An Atypical Case of Dermatomyositis Associated with Clear Cell Renal Cell Carcinoma

Sir,

A 43-year-old male without any co-morbidity presented with acute onset and progressive weakness of bilateral upper and lower limbs. Two weeks before presentation to us, he had developed a fever with generalized body aches. Two days into fever, he was unable to lift both hands above shoulder. At around the same time, he noticed difficulty in getting up from a squatting position. The weakness was progressive, and in a week's time, he was unable to stand even with support. He became bed-bound and needed constant nursing care and attention. A non-itchy reddish purple rash was noticed over the upper chest, back, and bilateral shoulders.

He was presented to us two weeks after the onset of the illness. Examination revealed a conscious, cooperative patient with a maculo-papular rash over the upper chest, back, and both shoulders [Figure 1a]. Muscles were tender on palpation; no thinning was noticed. Power in bilateral proximal upper limbs was Medical Research Council (MRC) Grade 2/5 and distally, it was 4/5, symmetrically. In the lower limbs, power proximally was 2/5 and distally 4/5, symmetrically. Deep tendon reflexes were symmetrically normal and also sensory examination.

Clinically, the possibility of inflammatory myopathy was considered, likely dermatomyositis (DM) or viral myositis. Investigations revealed a normal hemogram [Table S1], with elevated serum aspartate transferase (713 U/L, N <41 U/L) and alanine transferase (295 U/L, N <40 U/L). Serum creatine kinase (CK) was highly elevated (22,000.00 U/L, N–39-308 U/L). Electromyography showed a myopathic pattern with evidence of spontaneous activity in both upper and lower limb muscles. Muscle biopsy showed maintained fascicular architecture with mild endomysial inflammatory infiltration comprising an admixture of CD4 and CD8 lymphocytes [Figure 1b, 1c]. A skin biopsy from the site of rash showed mild mononuclear cell infiltrate without any evidence of basal cell degeneration or active vasculitis [Figure 1d]. Based on these findings, diagnosis of DM was made. He was started on pulse methylprednisolone 1000 mg intravenous for five days, followed by oral steroids at 1 mg/kg/day. Subsequently, there was improvement in muscle power, and within the next one-week, power in the proximal bilateral upper and lower limbs improved to MRC grade 4/5 and distally to MRC grade 5/5, symmetrically. There was a concurrent reduction in serum CK levels (4740 U/L at four weeks).

^{18}Fluoro-deoxy-glucose positron emission tomography (FDG PET) screening for underlying occult malignancy revealed an FDG avid solid nodule with well circumscribed margins and measuring 2 cm in diameter with contrast enhancement in the lower pole of the right kidney [yellow arrows in Figure 1e]. An elective laparoscopic right partial nephrectomy was performed after four weeks. Histopathology of the excised sample showed tumor in sheets with round to polygonal shaped cells with abundant clear cytoplasm, consistent with the morphology of clear cell renal cell carcinoma (RCC) [Figure 1f]. The patient made an uneventful recovery from surgery and was discharged on Mycophenolate Mofetil (MMF) 500 mg twice daily and oral prednisolone 30 mg once daily.

At six-month follow-up, the patient had made a complete recovery and there were no post-surgical complications either. Power was MRC grade 5/5 in all four limbs, and the rash had completely resolved. CK at the last follow-up was 154 U/L, a remarkable decline. The patient was modified Rankin score 0, having resumed his job and routine day-to-day activities.

DM is a rare inflammatory muscle disorder with estimates in the general population ranging from two to nine in every 100000 person per year.[1,2] The association of DM with RCC is rare.[3] A literature search revealed only 10 case reports prior to this. A clinic-pathological comparison between the cases described and the present case is depicted in Table S2. In the present case, there was remarkable recovery following right renal partial nephrectomy, both clinically and in the values of serum CK. Six of the eight previously reported cases for whom full text was available [3-8] had shown persistent clinical improvement following removal of the underlying renal lesion, with four of these reporting concurrent decline in the CK levels [Table S2].[5,3,6,7] The rest of the two cases,[9,10] reported either no improvement[9] or recurrent relapse.[10] Notably, the 72-year-old

