Case Report

MDA5 Positive Juvenile Dermatomyositis with Interstinal Lung Disease

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Juvenile Dermatomyositis (DM) is a form of dermatomyositis which occurs in two peaks at age group 6 years and 11 years characterised mainly by calcinosis, cutaeous ulceration, lipodystrophy more prominent than adult population along with Interstinal Lung Disease (ILD). A rare variant of this population have Melanoma Differentiation Associated protein 5 (MDA-5) autoantibodies which is particular for rapidly progressive interstinal lung disease. Here we are reporting such rare variant of juvenile dermatomyositis which is MDA-5 autoantibodies positive.

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***Key words* : Juvenile Dermatomyositis, Interstinal Lung Disease, Melanoma Differentiation Associated protein 5 autoantibodies.**

Juvenile Dermatomyositis is a rare disease with a incidence of 1.5 to 3 per million of children . The disease has two peaks at age 6 years and 11 years and occurs more commonly in girls. Juvenile-onset DM presents an increased risk of multiorgan vasculopathy, fasciitis and soft tissue calcinosis but a decreased risk of associated internal malignancy compared to adult population[1]. The most common clinical manifestations at disease onset are muscle weakness, easy fatigability, skin rash, malaise and in some cases, fever. Melanoma differentiation-associated protein 5 autoantibodies against MDA5 are detected in 14.7% and 22.7% of DM patients and clinically amyopathic dermatomyositis respectively[2]. MDA-5 is highly specific for clinically amyopathic DM (95% of these patients are anti-MDA5-positive) or dermatomyositis combined with interstitial lung disease[3].

We are presenting a 12 year old female with MDA5 positive juvenile dermatomyositis with intestinal lung disease.

Case Report

Our patient is a 12-year-old non-diabetic, non-hypertensive, non-hypothyroid female patient (Fig 1) who presented to us with a history of moderate grade fever without any chills and rigor for a week along with chest pain predominantly on the left side of the chest along with shortness of breath for last three days prior to admission without any history of cough or expectoration of sputum.

Editor's Comment :

- MDA-5 autoantibodies positive juvenile dermatomyositis typically present with a symmetric inflammatory polyarthropathy, which was frequently clinically indistinguishable from rheumatoid arthritis.
- A majority of MDA5 antibody-positive patients had a clinical myopathy and ILD, when present.
- Interstinal lung disease is rapidly progressive in this rare variety of juvenile dermatomyositis.

Prior to this episode she had a history of multiple joint pain which started 6 months back in the hip joint symetrically and then gradually involved the knee (Fig 1), elbow, wrist and also small joints including the carpometacarpal and interphalyngeal joints. During this period she developed low grade fever which was present for a period of 2 months without any diurnal variation, chills or rigor. Deformity of joints started 4 months back specially in the knee, elbow, wrist and inter phalyngeal joints and was present at the time of admission. Following this she developed oral ulcer along with multiple skin rash which started as a small papule and then gradually increased in size until it become ulcerated predominantly in the back of the elbow joint, lower back of the patient and also over the dorsal aspect of the interphalyngeal joint (Fig 1).

After admission, on examination, she was found to be tachypneic with respiratory rate of 40/min, SpO2 of 70% without O_2 and 92% following nebulisation with bronchodilators and oxygen therapy. Respiratory system examination shows decreased movement of the left side of the chest wall, percussion shows dull note from the left 5th intercostal space along the midclavicular line and on auscultation crepitation was found bilaterally but predominantly in the left lower region of the lung along with increased vocal

