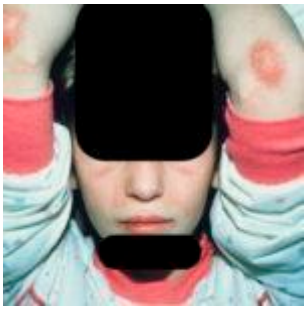
A 7 year old with severe muscle weakness and difficulty walking



Patient presentation

A 7 year old female presents with a three week history of painful elbows, wrists and hands, generalised weakness and difficulty walking.

Acknowledgement

This case study was kindly provided by Dr Bhadrish J Mistry, Paediatrician, Department of Paediatrics, Chris Hani Baragwanath Hospital and the University of Witwatersrand.

Partnership

We have partnered with The International Union of Basic and Clinical Pharmacology (IUPHAR) to bring you in-depth

information about drugs and pharmacology with links to the Guide to ImmunoPharmacology.

History

- Painful elbows, wrists and hands for 3/52
- Sore throat
- No early morning stiffness, but a generalised weakness and family reports that she is “walking funny”
- First episode of any illness, otherwise previously well
- No history of rash, fever, headache or abdominal pain
- No chronic medication or traditional medicines, no medication taken for these symptoms
- No known allergies

Past Medical History:

- No previous hospital admissions
- No major illness
- No history of TB

Family history:

- Patient is an orphan. Father died in a work related accident 4 years ago, with some lower limb weakness reported at the time (details not available). Mother died of a brain tumor 2 years ago
- Child has still not come to terms with loss of her parents, often quiet and withdrawn

Social History:

- Grandmother is primary care giver
- Lives in house with all amenities
- Currently at school in grade 2

Differential Diagnosis

- Oligoarthritis- evolving juvenile arthritis
- Myositis- idiopathic or infective
- Dermatomysositis- no rash, no calcinosis on history
- Systemic Lupus Erythematosus
- Neuromuscular disease
- Muscular dystrophy

Examination

- Pleasant co-operative child
- Growing well, 25th centile for height and weight (23 kg and height 120 cm)
- Vital signs are normal
- Mild pallor observed in conjunctiva and palms
- Oedema of the face with periorbital puffiness and a swollen upper lip
- Bilateral oedema of the elbows, knees and shins
- No clubbing present
- Shotty generalised lymphadenopathy found in anterior and posterior cervical nodes, axillary nodes and inguinal nodes.
- Heliotrope rash on left eyelid
- Capillary changes in nail bed, no other skin lesions

Chest

- No chest deformity, trachea central and good bilateral air entry.

CVS

- No precordial bulge, no heaves or thrills, apex beat in 6th intercostal space mid axillary line. Normal heart sounds, no murmurs.

Abdomen

- Soft, non-tender, no ascites

Central nervous system

- Alert and awake higher function is appropriate
- No muscle wasting
- Decreased tone, cannot sit up in bed unassisted
- Decreased reflexes bilaterally upper and lower limbs
- Decreased power, bilaterally, upper and lower limbs
- No clonus

Musculoskeletal system

- Generalised weakness, more proximal than distal
- Waddling gait, leans to right when walking
- Gower's sign present

Investigations

WCC	**6.19**	**(4.5 – 13.5)**
HB	10.3	(11.5 – 13.5)
MCV	86.1	(75 – 87)
HCT	0.31	(0.34 – 0.40)
RDW	0.13900000000000001	
PLTS	380	(150 – 550)
Neutrophils	0.81200000000000006	(absolute 5.03) N
Lymphocytes	0.11899999999999999	(absolute 0.73) L
Monocytes	6.3E-2	(absolute 0.39) N
ESR	74	
CRP	9.8000000000000007	
NA	138	
K	3.7	
Cl	103	
Co2	20	

WCC	**6.19**	**(4.5 – 13.5)**
Urea	4.0999999999999996	
Creatinine	33	
C3	1.02	
C4	0.307	
RF	<11.0	
ANA	Positive	8.3333333333333329E-2
CK	6954	
TP	67	
Albumin	26	
Globulins	41	
Alk Phos	77	
GGT	18	
AST	242	
ALT	84	
LDH	2663	
Ca	2.44	
Mg	0.79	
P04	1.4	
Anti-DS-DNA	Negative	
ASOT	452	(0 – 250)
Muscle Antibodies		
Ribonuclear protein	Negative	
Anti-sm ab	5	
Anti-Ro	7	
Anti-Ha	2	
Anti-Jo-1	Negative	
Free T4	13.8	(11 – 18.8)

