EJMO

DOI: 10.14744/ejmo.2019.53051
EJMO 2019;3(3):219-223

Case Report

Interstitial Lung Disease in Dermatomyositis Complicated by Right Ventricular Thrombus Secondary to Macrophage Activation Syndrome

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Abstract

Course of dermatomyositis (DM) can be complicated by multi organ failure, by complex pathophysiological mechanisms involving auto antibodies. Pulmonary complications are the leading cause of mortality, accounting for 30% deaths. There is a strong association between DM and interstitial lung disease (ILD); clinically amyopathic dermatomyositis (CADM) has stronger association with ILD as compared to classic form of DM. ILD can be in the form of fibrosing alveolitis, interstitial pneumonia and desquamative interstitial pneumonia or diffuse alveolar hemorrhage. Auto antibodies linked to ILD are anti Jo-1, PL12, PL7, EJ, and OJ and anti Mi 2.

Our case describes a fifty three years old woman who presented with symptoms of lower respiratory tract infection, diagnosed with CADM on the basis of typical skin rash and polyarthritis and anti-CADM 140 antibodies. Systemic steroid therapy (initiated after ruling out sepsis) failed to provide improvement. Medical course was complicated by multisystem involvement (respiratory failure, cerebral edema, renal failure, coagulopathy, hepatic failure and thromboembolism). Transthoracic echocardiogram revealed thrombus in right ventricle which was the result of prothrombotic state.

Keywords: Amyopathic dermatomyositis, myositis, macrophage activation syndrome, right ventricular thrombus, thromboembolism in dermatomyositis

Cite This Article: *Paul N, Vasudev R, Chandran C. Interstitial Lung Disease in Dermatomyositis Complicated by Right Ventricular Thrombus Secondary to Macrophage Activation Syndrome. EJMO 2019;3(3):219-223.*

Dermatomyositis (DM) is a rare connective tissue disorder that results from auto immune antibodies by humoral immune system activation. Reported incidence of amyopathic DM (46.4 %; 21%) is less as compared to classic DM and has a female preponderance.[1, 2] Prior to the introduction of corticosteroids in the treatment of DM, prognosis was extremely poor with a mortality rate as high as 50 to 61%.[3, 4] Muscle or skin biopsy is required to support the diagnosis, however is no t necessary if there is a typical clinical presentation suggestive of DM. Cytokine storm known as Macrophage activation syndrome (MAS) is fatal and uncommon complication of DM.

This case highlights MAS, which depicts a miscellaneous clinical scenario with multiple differential diagnoses which is the real challenge and can be extremely tricky to manage if the pathogenesis is not fully understood.

We report a fatal case of DM with rapidly progressive ILD which failed to respond to systemic steroids and consequently resulted in MAS leading to multi organ failure and thromboembolism (right ventricular thrombus) (RVT). To

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Submitted Date: January 30, 2019 **Accepted Date:** April 14, 2019 **Available Online Date:** August 01, 2019

the best of our knowledge, a case of DM with RVT has never been reported so far.

Case Report

A fifty three years old Hispanic female with history of polyarthritis for past 3months [with no definite diagnosis] presented in the emergency department (ED) with intermittent fever, dyspnoea sore throat and dry cough for 10 days. She denied chest pain, hemoptysis, rhinorrhea, nasal stuffiness or post nasal discharge. There were no sick contacts and no history of recent travel. Patient had been experiencing arthralgias involving shoulder, elbow, wrist, interphalangeal, knee and ankle joints, burning sharp pain aggravated on movement with no relieving factor. There was erythematous rash located in periorbital areas bilateral, lateral aspect of right leg and thigh, around the neck, bilateral shoulders, left elbow and bilateral knuckles (Fig. 1). Patient had an unintentional weight loss of ten pounds since last 4 months with reduced appetite.

