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An unusual cause of speech and swallowing difficulty

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THE STORY

A retired man in his 60s had been well until December 1998 when he had let out a sudden involuntary cry and then a yawn, and for a few seconds found that his speech was quiet and breathy. Over the following 8 weeks he developed slurring of speech and swallowing difficulties with regurgitation. He noticed generalized weakness and fatigue, with symptoms fluctuating from week to week. By March 1999 he had taken to using a buggy to get around his local 18-hole golf course. In April, he had a barium swallow, which showed aspiration (Fig. 1). Nerve conduction studies (NCS) and electromyography (EMG) were normal, and computerized tomography (CT) of his brain showed 'small vessel disease'. By July 1999 he had swollen legs and had lost 6 kg in weight. He was found to be in fast atrial fibrillation (AF). A transthoracic echocardiogram was normal. In October he was admitted to his local hospital with pneumonia and heart failure. Amiodarone and warfarin were given, but he eventually required DC cardioversion. He became so debilitated that he needed help to turn over in bed. The amiodarone was stopped in



Figure 1 Barium swallow showing aspiration (arrow).

December and his condition improved. By January 2000, he was walking with a stick, but he was still breathless and lung function showed a low forced expiratory volume and forced vital capacity with no reversibility. His chest X-ray showed a single area of calcification thought to be old TB. He was treated with spironolactone for his heart failure. He complained of persistent problems with speech and swallowing. However, his neurological signs were unchanged and a brain MR scan showed altered signal around the ventricles, but nothing else. In March 2000, he deteriorated rapidly. He had swollen legs, was breathless at rest, drowsy and complained of headache. He was found to be in type 2 respiratory failure and transferred to us at King's College Hospital on 5 March. There was no notable past medical or family history. His father had died of carcinoma of the prostate and his mother of heart failure. He was a life-long non-smoker.

EXAMINATION

He had respiratory paradox (respiratory rate 20), reduced air entry at his right base and rhonchi throughout both lung fields. His oxygen saturation was 84% on air and 94% on 2 L of oxygen. His vital capacity was 0.97 L lying and 1.27 L sitting. He had a sinus tachycardia with pitting oedema to his knees. He had bulbar-sounding speech. There was marked restriction of up-gaze, which was not overcome by the doll's eye manoeuvre. His palatal movement appeared restricted but he had a brisk gag reflex. He was unable to protrude his tongue beyond his teeth and his tongue movements appeared slow and spastic. No fasciculation was seen and there was no wasting. He had normal tone with proximal fatiguable weakness of grade 4/5 in all four limbs. His reflexes were absent or present only with reinforcement – there was no enhancement after exercise. His plantar responses were flexor. Sensory testing revealed reduced pin-prick sensation over his toes only.

INVESTIGATIONS

The following blood tests were normal: erythrocyte sedimentation rate; C-reactive protein; renal, liver and thyroid function; parathyroid hormone; B12, folate; creatinine phosphokinase; autoantibodies, including antithyroid microsomal, antithyroglobulin, antigastric parietal cell, antimitochondrial antibodies; extractable nuclear antigens; antineutrophil cytoplasmic antibody; double-stranded DNA; antineuronal antibodies; antiganglioside antibodies (GM1 and GQ1B); antiacetylcholine receptor and voltage-gated

calcium channel antibodies; complement studies (C3 and C4); serum immunoglobulins and serum electrophoresis. The white cell count was $17.4 \times 10^9/L$. Calcium 2.04 mmol/L (2.40 mmol/L corrected), albumin 24 mmol/L. Arterial blood gases (on 4 L oxygen): HCO_3^- 35 mmol/L, pH 7.1, PCO_2 14 kPa, PO_2 13 kPa. Normal chemistry, microscopy and cytology in the cerebrospinal fluid, faint matched oligoclonal bands.