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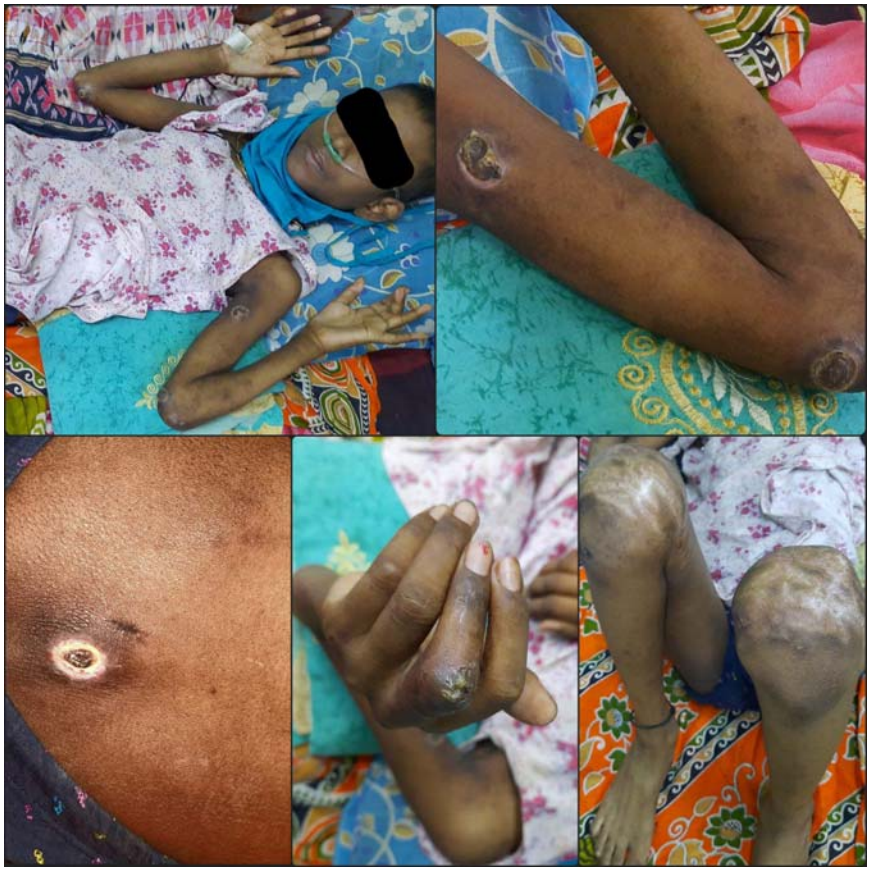

Fig 1 — *upper left* : The patient ; *upper right* : ulcerated papule on the back of elbow and near the axillary region ; *lower left* : Ulcerated papule in the back ; *lower middle* : Ulcerated lesion in the inter phalyngeal joint ; *lower right* : Knee joint involvement

reasonance in the left inframammary, infra-axillary, interscapular and infrascapular region. Cardiovascular system showed tachycardia with pulse rate of 177 bpm. Severe muscular weakness was noted particulary of the truncal muscles and neck extensors.

Chest X-Ray shows left lower lobe consolidation (Fig 2) with blood investigation showing neutrophilic leucocytosis. Intravenous antibiotics were started and HRCT Thorax was performed which suggested cryptogenic organising pneumonia, a form of interstinal lung disease (Fig 3). Blood report also shows elevated AST, LDH, aldolase level but CPK level was normal. Due to multisystem involvement rheumatological workup was initiated for lupus, rheumatoid arthritis and myositis. Lupus workup showed albuminuria (770mg/ 24 hr), DCT positive, echocardigraphy showing chink of pleural effusion but ANA was negative with normal C3, C4, anti ds-DNA levels . Anti CCP, RA factor, anti GBM , anti synthetase antibody was also negative. MRI bilateral thigh showed left sided hip effusion, joint capsular thickening and high signal intensity seen in fat supressed T2 weighted image suggestive of presence of muscle oedema (Fig 4). EMG study shows proximal myopathy and myositis profile (16 antigen) study revealed MDA5 positive along with weak positivity for MI-2beta. As serum markers for myositis were elevated, MRI findigs were suggestive of myositis and myositis profile was positive for MDA5 along with weak positive for MI-2beta invasive procedure such as muscle biopsy was not performed in this patient.

After proper discussion with the respective departments it was concluded that the patient is suffering from a rare form of MDA5 positive form of juvenile dermatomyositis and was started with oral prednisolone along with she received 500mg of intravenous cyclophosphamide for intestinal lung disease and presently discharged for follow-up for further cyclophosphamide threapy or rituximab therapy (Table 1).