Patient was a lifetime non smoker, non alcoholic, never used illicit drugs, and no history of sexually transmitted diseases. No history of similar complaints and no similar history in any family member. Initial vitals in ED were ,blood pressure (BP) 108/59 mmHg, heart rate 88 beats per minute, temperature 104 degree Fahrenheit, respiratory rate 30 per minute, oxygen saturation 98% with nasal cannula at 4 liter per minute. Physical Exam was positive for mild respiratory distress, heliotrope rash, Gottron's patches, and Shawl sign, coarse crackles on lung auscultation, equal air entry bilateral. Joints were not deformed. No organomegaly on abdominal exam. No genitourinary rash or discharge noted. Blood work showed normocytic anemia with anisocytosis, hypocalcaemia, hypophosphatemia, hypoalbuminemia and raised aspartate aminotransferase. Chest radiogram showed increased interstitial markings on left lower lung field. Initial diagnosis was community acquired interstitial pneumonia. Antibiotics for atypical coverage were started. Patient deteriorated despite changing antibiotics; in the meantime blood cultures and sputum culture were negative. Throat swab was negative for Streptococcus pneumoniae. Arterial blood gas showed fully compensated respiratory alkalosis while on 100% oxygen on a non rebreather mask. Computed tomography (CT) scan of chest showed ground glass appearance of the interstitium (Fig. 2). CT angiography ruled out pulmonary embolism. A high dose systemic steroid was started. Subsequently patient became hypoxemic and hypotensive and had to be placed on mechanical ventilation. Ferritin 1600 ng/ml, Lactate dehydrogenase (LDH) was 490 Units/Liter, erythrocyte sedimentation rate (ESR) was 60 mm/hour, C-reactive protein (CRP) was 176 mg/L. Thereafter acute renal failure set in along with bicytopenia (anemia and thrombocytopenia). Continuous veno-venous hemofiltration was initiated. Transesophageal echocardiogram revealed a thrombus in right ventricle. There was no evidence of deep vein thrombosis on Doppler ultrasound of extremities.

There was evidence of myositis [high creatine kinase 279 U/L and myoglobin: 142ng/ml, although aldolase (6.7U/L) was normal; TSH (0.54 mIU/L) was within normal limits. Anti CADM 140 antibody was positive; rest of the auto immune panel was unremarkable; antinuclear antibodies, anti-smith antibodies, anti double stranded deoxy-ribonucleic acid antibodies, anti-jo-1 antibody, anti-smooth muscle, rheumatoid factor, antineutrophil cytoplasmic antibodies were negative. Complement levels (C3 and C4) were within normal limits, 128mg/dL and 34mg/dL respectively. Human immunodeficiency virus serology was negative. Lyme serology was negative. Hepatitis C antibody was negative. Lupus anticoagulant was negative. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) was mildly elevated (PT 16.1 sec, aPTT 38.7 sec), and international nor-

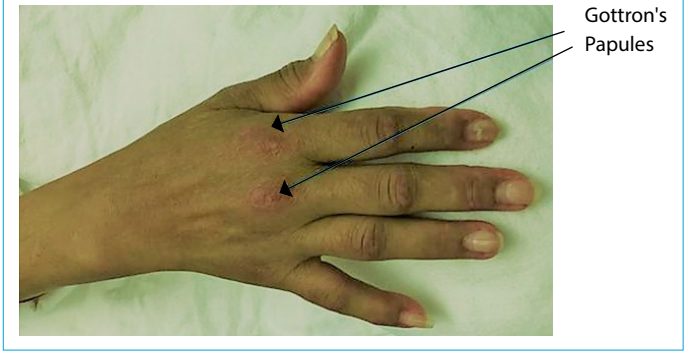

Figure 1. Erythematous rash located left elbow and bilateral knuckles.

