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CASE REPORT

Hereditary transthyretin amyloidosis presenting with neuropathy and a bullous rash

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Introduction

Hereditary transthyretin amyloidosis usually presents with a painful, length-dependent neuropathy with autonomic features. Early recognition is increasingly vital because of the availability of genetic therapies. This article describes the case of a 67-year-old man presenting with a 5-year history of a mixed demyelinating/axonal neuropathy, who was initially presumed to have an inflammatory neuropathy. He also reported an unusual blistering rash of his extremities. Transthyretin genetics confirmed a V30M mutation, and sural nerve and skin biopsy both confirmed the presence of amyloid deposition. Bullous skin lesions are rarely described in systemic amyloidosis and only one prior case has been reported in hereditary transthyretin amyloidosis with a similar mutation. Bullous skin lesions and a compatible neuropathy should trigger suspicion of amyloidosis as the underlying disorder.

Case report

A 67-year-old man with no significant past medical history presented with a 5-year history of ascending lower followed by upper limb numbness without pain, followed by a gradual reduction in hand dexterity. He was an ex-smoker and had previously drunk significant amounts of alcohol but had reduced his intake in recent years.

Examination revealed normal cranial nerves, with wasting of the intrinsic hand muscles and distal lower limbs, with symmetrical bilateral upper and lower limb weakness (hand muscles MRC grade 2–4/5, ankle dorsiflexion 3/5 and plantarflexion 2/5 bilaterally). He was globally areflexic, with vibration lost to the right knee, left ankle and bilateral proximal interphalangeal joints in the hands. Pinprick sensation was lost to both elbows and mid-thighs. Romberg testing was abnormal at 1 second and he displayed pseudoathetosis of the upper limbs on eye closure in keeping with sensory ataxia.

Neurophysiology showed a severe sensory-motor neuropathy with conduction slowing and reduced amplitude, which was interpreted as showing a mixed demyelinating/axonal neuropathy. CSF analysis was acellular with a slightly raised CSF protein at 0.83 g/litre, a normal glucose ratio of 58%, and no oligoclonal bands. There was no evidence of a paraprotein on blood analysis.

The initial impression was a chronic inflammatory demyelinating polyradiculoneuropathy, and he was referred to a subspecialty neuromuscular clinic for further evaluation.

In recent years the patient had been noted to have a blistering rash of his extremities without any oral or genital lesions (Figure 1), which had been evaluated separately under the dermatology team. An initial blister biopsy was reported as possibly showing changes in keeping with trauma but no definite diagnosis was reached. A porphyria screen was also negative, as was a connective tissue disease screen and skin antibody testing. He also reported some Raynaud's-like symptoms with poor capillary refill, but thermographic testing with rheumatology and nail fold capillaroscopy were not diagnostic of a clear underlying systemic sclerosis spectrum disorder.

Owing to the combination of a neuropathy and rash, genetic testing for hereditary transthyretin amyloidosis was performed which confirmed a V30M mutation (where the valine in position 30 is replaced by methionine), in keeping with hereditary transthyretin amyloidosis. A sural nerve biopsy (Figure 2) and skin biopsy (Figure 3) confirmed the presence of amyloid deposition.

He was referred to the National Amyloid Centre for consideration of antisense oligonucleotide treatment.