WCC	6.19	(4.5 – 13.5)
TSH	4.9400000000000004	(0.48 – 4.67)
Vit B12	301	(145 -637)
Red cell folate	1617	(924 – 3337)

- Abdominal ultra sound – normal
- ECG- normal
- Chest X-ray: normal
- PPD- negative
  Childhood myositis assessment scale (CMAS) score = 14/52, indicates low muscle strength and low endurance.
- Muscle biopsy – features are those of an inflammatory myopathy.
- EMG- of biceps brachii , shows axonopathy
- MRI of thighs- confirmed myositis

Discussion

Initial Management

Patient was initially treated with polygam 2g/kg twice a week and oral steroids (meticorten) 2mg/kg daily. Physiotherapy and Occupational therapy were prescribed daily and she was assessed by a dietician for nutritional support.

Progress

Week 1-3

For the first three weeks of treatment the patient reported feeling better, with joint swelling and pain resolving. She still complained of proximal muscle weakness but this had also improved since admission.

Week 3-4

After three weeks the patient started feeling unwell again with proximal weakness worsening and unable to move from a lying to sitting position without assistance. She also started drooling excessively and was reluctant to eat.

Management

A Barium swallow was ordered but was normal. Treatment with polygam and oral steroids was continued. Muscle biopsy was ordered with showed an inflammatory myopathy.

Progress

Week 5

Patient continues to deteriorate. Developing bulbar speech and inability to swallow.

Management

Patient was intubated and admitted to medical ICU for intermittent positive pressure ventilation (IPPV). She was continued on treatment with polygam, also given methyl prednisone IV and 15 mg of Methotrexate sub cutaneously.

Progress

Week 6

Patient continued to deteriorate. ESR, CRP and CK levels remained elevated. She also developed pseudomembranous colitis (treated with metronidazole) and MRSA sepsis (treated with meropenem and Vancomycin). Child had a cardiac arrest and was successfully resuscitated.

Management

Tracheostomy was placed and Rituximab therapy, a monoclonal antibody was started.

Progress

Week 8

Patient started to respond to treatment showing steady improvement, able to sit up unassisted and move arms, head and feet.

Management

Patient was released from ICU to high care. Nerve conduction studies were done which showed a secondary axonopathy. Treatment and therapy were continued

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Final outcome

For two weeks post ICU the patient continued to improve steadily. She then developed a nosocomial pneumonia for which she was successfully treated and thereafter continued to improve.

At the start of the third week she started gasping, resuscitation attempts failed and the patient died 11 weeks post admission.

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Evaluation – Questions & answers

What is the diagnosis?

Juvenile dermatomyositis (JDMS), which is a systemic vasculopathy affecting primarily the skin and muscles. Females are affected twice as often as males and there are typically two peak ages of onset; adults at 50 years and children at

5-10 years. This is typically a small vessel vasculitis which can also affect the GIT (especially the oesophagus), myocardium and lungs. Calcinosis is a complication that is observed most often in children or adolescents. The weakness experienced is variable. It can have a gradual onset with slowly progressive weakness or it can be catastrophic with severe weakness (or paralysis) with swallowing abnormalities and myocarditis. The prognosis depends on the severity of the myopathy, the presence of a malignancy, and/or the presence of a cardiopulmonary involvement.
Diagnosis is also based on a set of the following criteria proposed by Bohan and Peter; where the presence of three of the findings listed indicates probable myositis; four indicates myositis and diagnosis of juvenile dermatomyositis requires the skin changes mentioned in point 5 (see below).

- Proximal muscle weakness (upper or lower extremity and trunk); typically symmetrical
- Elevated serum creatine kinase (CK) or aldolase levels
- Muscle biopsy showing inflammation, damage or other characteristic changes in muscle tissue
- Myopathic changes on electromyogram (EMG)
- Skin rash

– Heliotrope rash (reddish-purple erythema on the upper eyelids, often with oedema)
– Gottron's sign (reddish-purple nodules on the extensor surface of finger, elbow or other joints)

What is believed to trigger the autoimmune response in dermatomyositis?