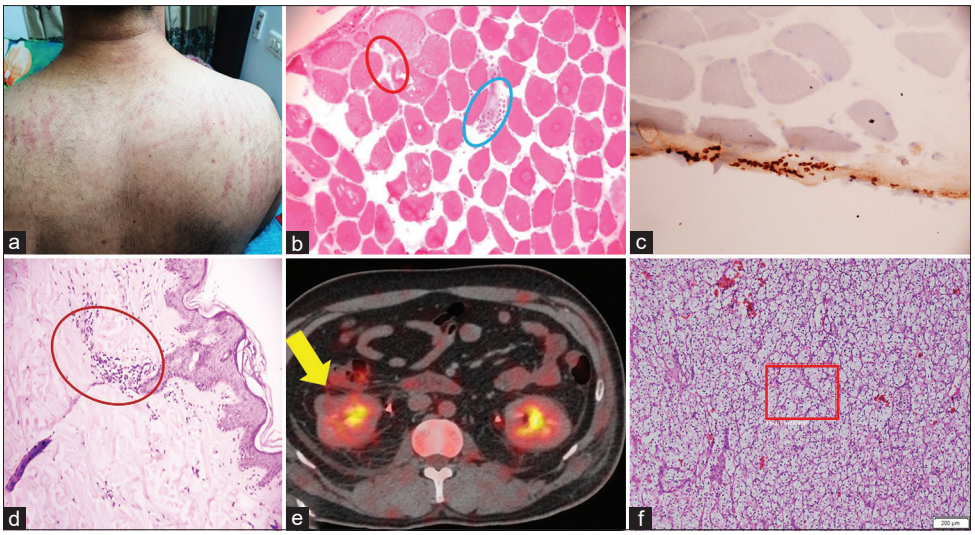

Figure 1: Showing histopathology photomicrographs of the muscle, skin, and right renal mass biopsy specimens and the PET scan images. A maculopapular non-itchy rash was noticed over the back (1a). Photomicrographs of the muscle biopsy showing maintained fascicular architecture (H and E, 40x) with myofibers showing mild variation in size long with few degenerated fibres (1b, red oval) and mild endomysial inflammatory cell infiltrate (1b, blue oval; H and E, 200x), with an admixture of CD4 and CD 8 positive lymphocytes (1c). Photomicrographs of skin biopsy showed no evidence of basal cell degeneration or active vasculitis (1d, maroon oval; H and E, 200x). PET showing FDG avid solid nodule with well circumscribed margins and measuring 2 cm in diameter (yellow arrrow in 1e) with contrast enhancement noted in lower pole of right kidney suggestive of renal cell carcinoma. No FDG avid retroperitoneal lymph nodes noted. Microscopic image of the excised renal lesion showing round to polygonal shaped cells with abundant clear cytoplasm, consistent with the morphology of clear cell RCC (1f, red rectangle; H and E, 100x)

female reported by Ofori *et al*.,[9] had multiple other malignancies apart from RCC, which may have contributed to the persistence of symptoms of DM. The 27-year-old male with recurrent relapses had antibodies to NXP–2 during follow-up re-evaluation.[10]

Perifascicular atrophy on muscle histopathology, which is considered characteristic of DM, was reported in two of the ten cases [Table S2, column 8].[5,10] In the majority of the cases (five out of ten) described muscle fiber inflammatory infiltration similar to the present case, while in the rest of the three, no description was given. The present case, though notable for its lack of perifascicular atrophy and classic rash, had all other clinical and biochemical and electromyographic features suggestive of DM. In all the reported cases, renal cell mass was promptly treated with either excision or, if unfit for surgery, with ablation or chemotherapy.

Focal incidental renal lesions are commonly encountered on PET/computed tomography (CT) imaging. The vast majority of these lesions are benign.[11] Needless to say; in the present case also, the small right renal mass was initially considered as an incidental finding, possibly unrelated to the clinical picture of the patient. It is yet to be discovered whether an antibody or any other biochemical marker directly links RCC with DM. However, in all the cases described in the literature, any renal mass detected on a malignancy screen, which pre- or post-dated DM and underwent definitive treatment, resulted in clinical improvement in most patients [Table S2]. Accordingly, the urology team was pursued to operate on the malignancy as early as possible. The clinical and laboratory courses after nephrectomy showed that it was highly probable that DM in the present case was a paraneoplastic event. Clinicians should have a high degree of suspicion if they encounter an incidental renal mass in patients with DM, and instead of considering it as an incidentaloma, early removal of the lesion is most likely to result in clinical improvement. At the same time, more and more such cases need to be reported, such that better diagnostic and specific biochemical markers may be uncovered, resulting in early diagnosis and treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 03-Sep-2022 **Revised:** 30-Sep-2022 **Accepted:** 13-Oct-2022
Published: 03-Dec-2022