NEUROPHYSIOLOGY AND TESTS OF NEUROMUSCULAR FUNCTION

No improvement in vital capacity after iv tensilon. NCS/EMG (8 March) showed no evidence of neuromuscular dysfunction with no incremental response after exercise and no decrement or increment on repetitive stimulation. There was no evidence of acute or chronic denervation and fasciculations were only seen in left tibialis anterior. NCS/EMG (23 March): repetitive nerve stimulation failed to demonstrate any defect of neuromuscular transmission. There was no increase in the compound muscle action potential after exercise. Motor conduction in the right upper limb was normal (median distal motor latency 4.4 ms; conduction velocity 46 m/s elbow-wrist; F-wave 33 ms). The sensory potentials were small (median sensory action potential 5 μ V, peak latency 3.6 ms; ulnar absent). EMG of the tongue showed no spontaneous activity at rest.

There was no diaphragmatic response to bilateral anterolateral magnetic phrenic nerve stimulation, no diaphragmatic EMG demonstrable with surface or oesophageal electrodes and no improvement after tensilon. Impaired cough (pressure = 76 cm water, normal > 120 cm). Reported as being consistent with a neuropathy affecting the phrenic nerves resulting in complete diaphragmatic paralysis.

Imaging

Chest X-ray on admission showed an elevated right hemi-diaphragm. MRI of brain and cervical spine showed minimal white matter disease, CT chest and abdomen showed free fluid in the chest and ascites in the abdomen consistent with his known heart failure. Video-fluoroscopy showed the oral and pharyngeal phases of swallowing to be slow and abnormal but with the pharyngeal phase most affected. There was bilateral incomplete vocal cord adduction.

Other tests

Open quadriceps muscle biopsy showed type II atrophy but no neurogenic changes. Mildly in-

creased endomysial connective tissue was noted. HLA-ABC was negative excluding an inflammatory myopathy.

Transthoracic echocardiogram showed normal left ventricular function but the fast heart rate and small amount of pericardial fluid (haemodynamically insignificant) made accurate assessment difficult.

CLINICAL COURSE

He was transferred to intensive care and required non-invasive positive pressure ventilation (NIPPV). He had a 5-day course of plasma exchange. His respiratory function improved significantly and he could manage 12 h off NIPPV but he was still not able to swallow and required nasogastric feeding, and later a gastrostomy. He had a persistent sinus tachycardia and a bicarbonate of 50 mmol/L. He was started on an increasing dose of alternate-day steroids. By the 26 March there was little change on neurological examination despite a general improvement in his condition. His speech was more audible and his tongue protruded a little further. His vital capacity was 1.01 L. He remained unable to swallow without aspirating. He had mild proximal weakness grade 4+ in all four limbs with no demonstrable fatigue. His reflexes were now elicitable without reinforcement. At the end of March he was transferred to high dependency care and over the next month his clinical condition fluctuated. He had a persistent sinus tachycardia. He required various amounts of respiratory support with NIPPV and his bicarbonate remained elevated. He did not require intubation. At best he mobilized with the help of two physiotherapists. He commented that he felt generally better on his steroid days (prednisolone 80 mg on alternate days). However, despite two courses of intravenous immunoglobulin his respiratory function continued to deteriorate. The clinical team felt that the fluctuation in his condition was due to his general medical status in terms of his heart failure and the intensity of his respiratory support, rather than to any change in the underlying unknown pathological process. It was felt that he had not responded to plasma exchange, steroids or intravenous immunoglobulins. He died on 4 May.

DR MARY REILLY'S DISCUSSION

We were told that at the onset of his illness the patient remembered an involuntary cry and a yawn. This might suggest a sudden brainstem event. He then developed progressive speech and swallowing difficulties, but it is not clear wheth-

er this was bulbar or pseudobulbar. There was generalized weakness. His symptoms fluctuated and he reported fatigue, but although these are cardinal symptoms of neuromuscular junction dysfunction, they are also seen in neuropathic disease – specifically in motor neuron disease – but they may simply have been a reflection of his underlying systemic disease. Six months into his illness he developed severe resistant AF with heart failure complicated by pneumonia. He became very weak but recovered sufficiently to mobilize independently with a stick. He complained of persistent speech and swallowing difficulties but the neurological signs were unchanged. He then deteriorated rapidly with heart failure and respiratory failure. Neurological examination showed bulbar/pseudobulbar palsy and restricted upgaze (not supranuclear). He had fatiguable weakness and decreased deep tendon reflexes but no upper motor neuron limb signs and no ataxia. The decreased pinprick sensation over his toes could probably be attributed to oedema.

