Tangier disease—a diagnostic challenge in countries endemic for leprosy

S Sinha, A Mahadevan, L Lokesh, V Ashraf, B K Chandrasekhar Sagar, A B Taly, S K Shankar

A case of Tangier disease (TD) is reported from India. The patient had presented with indolent mononeuritis multiplex and trophic ulcers of 16 years duration mimicking Hansen’s disease. He received antileprosy treatment for one and a half years. Nerve conduction studies revealed features of demyelinating neuropathy. Biopsies of the sural nerve and skin showed striking vacuolation of Schwann cells and myelin sheaths, and foamy vacuolated fibroblasts, respectively, and no evidence of Hansen’s disease. Low levels of apolipoprotein A1 (ApoA1) and cholesterol in the serum and undetectable levels of high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol in the blood confirmed the diagnosis of TD. This is the first reported case of TD from a tropical country—India. An attempt to establish a correct diagnosis should be made by demonstrating the histopathological and lipoprotein abnormality to avoid long term medications that are chosen empirically and are unnecessary. The importance of recognising this disease in a country where Hansen’s disease is highly endemic cannot be overemphasised.

Trophic ulcers are observed in the setting of sensory or autonomic neuropathy. The common diseases associated with this feature are Hansen’s disease, diabetic small fibre neuropathy, vasculitic neuropathy, hereditary sensory autonomic neuropathies, and Tangier disease. In areas endemic for Hansen’s disease, patients with trophic ulcers often receive anti-leprosy treatment without establishing the definite diagnosis.1

Tangier disease, first described by Fredrickson2 in 1961 is a rare inborn error of metabolism characterised by virtual absence of high density lipoproteins (HDLs) in plasma and accumulation of cholesterol esters in many tissues throughout the body including tonsils, liver, spleen, lymph node, thymus, intestinal mucosa, peripheral nerves, and cornea.3 These patients may present with a slowly progressive debilitating small fibre neuropathy with trophic ulcers or a multifocal neuropathy with striking remissions.

We describe a patient of Tangier disease from India, who presented with indolent mononeuritis multiplex with trophic ulcers mimicking Hansen’s disease and discuss problems in reaching the correct diagnosis.

CASE REPORT

A 36 year old gentleman presented in May 2002 with numbness of the left little finger since the age of 16. It was non-progressive till the age of 30, when the numbness extended to other fingers of both hands along with weakness of the left hand, which had gradually worsened. For the past three years, numbness in both the feet appeared along with recurrent burns and injuries over both hands and forearms. In 1998, he was prescribed Dapsone, Rifampicin, and Clofazamine on a clinical suspicion of Hansen’s disease because of endemcity and clinical presentation. This regimen was continued for one and a half years. He developed hepatitis induced by Rifampicin and was advised to discontinue taking it. While on treatment, he had developed progressive neurological deficits. He is a restaurant owner at Kuala Lumpur in Malaysia, though his place of origin is Tamil Nadu, South India. There was no family history of similar disorders or any major illness in the past. At seven years of age, tonsillectomy had been performed, probably for recurrent tonsillitis.

He had hypopigmented macular patches over the abdomen and a large non-healing burn wound over the left forearm. There was splenomegaly but other abdominal viscera were not palpable. He had bilateral facial weakness, wasting of small muscles in the hands with the left hand being weaker than the right. Pain, touch, and temperature sensations were impaired over both hands, the face, the chest, the back, the abdomen, and the proximal third of the thigh. The remaining lower extremities were spared except for the feet. Touch sensation was relatively preserved as compared to pain and temperature. The stretch reflexes were brisk in lower limbs and normal in the upper limbs. There were no thickened nerves.

Routine urine examination and haemograms were normal except for low platelet count (78,000/mm3). Rheumatoid factor, LE cell phenomena, antinuclear antibody, and HIV serology were negative. Cerebrospinal fluid examination was normal. A “split skin” smear for lepra bacilli was negative. Ultrasound examination of the abdomen confirmed splenomegaly along with fatty liver. Electrocadioigraph and 2D echocardiograms did not reveal cardiac involvement. Magnetic resonance imaging of the cervical cord excluded syringomyelia and any other cause of myelopathy. Slit lamp examination confirmed the presence of corneal opacities as deep stromal haze. Nerve conduction studies demonstrated features of demyelinating neuropathy (table 1). Sympathetic skin responses were absent in all four limbs.

Full thickness biopsy of the left sural nerve and a skin biopsy from the abdominal anaesthetic patch were performed. The sural nerve was fixed in 2% glutaraldehyde and was processed for routine paraffin sectioning and electron microscopy. Paraffin sections were stained with Hematoxylin & Eosin, Masson’s trichrome for collagen, Loyez Hematoxylin for delineating myelin and Lepra stain for acid fast bacilli. The skin biopsy was also processed for light microscopic examination and a portion of it for lipid stain (oil red O) on frozen sections.