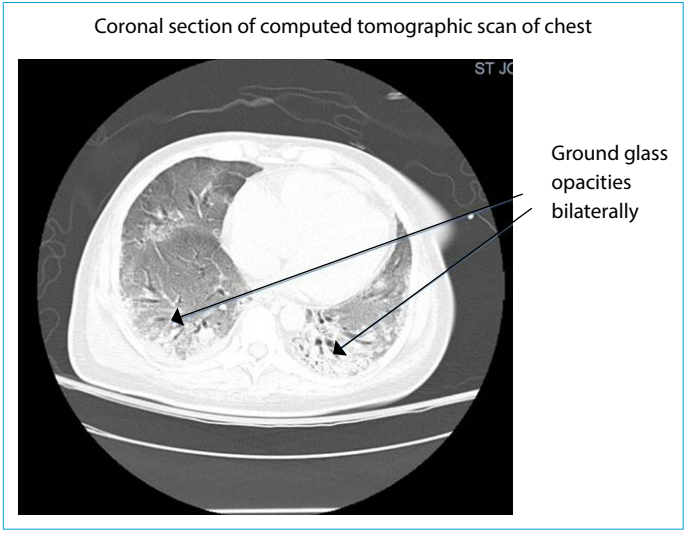

Figure 2. Ground glass appearance of the interstitium in computed tomography.

malized ratio (INR) was normal 1.3. Fibrinogen was normal (274 mgm %), fibrin degradation products were elevated (>20 µgm/ml), D-dimer was >20 µgm/ml. Peripheral blood film did not show schistocytes. LDH was elevated, however haptoglobin level was normal. The direct Coombs test was negative. Heparin induced thrombocytopenia panel was negative. CT brain showed diffuse cerebral edema. Hypotension was refractory to vasopressors. Patient expired on day tenth of hospitalization.

Discussion

DM population is prone to development ILD, more so in presence of factors like older age at diagnosis, arthritis or arthralgias, fever, presence of anti-Jo-1 antibodies, elevated ESR, presence of anti-MDA5 antibodies, and elevated CRP level. In a genetic study on Chinese Han population involving 1017 patients with DM/PM, it was observed that there is a positive association between ANKRD5 gene polymorphism and DM-ILD.[5, 6]

Thrombosis in autoimmune disease is multi factorial. Overall incidence of pulmonary embolism in DM is 3 times more as compared to general population; risk increases to sixteen folds during one year follow up.[7–10] Humoral immune response flare mediates Microangiopathic vascular damage that sets in cascade of thrombogenesis. Risk is augmented with co morbid conditions and other systemic diseases.[11, 12] There is evidence suggesting strong association between thromboembolism that includes deep vein thrombosis and pulmonary embolism, in DM.[13] Most common presentation is deep vein thrombosis or pulmonary embolism; however our patient developed a right ventricular thrombus.[14–18]

Thrombosis can be best explained by systemic inflammation by auto immune attack. There is induction of tissue factor expression and inhibition of fibrinolysis by up regulation of plasminogen activator inhibitor levels.[19] There is multisystem involvement like cardiovascular, pulmonary, hematological and central nervous system. Severity and progression of ILD depends on patient factors like age, skin rash, presence of anti Jo antibodies.

Pro thrombotic state is also attributed to inflammatory mediators like interleukin 6 which are responsible for reducing levels of protein S, and TNF alpha which down regulates endothelial protein C receptor and thrombomodulin to experimental studies suggest that.[20] Once ILD starts to develop, the disease can progress rapidly and is highly fatal. There are various types of ILD based on high resolution computed tomography features (HRCT) like non specific interstitial pneumonia, lymphocytic interstitial pneumonia, cryptogenic and acute interstitial pneumonia. Our patient had ground glass appearance along with bilateral lower lobar interstitial pneumonia, consistent with non specific interstitial pneumonia.