At what level was the pathology?

There was evidence of brainstem pathology with bulbar/pseudobulbar palsy and restricted upgaze possibly implicating the dorsal mid-brain. However, there were no other cranial nerve signs and no upper motor neuron signs to support an intrinsic brainstem lesion. A meningeal or infiltrative process would explain the lack of upper motor neuron signs, but not the nuclear gaze palsy, or the lack of other local signs or significant progression. Could the pseudobulbar signs be explained by white matter disease? The MRI was unhelpful, gadolinium was not given and anyway it showed only minimal white matter disease.

He had no risk factors for, or symptoms of, ischaemic heart disease. And yet over the course of a year he developed severe cardiac failure and resistant atrial fibrillation. This is a very aggressive disease and raises the possibility of a vasculitis. Could there have been an infiltrative process with deposition in the conducting system? There was no objective evidence of a cardiomyopathy. His chest X-Ray showed a normal heart size. He had two normal transthoracic echocardiograms but the second study was difficult with the patient on intensive care and in fast AF. No transoesophageal echocardiogram was performed.

He had respiratory paradox indicating diaphragmatic weakness. His arterial blood gases showed chronic type II respiratory failure with

acute decompensation. There was no EMG response to phrenic nerve stimulation excluding a central cause for the diaphragmatic weakness. Although the recordings were made with surface electrodes and no needle EMG was performed, an absent EMG and the lack of response to tenosion would not be consistent with neuromuscular junction pathology. The lack of response suggests either bilateral phrenic nerve pathology or primary muscle disease. The skeletal muscle EMG was not myopathic and this raises the possibility that there was a local infiltrative process causing diaphragmatic weakness.

There was no evidence of a major neuropathic, denervating, myopathic or neuromuscular junction process. The NCS did not support a major generalized neuropathy. The absent sensory action potentials in the intensive care setting are unhelpful. Mononeuritis multiplex causing bilateral recurrent laryngeal (adductor paralysis) and bilateral phrenic nerve palsies would be extremely unusual in isolation. A radiculopathy would explain the apparent absent or decreased reflexes at presentation but these became elicitable later and we were not told what drugs he had received on transfer. There was no EMG evidence of denervation outside tibialis anterior and so any radiculopathy was not significant. There was no EMG or autoantibody evidence to support a diagnosis of myasthenia gravis or Lambert–Eaton syndrome. There was no evidence of a widespread myopathic process. The muscle biopsy was mildly abnormal with type II atrophy but no evidence of metabolic or inflammatory disease. There is no mention of a Congo Red stain. It therefore seems likely that the fluctuating limb weakness was a reflection of his heart failure and respiratory failure.

In conclusion there was clinical evidence of brainstem disease with involvement of the medulla plus or minus the midbrain. There was cardiac disease involving the conducting system plus or minus a cardiomyopathy. There was definite diaphragmatic paralysis but it is not clear if this was due primarily to muscle or nerve pathology.

The differential diagnosis

The cardiac disease was the most aggressive feature and in combination with the neurological symptoms would suggest either ischaemic heart disease with cerebrovascular disease, a vasculitis, or amyloidosis (light chain or familial). Ischaemic heart disease and cerebrovascular disease are both common and could explain the cardiac and

brainstem findings but not the diaphragmatic paralysis and the investigations did not provide any objective evidence of ischaemic heart disease or of significant brainstem ischaemia.

Could this be vasculitis with patchy brainstem ischaemia, coronary artery disease and a possible mononeuritis multiplex? The normal CSF and the relatively normal brain MRI would not be typical. And mononeuritis multiplex causing bilateral phrenic nerve paresis would be very atypical. Cardiac disease consisting purely of an arrhythmia with no ischaemic symptoms would also be unusual and the lack of systemic markers of a vasculitis in the setting of widespread disease would be unlikely. Furthermore there was no convincing response to immunosuppression.

