CASE REVIEW

Proximal muscle weakness and skin rash

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A 34 year old woman presented with a 9 day history of progressive proximal bilateral limb weakness and mild dysphagia with fluids. On examination, she had a peri-orbital rash (fig 1). Neurological findings included moderately severe (grade 3-4/5) bilateral proximal limb and neck flexor weakness with preserved deep tendon reflexes and sensation.

Her laboratory test findings were
- Serum creatine kinase of 35 766 U/L (reference range: 26-192 U/L)
- Positive anti nuclear matrix protein 2 antibody
- Weakly positive anti-nuclear antibody (1 in 80 titre) and negative anti-double stranded DNA antibody.

Fat suppressed magnetic resonance imaging (MRI) of the thigh muscles showed abnormal signals (hyperintensities) of the lateral, medial, and anterior compartments (fig 2).

Needle electromyography of the proximal arm and leg muscles showed fibrillation, positive sharp waves, and early recruitment of volitional motor unit potentials.

Questions

1. What is the diagnosis?
2. How would you manage this condition?
3. What is the relevance of the positive anti nuclear matrix protein 2 antibody?

Answers

1. What is the diagnosis?

Dermatomyositis—an inflammatory disorder involving the skin and muscles. Figure 1 shows dusky bilateral erythematous macular rashes in the slightly swollen peri-orbital regions. This is a heliotrope rash and is characteristic of dermatomyositis. The patient’s proximal limb weakness, mild dysphagia, preserved deep tendon reflexes, elevated creatine kinase, MRI findings (fig 3), and needle electromyography findings are also suggestive of myopathy.

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A muscle biopsy is useful for confirming the diagnosis of inflammatory myopathy, metabolic myopathy, and others.

How would you manage this condition?

Immunosuppressive medication. An initial high dose of steroid is followed by maintenance therapy, along with a long term steroid sparing agent such as azathioprine, methotrexate, cyclosporine, rituximab, or cyclophosphamide (the latter agent is required in steroid refractory cases).

Arrange physiotherapy, assess swallowing, and consider prophylaxis against aspiration and deep vein thrombosis.

Discussion

Dermatomyositis may present with a variety of cutaneous findings (box 1).

Box 1: Cutaneous signs of dermatomyositis

- Heliotrope rash
- Gottron papules
- Gottron sign
- Shawl sign or V sign
- Holister sign
- Reddish nail folds
- Mechanic hand

This patient had a heliotrope rash and the following findings suggestive of an acute myopathy:

- Proximal limb and neck flexor weakness and dysphagia of short duration
- Preserved deep tendon reflexes
- Absence of sensory abnormalities
- Elevated creatine kinase
- Hyperintensities (abnormally bright signals indicative of muscle oedema/inflammation) in the anterior, medial, and lateral compartments of bilateral thigh and hip muscles visible on fat suppressed MRI (fig 2)
- Early recruitment of volitional motor unit potentials on needle electromyography (spontaneous activity such as fibrillation and positive sharp waves result from muscle membrane instability in acute myopathy)

The absence of ptosis, diplopia, restriction of eye movements, and fatigable or fluctuating weakness rules out neuromuscular junctional disorder such as myasthenia gravis. Differential diagnoses of treatable acute myopathic disorders include

- Inflammatory myopathy (dermatomyositis and polymyositis)
- Hypokalaemic periodic paralysis
- Osteomalacic myopathy
- Drug induced myopathy (eg, statin- or steroid-induced myopathy)
- Rhabdomyolysis resulting from metabolic myopathy or other causes such as seizure, heat stroke, snake bite
- Thyrotoxic periodic paralysis, acute worsening of hypothyroid, and other endocrine myopathies.