DOI: 10.4103/aian.aian_748_22

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Table S1: Showing initial investigations done in the present case after hospitalization with us

Tests, Units	Patient's value	Normal Range
Hemoglobin, g/100 mL	13.8	12.00-18.00
Total Leukocyte count, X 10^3/L	7.44	4.00-11.00
Differential Leucocyte Count, %		
Neutrophils	77.3	40.00-80.00
Lymphocytes	10.5	20.00-40.00
Monocytes	9.9	2.00-10.00
Eosinophils	2.2	1.00-6.00
Total Platelet Count, X 10^9/L	150	130.00-400.00
C- Reactive protein, mg/dL	1.3	<0.5
Serum Urea, mg%	16	15-50
Serum Creatinine, mg%	0.4	0.5-1.2
Serum Sodium, mEq/L	139	136-146
Serum Potassium, mEq/L	3.8	3.5-5
Serum Calcium total, mg%	8.7	8.5-10.5
Serum Phosphorus, mg%	4.4	2.5-4.5
Serum Total Bilirubin, mg%	0.19	0.3-1
Serum Aspartate Aminotransferase, (AST) I.U.	713	0-50
Serum Alanine Aminotransferase, (ALT) I.U.	295	0-50
Serum Alkaline Phosphatase, I.U.	92	80-240
Total Serum Protein, gm%	4.8	6.4-8.3
Serum		
Albumin, gm %	2.7	3.5-5.2
Globulin, gm %	2.2	3.8-4.0
Serum Gamma Gluatmyl transferase, U/L	182	8-61
Serum uric acid, mg/dL	2.8	3.4-7.0
Lactate dehydrogenase, U/L	835	135-225
Myoglobin, ng/mL	2778	23-72
Creatine Kinase (CK), U/L	>22,000	0-25
Total Cholesterol mg/dL	141	<200
Triglycerides, mg/dL	247	<150
VLDL – C, mg/dL	49	0-40
LDL-C , mg/dL	55	<100
HDL – C , mg/dL	36	>55
Serum Ferritin , mg/dL	1699	30-400
Vitamin B12 ,	359	197-771
Thyroid Stimulating Hormone, uIU/ml	2.95	0.27-4.20
T3, ng/dL	113	80-200
T4, ug/dL	7.6	5.1-14.1
Fasting Plasma Glucose, mg/dL	108	70-110
Serum Ceruloplasmin, mg/dL	26.3	20-60
Rheumatoid Factor, IU/mL	Negative	0-20
HbA1c, %	6.10	4.8-5.6
HIV 1, 2	Negative	
Anti HAV IgM	Negative	
Anti HEV IgM	Negative	
HBsAg	Negative	
Anti HCV Ab	Negative	
IgM Anti HBc	Negative	
PT, sec	9.7	9.70-12.70
INR	1.03	
Antinuclear Antibodies Hep 2	Negative	
Anti- ds DNA, IU/mL	5	0-100
Complement C3, md/dL	83	90-180
Complement C4, mg/dL	42	10-40
Anti-Neutrophilic Cytoplasmic Antibody (ANCA)	Negative	

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Table S1: Contd...

Tests, Units	Patient's value	Normal Range
ENA profile (nRNP-Sm, Sm, SS-A, Ro-52, SS-B, Scl-70, PM-Scl 100, Jo-1, Ribosomal P -Protein)		
Neuronal (paraneoplastic) Autoantibodies profile (Amphiphysin, CV2.1, PNMA2 (ma2/Ta), ANNA-1/Hu, ANNA-2/Ri, PCA-1/Yo)	Negative	
Myositis profile (Serum, Immunoblot), - Mi-2, Ku, PM-Scl 100, PM-Scl 75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, R0-52	Negative	

ds- DNA – Double stranded deoxyribonucleic acid, ENA – Extra Nuclear Antigen, HbA1c – Glycosylated Hemoglobin, HIV – Human Immunodeficiency Virus, HAV – Hepatitis A Virus, HEV – Hepatitis E Virus, HDL – high density lipoprotein, INR – International Normalized Ratio, LDL – Low Density Lipoprotein, VLDL – Very low density lipoprotein