Multi system failure has been attributed to macrophage activation syndrome (MAS) which is phagocytosis of hematopoietic elements by activated macrophages. Mostly seen in association with rheumatoid arthritis and lupus, however has been reported in several cases of juvenile DM. MAS leads to multi system failure that includes cytopenias, thrombosis, renal failure, heart failure. Major Cytokines involved are Interleukin 6, 8, 18, tumor necrosis factor alpha and interferon gamma. MAS can result from triggers like infections (viral/bacterial/parasitic), malignancy (like lymphocytic leukemia and Hodgkin's lymphoma), auto immunity and environmental factors and lung transplantation .In such cases it is better known as reactive or secondary hemophagocytic syndrome (HPS). HPS leads to major spill of cytokines from activated macrophages which attacks and destroys host tissue.

In our case, most likely underlying cause of right ventricular thrombus was primary MAS. Although, patient had positive Streptococcal pneumoniae IGG antibodies (IGM antibodies were negative) and hepatitis B core antibodies positive, both reflect past infection.

Patient was on systemic steroids since the diagnosis (one month) of DM. There was minimal relief in arthralgias. Thereafter patient presented with non specific symptoms of suggestive of pneumonia. It is crucial to have a complete understanding of inflammatory myopathies as their presentation can mimic sepsis. Fever, cough, dyspnoea and lung involvement on radiogram can easily be confused with bacterial or viral pneumonias.

Diagnosis is based on a collaboration of clinical and laboratory parameters. There is no established diagnostic criteria for MAS/HPS, however researchers have designed criteria that have been validated. There are several criteria reported for MAS is in association with juvenile idiopathic arthritis (JIA), lupus, adult onset Still's disease and systemic sclerosis. PRINTO criteria is one such criteria (designed for JIA) Sensitivity of 72 percent and specificity of 97 percent; it was designed after a multiprocess approach involving a questionnaire answered by expert consultants in rheumatology.[21]

There is no criterion specific for MAS diagnosis in DM; however the basic mechanism of MAS is similar in all connective tissue and auto immune disorders; therefore the diagnosis can be established keeping in consideration multi system involvement. Laboratory findings include cytopenias, coagulopathy, hypofibrinogenemia, hyperferritinemia, hypertriglyceridemia, hypoalbuminemia, ab-

normal liver enzymes. High ferritin relates to resistance to response to therapy and worse outcome compared to low or normal ferritin level. In presence of high ferritin, a low glycosylated ferritin is a known prognostic factor. Bone marrow may show active phagocytosis of hematopoietic elements by phagocytes; however negative bone biopsy does not preclude the diagnosis of MAS. Biopsy from other organs like lymph nodes, liver and spleen may show similar histopathological features. Testing for specific genetic expression is a useful diagnostic tool; however not utilized commonly as it is not readily available in all centers.

In our case, MAS rapidly spread to involve almost every organ system and was resistant to therapy. Such patients must be heparinized and treated with high dose corticosteroids, tacrolimus, cyclosporine, etoposide, intravenous immunoglobulin. Plasmapheresis is the last resort for unresponsive cases.[22–26] Familial cases are Primary MAS and have better prognosis compared to secondary. Increased risk of systemic thromboembolism is secondary to systemic inflammation which up regulates procoagulants in blood with simultaneous suppressing fibrinolysis. Inflammatory myopathies have been reported to cause deep vein thrombosis, pulmonary embolism and cerebral thromboembolism, however MAS with right ventricular thrombus is a unique finding in our case.

Conclusion

Rapidly progressive ILD in a patient with autoimmune myopathy like DM is a dreaded complication of the disease. In case of rapidly deteriorating ILD, one must anticipate MAS and evaluate for thromboembolism along with of initiation aggressive therapy.

Disclosures

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – N.P., R.V., C.C.; Design – N.P., R.V., C.C.; Supervision – N.P., R.V., C.C.; Materials – N.P., R.V., C.C.; Data collection &/or processing – N.P., R.V., C.C.; Analysis and/or interpretation – N.P., R.V., C.C.; Literature search – N.P., R.V., C.C.; Writing – N.P., R.V., C.C.; Critical review – N.P., R.V., C.C.

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