Could this be primary amyloid – light chain (AL) or transthyretin (TTR)? Amyloid deposition in the conducting tissue and cardiac muscle could cause a resistant arrhythmia and a cardiomyopathy, but there was no objective evidence for a cardiomyopathy. The diaphragmatic paralysis could be explained by amyloid deposition in the diaphragm or possibly meningeal deposition causing a radiculopathy. Brainstem presentation is rare in AL amyloid and even rarer in TTR amyloid. When it does occur, it is usually due to meningeal deposition and so the pseudobulbar signs here remain difficult to explain. Intraparenchymal deposition of amyloid is exceedingly rare. Amyloid deposition around blood vessels might result in a vascular lesion but the MRI did not support this. The CSF protein was normal, which would be unusual in the setting of meningeal disease. Normal serum immunoglobulins and protein electrophoresis would be against AL amyloid but the patient did have matched oligoclonal bands and there is no result of Bence Jones protein. This would be very aggressive disease for TTR amyloid. There was no definite family history although it is of note that his mother died of cardiac failure.

The differential diagnosis must also include lymphoma, paraneoplastic disease, neoplasia, and a metabolic lesion. The brainstem presentation, cardiac involvement, possible mononeuritis multiplex and patchy nature of the disease would do for lymphoma. The cardiac disease was severe and could be explained by secondary amyloid. However, the MRI, CSF, and blood film were all normal and the CT chest and abdomen showed no nodes or organomegaly. In addition, the progression to death would be slow for lymphoma with a primary brainstem

presentation. Brainstem presentations are described in paraneoplastic syndromes, but there was no evidence of tumour on CT, the antineuronal antibodies were negative, and the absence of voltage gated calcium channel antibodies and the neurophysiological findings do not support a diagnosis of Lambert–Eaton syndrome. Nor would it be easy to explain the cardiac symptoms as part of a paraneoplastic syndrome. The patchy nature of the brainstem disease would fit with carcinomatosis causing meningeal disease, mononeuritis multiplex and a possible radiculopathy, but again the slow progression of the disease, and the MRI findings and normal CSF would argue against this. Inherited and acquired metabolic defects cause multisystem disease. Mitochondrial disease commonly causes both neurological and cardiac symptoms but the patient's age, the muscle biopsy result and the MRI findings do not support this diagnosis.

Taking all of these arguments into account I would favour a diagnosis of Amyloid (AL type). This would best explain the time course of the disease, the cardiac arrhythmia, and the diaphragmatic weakness, but the pseudobulbar symptoms and nuclear gaze palsy are more difficult to explain without objective evidence of meningeal or vascular brainstem disease.

PATHOLOGY – DR ISTVAN BODI

After obtaining consent, a full post-mortem examination was performed. On macroscopic examination the tongue was firm and waxy on cut section and pale brown in colour (Fig. 2A). Skeletal muscles (diaphragm, intercostal, psoas and quadriceps), heart, oesophagus and stomach were also firm, waxy and pale with brownish discolouration (Fig. 1B,C). The lungs contained multiple yellowish white nodules, suggestive of necrotic lesions. The liver, spleen, kidneys and endocrine glands were normal. The brain and spinal cord were unremarkable and there was no evidence of anterior nerve root atrophy. Gross appearances of tongue, skeletal muscles, gastrointestinal tract and heart were suggestive of systemic amyloidosis. Therefore, iodine staining of the tongue and heart was performed and this was consistent with amyloidosis (Fig. 1D).

Histological examination with Congo Red confirmed the diagnosis of systemic amyloidosis. The tongue, skeletal muscles and the gastrointestinal tract were heavily affected, the heart was moderately affected (Fig. 3) and amyloid was also demonstrated in the thyroid and adrenal glands. Apart from a tiny amyloid deposit in the sural nerve, the extensively sampled peripheral nerves did not show evidence of amyloidosis. The liver,