Table S2: Depicting a comparison of demographic profile, clinical characteristics, biochemical parameters, electromyographic, histopathology findings, treatment and follow-up characteristics of the cases reported in literature and the present case, arranged in a descending order (all are case reports only)

Author, Year	Age in years, Race/ethnicity, Sex	Any co-morbidities	Clinical Presentation	CPK at presentation and other pertinent biochemical abnormality	EMG	Histopathology on muscle/ skin Biopsy	Initial Treatment given	Improvement
Present case, 2021	43, male, Indian	Nil	Progressive proximal muscle weakness, with maculo-papular rash over the upper chest and back. Myalgia No grotton's papules, no heliotrope rash.	CK - > 22000 U/L ANA, ANCA, myositis panel, paraneopalstic panel - negative	Myopathic with spontaneous activity	Muscle - Maintained fascicular architecture with mild endomysial inflammatory infiltration comprising of an admixture of CD4 and CD8 lymphocytes. Skin biopsy - mild mononuclear cell infiltrate without any evidence of basal cell degeneration or active vasculitis.	IV MPS 1000mg for 5 days followed by oral prednisolone 60mg , the taper 10mg every 4 weeks. Tab MMF 500mg BD	Yes
Kyaw *et al*., 2017	72, male	Clear Renal cell carcinoma 3 months back - interventional radiology–guided renal artery chemoembolization	1 month – generalized weakness and dysphagia. Walked with support. No skin lesions.	CK – 3222 U/L	-	Muscle - Perifascicular myofiber atrophy with perivascular infiltrates of chronic inflammatory cells	AZA 50 mg OD IV MPS 80 mg	Yes
Ofori *et al*., 2017	72, female	Renal clear cell carcinoma, breast cancer, papillary serous carcinoma of uterus	progressive weakness, 30-pound weight loss, and dysphagia over the past 3 months. Periungual hyperemia. No Heliotrope rash or grotton's papules.	CK – 3222 U/L ANA positive		Muscle - Inflammatory myositis with severe necrotizing component with targetoid changes on NADH-TR stain	-	-
George *et al*., 2016	27, Caucasian male Caucasian	Nil	Myalgia, proximal muscle weakness, dysphagia – 7 month. Cuticular and periungual erythema , No grotton's papules, no mechanic's hands. Dermatomyositis sine myositis.	CK - 26000 U/L, Positive ANA Myositis, paraneoplastic panel – negative.	Myopathic with Spontaneous activity	Muscle - Initial Biopsy - Non – diagnostic (no features mentioned) Muscle - Second Biopsy – macro-phagocytosis, peri-fascicular atrophy.	Prednisolone – 60 mg/day. IVIG Mtx- 25mg/week.	No
Adili *et al*., 2015	69, male	HTN, Osteoporosis, and GERD	Grotton's papules, Musculoskeletal system normal	-	-	Skin - cellular changes consistent with dermatomyositis	Prednisone, Hydroxychloroquine	-
Nevins *et al*., 2013	77, Caucasian Female	Rheumatoid Arthritis	Gottron papules, heliotrope rash and proximal muscle weakness – 4 months	CK - >6000 U/L Positive ANA	Myopathic with Spontaneous activity	Muscle - muscle fibre infiltration by lymphocytes and macrophages associated with muscles fibres necrosis	high dose steroids and IV-IG	No

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Table S2: Contd...

Author, Year	Age in years, Race/ethnicity, Sex	Any co-morbidities	Clinical Presentation	CPK at presentation and other pertinent biochemical abnormality	EMG	Histopathology on muscle/ skin Biopsy	Initial Treatment given	Improvement
Szwebel *et al*., 2008	77, male	Nil	Muscle proximal weakness with myalgia.	CK - 35634 U/L. ALT – 388, AST – 850 ANA - negative	Myogenic in all 4 limbs.	Muscle - pericapillary and perivenular inflammatory infiltrates in the interstitial tissue and C5b-9 deposits on the endomysial muscle capillaries	IV corticosteroids. IVIG	Yes
Schaefer *et al*., 2004	71, female	Nil	Poikiloderma, dysphagia, Cardiopulmonary dysfunction, fatigue and muscle weakness. Immobile.	CK -1966 U/L	-	-	Steroid	No