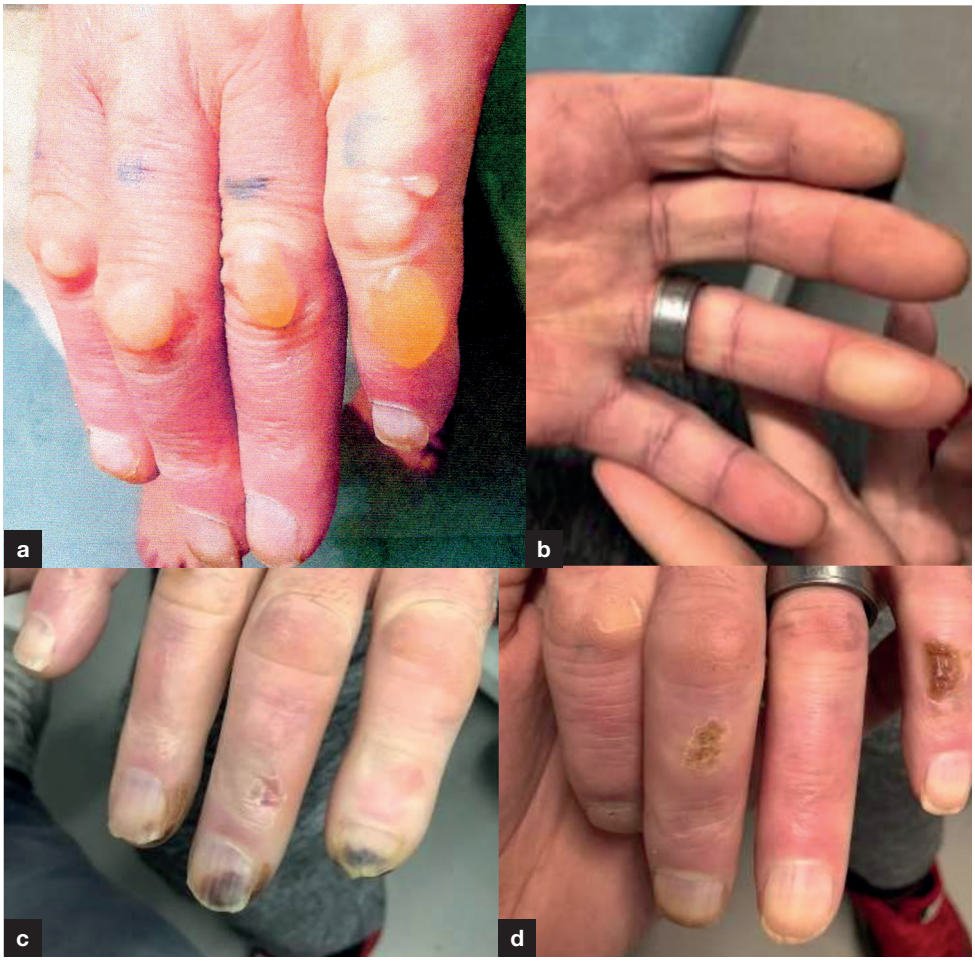

Figure 1. Photographs of the patient's hands demonstrating (a) a large blister on the dorsal aspects of the proximal interphalangeal joints of the left hand, (b) a further tense blister on the finger pad of the left fourth digit, (c) multiple crusted erosions on the dorsum of the hands and dorsal aspects of the fingers, (c and d) dystrophic nail changes and (d) purpuric areas under the fingernails and on his fingertips.

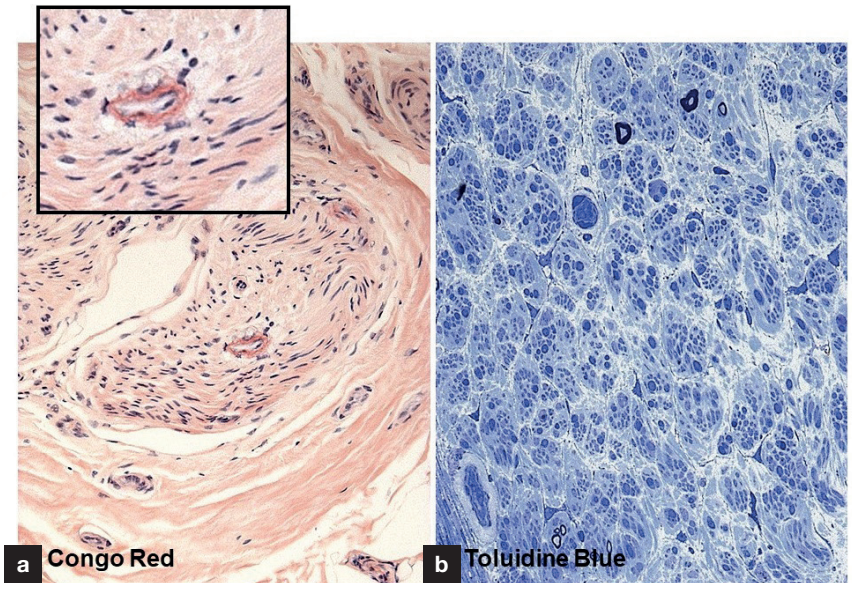

Figure 2. Right sural nerve biopsy displaying (a) faintly positive Congo red staining in epineurial arteries (inset). b. Toluidine blue semithin sections display fascicles almost entirely depleted of myelinated fibres, and reduced numbers of unmyelinated fibres with thickened endoneurial vessel walls and increase of endoneurial connective tissue.