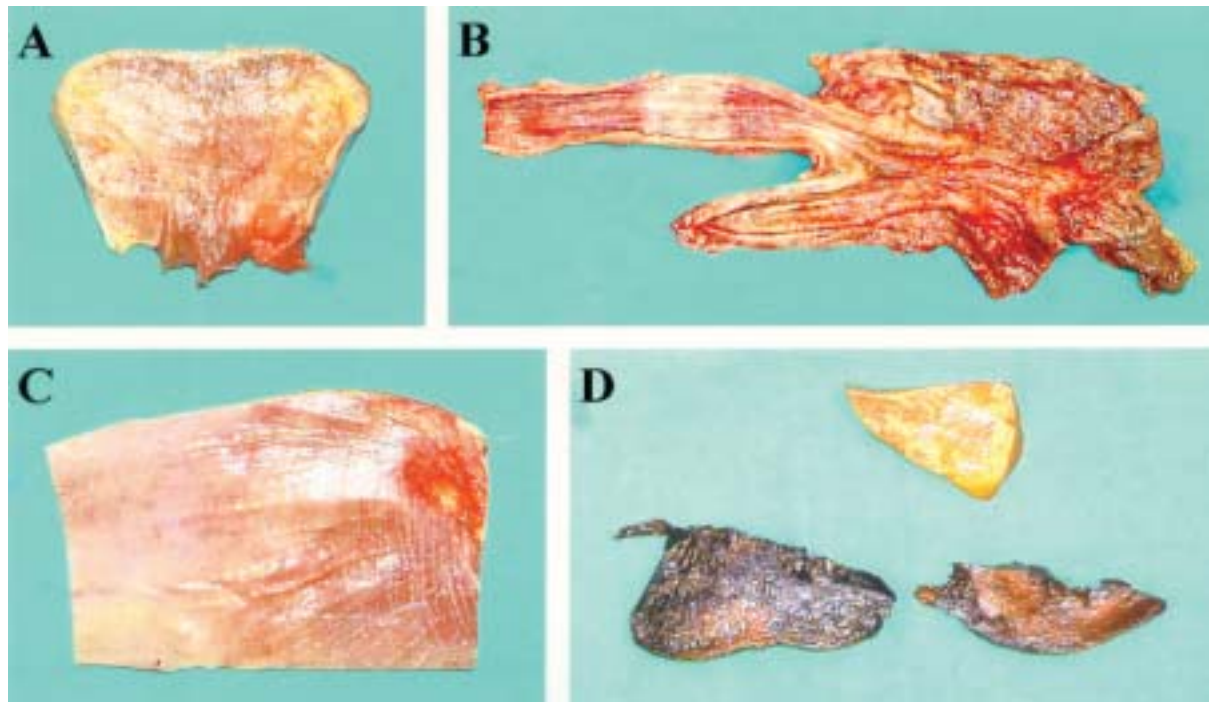


Figure 2 Post-mortem appearances. (A) Tongue, it was firm and waxy on cut section; (B) oesophagus and stomach showing focal rigidity of the wall; (C) diaphragm is firm, leather-like and waxy; (D) iodine test, slices from the tongue and heart (affected by amyloidosis) turned to dark-blue while the unaffected liver did not.

kidney and spleen showed no evidence of amyloidosis. The brain, brainstem and spinal cord were unremarkable with no evidence of motor neuron disease and no evidence of intraparenchymal or leptomeningeal amyloid deposition. The bone marrow showed normal haematopoiesis with no evidence of plasma cell proliferation. Histology of the lung did not confirm the presence of nodular amyloidosis, as had been expected, but instead showed typical miliary caseating granulomas with tuberculous pneumonia (Fig. 4A). Ziehl-Neelsen stain revealed large numbers of acid-fast bacilli, confirming miliary tuberculosis.

The ante-mortem skeletal muscle biopsy was re-examined for evidence of amyloidosis. In addition to non-specific type II atrophy, a few blood vessels were identified in which, although there was no evidence of amyloid with Congo Red staining on light microscopy, amyloid fibrils were identified on electron microscopy (Fig. 5B).

Immunophenotyping with commercially available antibody, performed in our department, showed positive staining against

transthyretin, but negative results with SAA, kappa and lambda immunoglobulin light chains. To confirm the diagnosis and for mutational analysis of the transthyretin gene, formalin fixed material and blocks from affected organs were sent to Professor Philip Hawkins in the National Institute of Amyloidosis at the Royal Free Hospital, London. Extensive immunostaining was performed using monospecific antibodies reactive with SAA, the circulating precursor of AA amyloid fibrils, transthyretin, and kappa and lambda immunoglobulin light chains. The amyloid material did not stain with any of these antibodies, suggesting that the initial positive transthyretin stain in our laboratory was a false positive. DNA sequencing of the TTR gene from archival formalin fixed tissues was attempted, but unfortunately adequate sequence was obtained from exon 2 only, and this was wild type. Exon 2 is about half the gene and does not include the commonest mutations in the UK population. Despite our initial laboratory findings it seems most likely that this is actually AL amyloidosis rather than systemic TTR-related amyloidosis.