In dermatomyositis an autoimmune reaction is thought to be triggered by an initial infection with a pathogen expressing protein antigens similar in structure to a membrane protein found on capillary endothelial cells in muscle and skin. Initially a normal immune response occurs which is initiated by phagocytes such as dendritic cells that engulf the pathogen and later present the pathogen-derived peptide antigens to naive CD4+ helper T lymphocytes in the lymph node for activation.

Where is the autoimmune reaction in dermatomyositis first triggered?

A normal antibody response to a pathogen that triggers an autoimmune reaction in dermatomyositis is first initiated by follicular dendritic cells in the B cell zone of the regional lymph node. These cells trap pathogen-derived antigens on there surface and present them to naive B cells for priming.

What is a normal antigen specific B lymphocyte activation?

Primed B lymphocytes are activated in the T cell zone by previously activated CD4+ helper T lymphocytes that recognise a peptide antigen derived from the same pathogen protein as recognised by the B cell. These CD4+ helper T cells have previously been activated by dendritic cells. Activated B lymphocytes then differentiate into plasma cells that secrete antibodies that will bind to the protein on the pathogen surface. The first antibody produced in a primary immune response is always IgM but later CD4+ helper T lymphocytes can also induce isotype switching to IgG antibodies of higher affinity.

What is the normal antibody mediated destruction process of a pathogen?

Class IgM and IgG antibodies are secreted and bind to the surface of the pathogen tagging them for destruction by the innate immune system. The components of this system include classical complement activation, antibody-dependant cell cytotoxicity mediated by natural killer cells and enhanced phagocytosis.

What antibody process occurs in dermatomyositis?

In dermatomyositis these antibodies trigger similar immune attacks on capillary endothelial muscle and skin due to the recognition of the these membrane proteins by the antibodies. This is because of structural similarities between a protein on capillary endothelial cells in muscle and skin and a protein antigen derived from a pathogen. These cells provide activation signals to autoreactive B cells that orchestrate autoimmune reactions that become self-perpetuating and do not require the presence of the initial triggering pathogen.

What are the processes which are involved in destroying the

capillary endothelial cells in dermatomyositis?

Bound antibodies on the surface of capillary endothelial cells in muscle and skin initiate an innate immune response which ultimately leads to destruction of these cells which include activation of the classical complement cascade antibody-dependant cell cytotoxicity and receptor-mediated phagocytosis. In skin this immune response is characterised by a rash.

In dermatomyositis what are the effects of destruction of the muscle cell capillaries

The destruction of the capillaries in muscle leads to necrosis of the muscle fibre cells and inflammation due to lack of oxygen and nutrient supply. The necrotic muscle fibre cells then attract dendritic cells and macrophages which engulf the muscle derived intracellular antigens resulting in secondary autoimmune antibody responses to muscle-specific antigens via activation of autoimmune B cells by autoimmune CD4+ helper T lymphocytes. There is an infiltration of CD4+ helper T lymphocytes and B lymphocytes into inflamed muscle that promotes phagocytosis and antibody production.

How is autoreactive B lymphocyte activation altered in dermatomyositis?

In normal immune responses, CD4+ helper T lymphocytes would not recognise self-peptides on HLA class II receptors because they would have been deleted in the thymus. However in dermatomyositis, a breakdown in this mechanism causes autoreactive CD4+ helper T lymphocytes that are able to recognise self-peptides on HLA class II receptors to escape from the thymus. These cells are then activated by dendritic cells and later by macrophages allowing them to provide T cell help to autoreactive B cells. Activation of the B cells thus leads to the generation of autoimmune antibody secreting plasma cells and new memory cells.The autoreactive antibodies continue to bind self-antigen on capillary endothelial cells leading to ongoing muscle destruction and skin inflammation as a consequence.

What are the aims of therapy and what therapy can be initiated?

Because the autoreactive antibodies continue to bind self-antigen on capillary endothelial cells with resulting muscle destruction and skin inflammation therapy must be targeted at this process. What has appeared to be successful is Rituximab an antiCD20 monoclonal antibody which removes B lymphocytes due to aiming therapy against CD-20 receptors.
Rituximab a monoclonal antibody therapy has been shown to have five possible mechanisms of action against dermatomyositis

CD20-induced apoptosis
Classical complement activation
C3b opsonisation and phagocytosis
IgG opsonisation and phagocytosis
Antibody-dependent cell cytotoxicity by natural killer cells

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