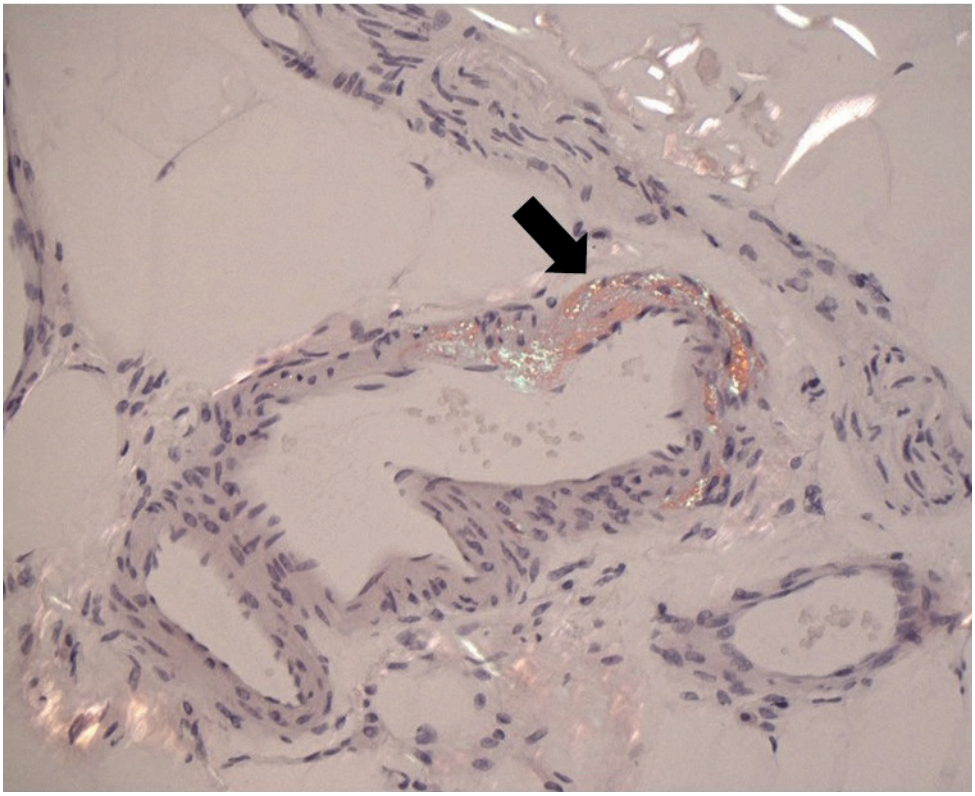

Figure 3. Incisional skin biopsy of the back displaying clear amyloid deposition in the dermal vessel walls (arrow).

Discussion

This article reports a case of a patient in his 60s with bullous skin lesions and a progressive sensory–motor neuropathy caused by hereditary transthyretin amyloidosis of the V30M mutation.

Hereditary transthyretin amyloidosis is the most prevalent type of hereditary amyloidosis, with more than 100 pathogenic transthyretin mutations reported to date (Kapoor et al, 2019). The V30M mutation is the most common transthyretin mutation worldwide, and presentation is usually with a length-dependent, painful, small fibre neuropathy progressing over time to a generalised sensory–motor neuropathy, with autonomic neuropathy being another common symptom (Kapoor et al, 2019). Age of onset varies and late onset cases are well recognised.

Cardiomyopathy is also a feature of hereditary transthyretin amyloidosis, and cardiac screening is recommended in patients with confirmed hereditary transthyretin amyloidosis to identify those at risk of adverse events (Damy et al, 2016).

Bullous skin lesions are rarely described in systemic amyloidosis, with histopathology of the skin revealing large amounts of amyloid deposits in the dermis with positive Congo red staining around dermal vessels (Ahmad et al, 2009). The blistering is thought to be caused by intradermal splitting within the amyloid deposits, and these blisters are often haemorrhagic as a result of amyloid infiltration into blood vessel walls (Ahmad et al, 2009). Vessel wall infiltration by amyloid is also thought to be responsible for other cutaneous features including purpura and ecchymoses (Ahmad et al, 2009). To the authors' knowledge, bullous amyloid has only been reported in one patient with hereditary transthyretin amyloidosis in the Japanese cohort, also with the V30M mutation (Sekijima et al, 2018).

Treatment for hereditary transthyretin amyloidosis-related neuropathy has been revolutionised with the development of genetic therapies to suppress synthesis of transthyretin within the liver, patisiran and inotersen (Kapoor et al, 2019). Diagnosing hereditary transthyretin amyloidosis in a timely fashion is essential to enable early access to treatment, to prevent cardiac and neurological morbidity.

Learning points

- Although a rare manifestation of a rare disease, bullous skin lesions in conjunction with a compatible neuropathy should trigger clinical suspicion of amyloidosis as the underlying disorder.
- Cardiomyopathy is a feature of hereditary transthyretin amyloidosis and cardiac screening should be performed in individuals with confirmed hereditary transthyretin amyloidosis.
- Patients with hereditary transthyretin amyloidosis and a confirmed neuropathy should be referred to an amyloidosis centre for consideration of genetic therapies to suppress transthyretin synthesis.

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