The biopsied sural nerve contained normal sized funicles enclosed within a thin, non-inflamed perineurium. The

**Abbreviations:** ApoA1, apolipoprotein A1; HDL, high density lipoprotein; LDL, low density lipoprotein; TD, Tangier disease

endoneurial matrix was oedematous, vacuolated and foamy. This was most pronounced in the subperineurial zone and along the endoneurial septa. Reduction in myelinated fibre density particularly affecting small diameter fibres was prominent with numerous pockets of Schwann cell subunits reflecting unmyelinated fibre loss (fig 1). A striking feature in the biopsy was vacuolation of Schwann cells and myelin sheaths. The Schwann cells, particularly those in association with Schwann cell subunits, were bloated with foamy, vacuolated, or finely granular cytoplasm (fig 1B) that displaced and indented the nucleus, suggesting accumulation of lipid storage material. Similar vacuolation affected the pericytes of endoneurial vessels (fig 1A), and perineurial cells. Loyez stain for myelin highlighted marked depletion in both small and large myelinated fibres, principally the former, accounting for the clinical presentation. There was no evidence of Hansen’s neuritis in the biopsied nerve, nor did the lepra stains detect any acid fast bacilli. Unfortunately no tissue was available for cryostat sections to confirm the lipid nature of the storage material in the nerve.

A portion of the nerve tissue from the paraffin block was retrieved for ultrastructural examination. It revealed marked loss of myelinated as well as unmyelinated fibres and increased numbers of denervated Schwann cell subunits. Numerous clear, electron lucent vacuoles were seen within these clusters of Schwann cell cytoplasmic processes and a few myelinated fibres. These intracytoplasmic vacuoles, singly or in multiples, ranged in size from 0.5 to 2 μm diameter and were most numerous in the Remak cells (fig 2). Similar cytoplasmic vacuolation was also seen within the pericytes and endothelial cells of the endoneurial capillaries, endoneurial fibroblasts, macrophages and perineurial cells. Few of the surviving myelinated fibres revealed large vacuoles along the adaxonal surface of the myelin ring lifting

**Table 1** Nerve conduction values

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Parameters</th>
<th>Control</th>
<th>Right side</th>
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<td>Median</td>
<td>DL (ms)</td>
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<td>4.8</td>
<td>*</td>
</tr>
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<td></td>
<td>CMAP (mV)</td>
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<td>6.2</td>
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<tr>
<td>CP</td>
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<td>5.4</td>
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D, Distal; P, proximal; DL, distal latency; CMAP, compound muscle action potential; CV, conduction velocity; FLAT, F latency; SNAP, sensory nerve action potential

*could not be tested due to large wound

**Figure 1** Low magnification view of nerve fascicle showing reduced myelinated fibre density, increased endoneurial fibrosis and vacuolated cells. Masson’s trichrome stain ×75. (A) Vacuolated foamy pericytes surrounding an endoneurial arteriole. Masson’s trichrome stain ×800. (B) A Schwann cell subunit shows ballooned, multivacuolated Schwann cell cytoplasm. Note the well preserved myelinated fibre on the left. Masson’s trichrome stain ×800.
The axoplasm (A). Note the Luse body along the basement membrane. A large myelinated fibre shows multiple fine vacuoles within the axoplasm (fig 3) and accumulation of dense lamellated bodies and enlarged mitochondria signifying ongoing axonal degeneration. No viable or fragmented lepra bacilli were found in the material examined. The skin biopsy revealed normal covering epidermis. In the upper dermis, spindle shaped fibroblasts with foamy, finely vacuolated cytoplasm indenting the nucleus were seen surrounding nerve twigs and capillaries. Similar foamy material was also observed in the periappendageal fibroblasts adjoining the sweat ducts. There was no histiocytic granuloma or inflammatory infiltrate to suggest Hansen’s disease. Oil red O stain showed fine, punctate droplets within the foamy vacuolated cells in the perineurial, periadnexal and periappendageal regions confirming the lipid nature of the storage material.

On biochemical analysis, serum cholesterol was 63 mg/100 ml while HDL and LDL cholesterol levels were not detectable in the blood. Serum ApoA1 was less than 0.195 (below the third percentile) confirming the diagnosis of Tangier disease. The serum lipid profiles of all the four sisters of the index patient were normal. The metabolic nature of the illness was explained to the patient and therapy for Hansen’s disease was discontinued. He learnt to take care while working with sharp and hot instruments and to do regular chiropody. The patient was counselled regarding avoidance of risk factors for cardiovascular and cerebrovascular disease. Periodic platelet counts were advised.

**DISCUSSION**

The index patient had features of longstanding mononeuritis multiplex involving both the sensory and motor nerves. He developed trophic ulcers over the fingers and forearms. Though the split skin smear done in the past was negative for lepra bacilli, he received treatment with a presumptive diagnosis of Hansen’s disease. He had brisk muscle stretch reflexes suggesting an alternative possibility of syringomyelia, which was excluded by normal magnetic resonance imaging. The biopsied sural nerve showed features diagnostic of Tangier disease. A similar case has been reported from Mayo clinic but with a shorter duration of illness. In an earlier report it had been emphasised that Tangier neuropathy might mimic syringomyelia or leprosy.