In the diagnostic approach to a treatable myopathy:

- Check whether the patient’s history includes myotoxic medications such as statin, steroid, chloroquine, azidotethymidine, D-penicillamine, colchicine, or interferon alpha
- Consider the following laboratory tests: erythrocyte sedimentation rate, liver function test, thyroid profile, lactate, ammonia, cortisol level, renal parameters, serum electrolytes, bone profile and serum vitamin D, vasculitis panel, and myositis specific autoantibody panel
- A muscle biopsy is useful for confirming the diagnosis of inflammatory myopathy, metabolic myopathy, and others.

2. How would you manage this condition?

Immunosuppressive medication. An initial high dose of steroid is followed by maintenance therapy, along with a long term steroid sparing agent such as azathioprine, methotrexate, cyclosporine, rituximab, or cyclophosphamide (the latter agent is required in steroid refractory cases).

Arrange physiotherapy, assess swallowing, and consider prophylaxis against aspiration and deep vein thrombosis.
3. **What is the relevance of the positive anti nuclear matrix protein 2 antibody?**

Dermatomyositis can be a paraneoplastic manifestation of an underlying malignancy, especially in the context of a positive anti nuclear matrix protein 2 antibody. Careful clinical evaluation and imaging (eg, computed tomography imaging of chest, abdomen, and pelvis) for malignancy are required.

**Discussion**

A longitudinal cohort study on the association of cancer with anti nuclear matrix protein 2 antibody in dermatomyositis found a standardised incidence ratio (cancer risk standardised to that of the general population) of 8.14 (95% confidence interval: 1.63 to 23.86). The positive anti nuclear matrix protein 2 antibody in this case necessitates careful clinical evaluation and imaging (eg, computed tomography imaging of chest, abdomen, and pelvis or whole body positron emission tomographic imaging) for malignancy.

Other myositis specific autoantibodies include anti-transcriptional intermediary factor 1 \(\gamma\) (anti-TIF1-\(\gamma\)), anti-nucleosome remodelling deacetylase (anti-NuRD), anti-melanoma differentiation-associated gene 5 (anti-MDA 5), anti-small ubiquitin-like modifier activating enzyme (anti-SAE), anti-arnimoacyl tRNA synthetases (anti-Jo1 and other than anti-Jo1), anti-signal recognition particle antibody (anti-SRP) and anti-postmeiotic segregation increased 1 (anti-PMS1).

**Learning point**

In a patient presenting with a short duration of proximal limb and neck flexor weakness, dysphagia, preserved deep tendon reflexes and sensation, and hyperCKemia, extra-neurological findings, such as heliotrope rash or Gottron papules, can aid a diagnosis of dermatomyositis, a potentially treatable condition.

**Patient outcome**

Muscle biopsy findings in this patient included: the presence of inflammatory infiltrates (fig 4 A-C), perimysial accentuation of major histocompatibility complex-1 stain (fig 4 E), and the identification of endothelial tubuloreticular inclusions (fig 4 F). The overall clinical features and findings in muscle biopsy are consistent with the diagnosis of an inflammatory myopathy, namely dermatomyositis.

**Findings consistent with a diagnosis of inflammatory myopathy, namely dermatomyositis:** (A, B, C) Hematoxylin and eosin stained section of muscle shows perivascular lymphocytes (A, arrow) in perimysial location (stars) (×200), occasional myofibres with small vacuolar degeneration (B, arrows) (×400), and epimysial oedema, perivascular, and interstitial mononuclear inflammatory cell infiltrates (C) (×400). (D, E) Normal control (D) on major histocompatibility complex-1 immunohistochemical staining (×200) for comparison with (E), which shows mild sarcolemmal up regulation with characteristic accentuation of perifascicular myofibres (arrows) (×200). (F) Characteristic tubuloreticular inclusions (red arrows) are seen in the endothelial cells of scattered blood vessels on electron microscopic examination.

The patient had no systemic clinical or pertinent serological features of systemic lupus erythematosus or other vasculitis. Computed tomography imaging of chest, abdomen, and pelvis did not show any underlying malignancy or interstitial pneumonitis. After receiving a high dose steroid, she experienced a substantial improvement of her limb weakness and dysphagia.

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