Author, Year	Malignancy screen	Management of the implicating lesion	Histopathology findings of Biopsy or the excised lesion	Maintenance therapy	Follow- up				
					Duration	CPK U/L	Clinical	Medications at follow-up	Relapses
Present case, 2021	Right renal mass of 2 cm in diameter	Laparoscopic partial nephrectomy	Tumour in sheets with round to polygonal shaped cells with abundant clear cytoplasm, consistent with clear cell Renal Cell Carcinoma (RCC).	40 mg , the taper 10mg every 2 weeks.	Six months	154 U/L	Power 5/5 in all 4 limbs , all rash had disappeared. No myalgia. Patient had resumed his job and routine day to day activity.	Tab MMF 500mg BD	Nil
Kyaw *et al*., 2017	No residual lesion in kidney	-	-	50 mg with a tapering dose of 5 mg/d for a period of 10 days	4 weeks	699 U/L	Steady improvement of her weakness. Tolerated oral liquid diet	AZA 50mg OD	Nil
Ofori *et al*., 2017	No recurrence	Status post chemotherapy completed 5 months prior	-	IV corticosteroids	-	-	No improvement	Percutaneous gastrostomy tube was place d.	-
George *et al*., 2016	Right renal mass of 2 cm diameter	Nephrectomy	Chromophobe renal cell carcinoma Grade 1	IVIG PLEX MMF 1500mg BD.	4 years	-	Recurrent flares – repeat myositis panel – antibodies to NXP-2	IVIG, AZA	Recurrent
					2 years later	-	Flare – proximal myopathy with grotton's papules and heliotrope rash. WB PET – negative	Anakira – ADR – stopped Then on 15 mg/day prednisone	

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Table S2: Contd...

Author, Year	Malignancy screen	Management of the implicating lesion	Histopathology findings of Biopsy or the excised lesion	Maintenance therapy	Follow- up				
					Duration	CPK U/L	Clinical	Medications at follow-up	Relapses
Adili *et al*., 2015	Left renal mass of 5.8 cm in diameter.	Left radical nephrectomy.	Clear cell renal cell carcinoma, Fuhrman grade 3/4.				Resolution of cutaneous lesions.		Nil
Nevins *et al*., 2013	Left renal mass of 4 cm in diameter	Laparoscopic nephrectomy 4 weeks after presentation	clear cell renal cell carcinoma with focal nuclear changes. Fulham grade 2.	steroids and monthly IV IG.	4 weeks	CPK - <200 U/L at	Improving muscle power. No rash. mRS – 0 at 6 months	Prednisolone	Nil
Szwebel *et al*., 2008	Mass in the left kidney	Left nephrourectomy and ganglial curettage	Urothelial carcinoma	-	7 days	Normal (value not mentioned)	Clear clinical improvement	-	Nil
Schaefer *et al*., 2004	Left renal mass of 6 cm in diameter	arterial embolization and CT guided percutaneous RFA	Renal cell carcinoma	Steroid	1 week	8 U/L	Patient mobile , dysphagia improving	-	Nil
Shinohara *et al*.,2005	Solid mass in the pelvis of the left kidney.	radical nephroureterectomy and retroperitoneal lymphadenectomy	moderately differentiated adenocarcinoma,	Prednisolone 30mg/day.	6 months	-	Walk by himself Rash disappeared completely	-	Relapse of malignancy but no relapse of dermatomyositis.
Pamies *et al*., 1997									
Triginer *et al*., 1989									

AZA - Azathioprine , ANA- , ANCA- Anti Neutrophilic Cytoplasmic Antibody , BD – twice daily , CK- Creatine Kinase, CT – Computed tomography, EMG- Electromyography, IV - Intravenous, IV IG- Intravenous Immunoglobulin, MPS- Methylprednisolone, MMF – Mycophenolate Mofetil , Mtx - Methotrexate, NADH-TR – Nicotinamide Adenine dinucleotide Dehydrogenase Tetrazolium Reductase, OD – Once daily , PLEX - Plasmapheresis, RFA – Radio Frequency Ablation