Discussion

MDA5 is a RIG-I-like receptor dsRNA helicase enzyme that is encoded in humans by the IFIH1

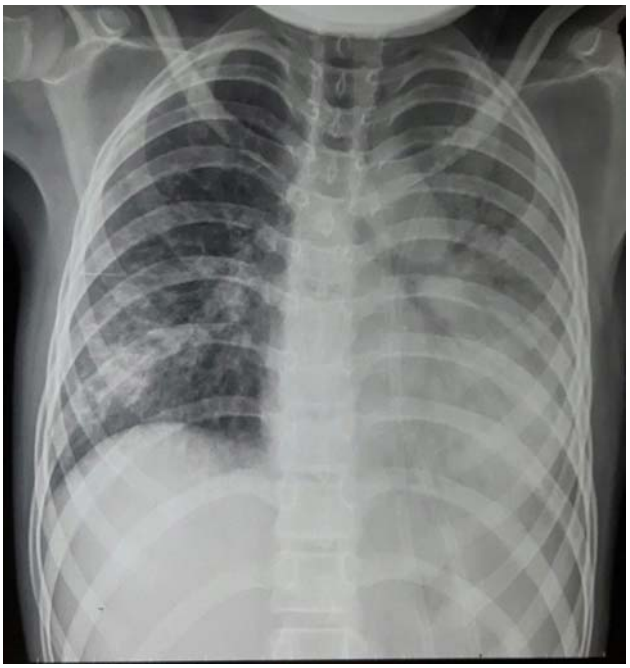

Fig 2 — Chest X Ray - PA View

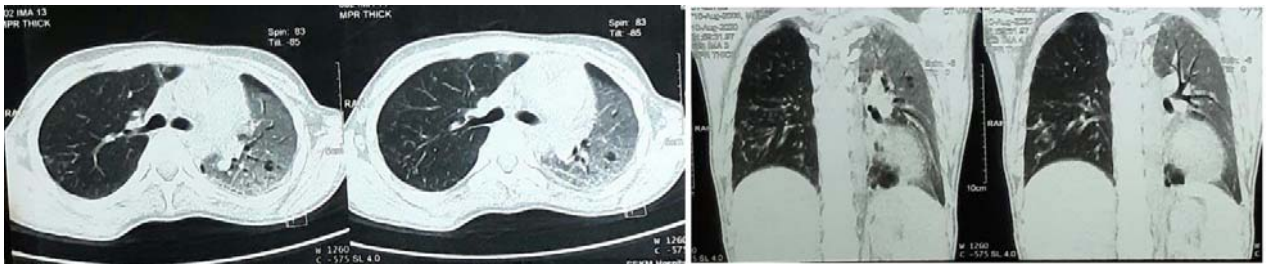

Fig 3 — HRCT Thorax

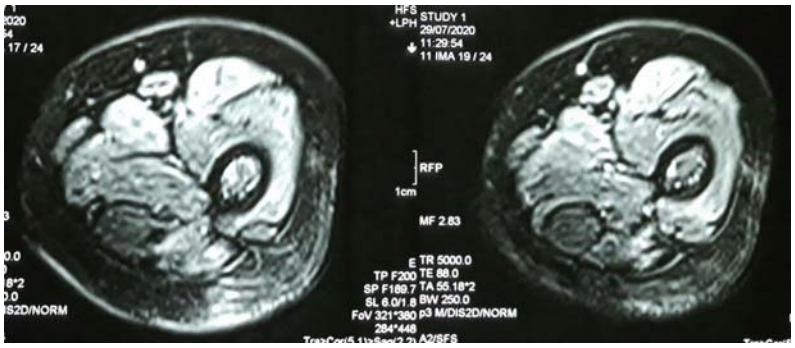

Fig 4 — MRI Thigh suggestive of myositis

Table 1 — *Laboratory reports of the patient*

Parameters	Observed Value	Reference Range
Hemoglobin	10.1 gm/dl	12 - 16 gm/dl
Total leucocyte count	25000 / mm^3	4000 - 11000 / mm^3
Platelet count	150000 /mm^3	150000-400000 / mm^3
Total Bilirubin	0.3 mg/dl	<0.8 mg/dl
ALP	47 U/L	<240 U/L
AST (SGPT)	20 U/L	<40 U/L
AST (SGOT)	136 U/L	<40 U/L
LDH	1200 U/L	<150 U/L
Serum aldolase	23 U/L	1.2-8.8 U/L
CPK	70 U/L	30-135 U/L
Urea	25 mg/dl	15-40 mg/dl
Creatinine	0.5 mg/dl	0.5 - 1.1 mg/dl
Urinary Albumin	(+)	Nil
24 hr urinary protein	770 mg	<150 mg
C3	116 mg/dl	90-180 mg/dl
C4	35.3mg/dl	10-40 mg/dl
Anti CCP	<1 RU/ml	<5 RU/ml
Anti dsDNA	17.62 IU/ml	<100 IU/ml
RF	9.5 IU/ml	<10.4 IU/ml
CRP	2 mg/dl	<0.6 mg/dl
ANA	Negative (1:160)	Negative
ANCA	Negative (1:10)	Negative
Myositis Profile	MDA5 positive	Negative
	MI-2 beta weak positive	Negative
Ferritin	729 ng/ml	12-150 ng/ml

gene[5,6]. Autoantibodies against it are found in DM patients presenting with a symmetric polyarthritis, clinically similar to rheumatoid arthritis. These patients often have features of the antisynthetase syndrome, but in the absence of antisynthetase autoantibodies.

The first symptom in majority of the patient with MDA5 positive patients is appearance of characteristic dermatomyositic rash. Most anti-MDA5 positive patients had overt clinical myopathy and ILD[12] with poor prognosis due to rapidly progressive interstinal lung disease[4] (RP-ILD). According to the International Consensus Statement on Idiopathic Pulmonary Fibrosis of the American Thoracic Society and the European Respiratory Society RPILD, including acute/subacute interstitial pneumonia, is a progressive deterioration associated with ILD within 3 months[13]. The frequency of ILD and Rapidly Progressive-ILD was higher in patients with anti-MDA5 Ab than those without (ILD: 100% *versus* 74%; $p < 0.01$, Rapidly Progressive-ILD: 71% *versus* 6%; $p < 0.01$)[11]. Sei-ichiro MOTEGI *et al* found that the cutaneous