Peripheral neuropathy is the most frequent symptom in adult patients with Tangier disease. Abnormal lipid deposition in Schwann cells is proposed to be responsible for the neuropathy. Two types of neuropathy are described in these patients—a relapsing mononeuritis multiplex similar to the case reported here and a pseudosyringomyelic syndrome. Electrophysiological evaluation of the peripheral nerves of the index case revealed sensory-motor, mainly demyelinating, neuropathy. However, both demyelinating and axonal abnormalities have been described in Tangier neuropathy. It had also been reported that the subgroup presenting as relapsing mononeuritis multiplex had predominant features of demyelination and remyelination on nerve biopsy, in contrast to those with the syringomyelic form in which axonal degeneration was prominent. Schmalbruch et al reported the first autopsy of a patient with TD. They examined only the lumbar cord and the L5 ganglion and found mild ganglion cell loss and accumulation of lipofuscin-like granules. Antoine et al studied the entire spinal cord and nerve roots and found no syringomyelic cavity. The authors hypothesised that the lipid accumulation in the Schwann cells followed nerve degeneration but was a transient phenomenon.

The patient described here presented with mononeuritis multiplex with demyelinating features on electrophysiology. The biopsied sural nerve showed striking vacuolation principally involving the Remak cells in addition to the myelin sheath, perineurial cells, pericytes of endoneurial vessels, and the endoneurial macrophages. Prominent loss of both small and unmyelinated fibres seen in the biopsy accounted for the clinical symptoms of the patient-like numbness followed by anaesthesia, trophic ulcers and recurrent burns over both arms and forearms that exactly mimicked Hansen’s disease. Perineuritis, inflammation, epithelioid granulomas or acid fast bacilli to suggest leprosy were absent in the nerve biopsy.

The characteristic yellow/orange discoloration of tonsils, adenoids, and colonic reticuloendothelial cells, the hallmark of Tangier disease, is attributed due to accumulation of fat soluble vitamin E, retinyl esters (yellow) and carotenes (orange) bound to cholesteryl esters. Thrombocytopenia due to sequestration of platelets in enlarged spleen is an important manifestation of Tangier disease. Our patient had splenomegaly and asymptomatic thrombocytopenia for several years prior to the establishment of diagnosis. Ocular
abnormalities in Tangier disease include corneal opacification, ectropion, retinal pigmentary changes. Corneal opacities detected in the index patient by slit lamp examination did not impair his vision.

The pathognomonic biochemical abnormalities in Tangier disease include deficiency of serum HDL, low cholesterol concentration with normal or slightly elevated serum triglyceride levels in association with low plasma apolipoprotein A1. Tangier fibroblasts have defective lipid efflux and signal transduction processes and are unable to release phospholipids and cholesterol in the extracellular presence of lipid free apolipoprotein and exhibit reduced capacity to release cholesterol in the presence of HDL. The genetic mutations have been detected in the human ATP-binding cassette transporter 1 (ABC1). Rust and colleagues localised the gene defect to the chromosome locus 9q31.

The diagnosis of Tangier disease was initially missed in the present case because of the endemicity of Hansen’s disease. Low platelet counts and splenomegaly, detected much earlier to the presentation to our centre, were not considered as a clue to the diagnosis, but were dismissed as laboratory error or a feature of tropical splenomegaly syndrome secondary to chronic malaria in the endemic areas. The pathognomonic large orange tonsils, when present, clinch the diagnosis but our patient had undergone tonsillectomy in childhood resulting in delayed diagnosis. Atherosclerosis of large arteries especially of coronary is the major cause of mortality. Since, clinical cardiac evaluation, electrocardiography and 2D echocardiography did not reveal any abnormality, coronary angiography was not planned.

Hansen’s disease was the initial diagnosis before this patient was referred to us. He received antileprosy treatment for many years. He developed drug induced hepatitis. Due to the social stigma of having leprosy, he remained in stress all these years. Further, since the diagnosis of Tangier disease was not entertained, he was not examined for the underlying metabolic abnormalities of the disease. Of clinical relevance is the fact that abnormal nerve histology has been documented even when neurological examination, quantitative tests for cutaneous sensation and nerve conductions have been normal in this disorder.

This is the first reported case of Tangier disease from a tropical country—India. A total of 70 patients have been reported in world literature, mainly from Tangier Island near Morocco. A high degree of suspicion and careful attention to ancillary investigations along with aggressive attempts to establish lipoprotein abnormality and tissue diagnosis are essential for early and accurate diagnosis and avoid empirical, long term medication. The importance of recognising this disease in a country where Hansen’s disease is highly endemic cannot be overemphasised.

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Competing interests: none

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REFERENCES