory parameters, **Figure:2.** Concurrently hemodialysis was initiated because of worsening renal function and fluid overload, however despite of all possible medical management patient expired on 14th post admission day.

Discussion:

Macrophage activation syndrome represents an exaggerated immune response with activation and proliferation of well-differentiated macrophages secondary to infections, malignancies, drugs and rheumatologic diseases[4,5]. It is characterized by hypersecretion of pro-inflammatory cytokines including Tumor necrosis factor-alpha (TNF-a), interferon-gamma (IFN-γ). Interleukin 1, interleukin 4, interleukin6, interleukin 8, interleukin 10, and interleukin 18[6,7].

Our patient met MAS criteria by having fever, pancytopenia, hyponatremia, hyperferritinemia, renal and CNS involvement. Our patient likely had MAS because of underlying infection. [8] Important diagnostic markers include low or absent NK-cell activity (assessed by chromium 51 or granzyme B proteolytic activity), increased plasma level of CD163, as a marker of macrophage activation, and CD25 as an interleukin 2 receptor (sIL-2R), is increased is in 79% of adult with MAS. [9,10] These investigations were not available. Confirmatory test was bone marrow aspiration, done in our patient which identifies mature histiocytes ingesting other blood cells in 84% of patients[11].

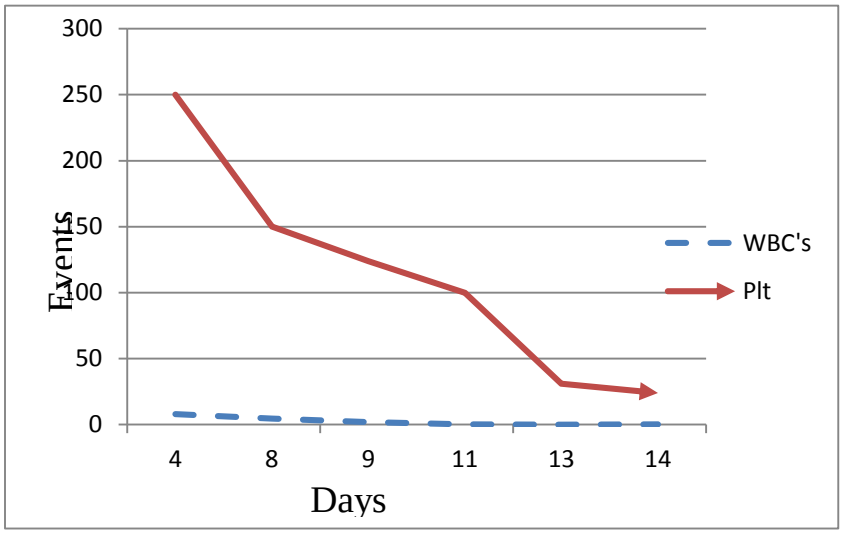

Figure 2: Course of WBC and Platelet count during hospital stay.

AKI is common with MAS but the prognosis of MAS related renal involvement is not good. Same was the case with our patient as his condition worsened gradually and never recovered. We were unable to perform a renal biopsy since the patient was deemed to be at extremely high risk because of coagulopathy and thrombocytopenia.

Acute tubular necrosis occurring in MAS is often associated with interstitial inflammation. Tubular destruction is the result of inflammatory cytokines damage and high serum level of tumor necrosis factor α[12,13]. TNFα binds to its receptor (TNFR1), mediates renal damage through increasing granulocyte infiltration and activation of apoptotic signaling kinase-1 (ASK1) in tubular cells[14,15]. TNFα can disorganize the podocytes actin cytoskeleton leads to increase glomerular permeability to albumin. Thrombotic microangiopathy is another type of glomerular involvement in MAS. Renal lesions in MAS are shown in table 2.

Table 2: Renal pathology associated with macrophage activation syndrome.

Glomerular	
Minimal change disease	Collapsing glomerulopathy
Thrombotic microangiopathy	Histiocytic glomerulopathy
Tubulointerstitial	
Acute tubular necrosis	Microcystic tubular dilatation
Interstitial nephritis with polymorphic T lymphocytes and CD68+ macrophages	
Tubular atrophy and interstitial fibrosis	
Vascular	
Thrombotic microangiopathy	

Prompt recognition and treatment of underlying cause is paramount in treating MAS. However, to manage the cytokine release syndrome which drives the pathophysiology of MAS, high-dose IVIG, Steroids and cyclosporine can be used. [16,17] Biological treatments such as rituximab, infliximab, and etanercept (Enbrel) have been proposed for adults patients who did not respond to cyclosporine and IVIG[18], tacrolimus and etoposide also have been proposed in refractory cases[19]. If there is a combination of MAS and TMA addition of therapeutic plasma exchange is useful. IV Methylprednisolone Pulse was started immediately in our patient with the suggestion of hematology when the possibility of MAS was raised. The diagnosis was confirmed on Bone marrow biopsy the next day. Calcineurin inhibitors were not given because of deranged renal function. It was not possible to use Immunoglobulins and other treatment options because of multiple comorbidities (sepsis, shock, decreased renal function, acute coronary syndrome) and cost issues.

Graft nephrectomy has been proposed for kidney transplant recipients with life-threatening MAS resistant to different therapies[20], our patient was however too sick to proceed for nephrectomy.

CONCLUSION

MAS is an increasingly encountered disorder in the realm of different medical specialties. In the course of acute renal failure, MAS can complicate the clinical picture of disease and is associated with poor prognosis.

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