manifestations are more prominent in patient with RP-ILD compared to ILD (Gottron's papules/signs 96.4% *versus* 74.4%, Palmar violaceous macules 82.1% *versus* 25%, Antihelix/helix violaceous macules 40.7% *versus* 18.6% , skin ulcers 25% *versus* 8.6%)[12] and such finding was also observed in our patient however cutaneous manifestations might not be associated with the prognosis of RP-ILD in DM patients with anti-MDA5 Ab.

According to study by J Tomasova *et al* invasive procedure such as muscle biopsy may not be required in case of MRI findings suggesting obvious feature of myositis[14] and hence muscle biopsy was not done in our patient as along with MRI findings there was elevated blood markers for myositis with positive myositis profile study. ILD which is often severe, includes treatment with cyclophosphamide therapy and in refractory cases CD 20 antagonists such as rituximab[7].

A recent meta-analysis by Li L, Wang Q, Yang F *et al* has shown anti MDA5 autoantibodies have a good

sensitivity (83%) and specificity (86%) for identifying the risk of Rapidly progressive-ILD in this subset of patients[8] and hence anti-MDA5 antibodies have been proposed as a useful surrogate marker of disease activity[9]. Gono *et al* also found that a serum ferritin cut-off value of 1600 ng/mL was the best indicator of survival among 14 anti-MDA5 antibody-associated ILD patients. In their study, no death was reported during a 60-month follow-up among patients with ferritin levels <500 ng/mL[10]. In another report by Allenbach and coworkers, there is the possibility that variant inducible NOS expression might be a biomarker for a milder pattern of myositis associated with anti-MDA5 production and observed that the presence of NOS2 expression on anti-MDA positive patients has association with markers of muscle regeneration as it has been suggested that inducible NOS expression might play a role in healing healthy muscle tissue that has been damaged[15].

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National President Dr. J. A. Jayalal & Hon. Secretary General Dr. Jayesh Lele met Hon. Minister of State in the Ministry of Health and Family Welfare Dr. Bharati Pawar and discussed about IMA demands. She patiently heard all the issues and assured to follow up.