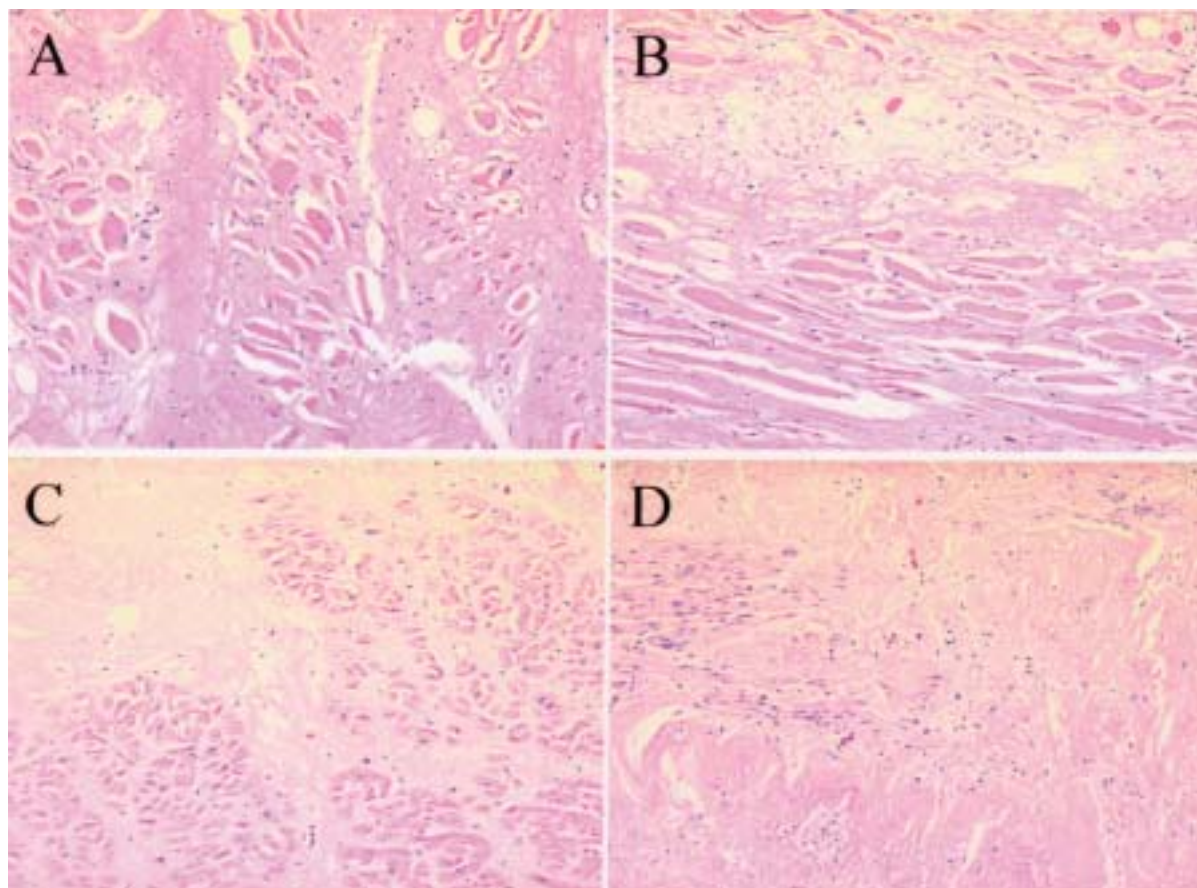


Figure 3 Histology (H&E). Heavy accumulation of homogenous eosinophilic material replacing the surrounding partly atrophic tissue. (A) Tongue; (B) diaphragm; (C) heart; (D) oesophagus.

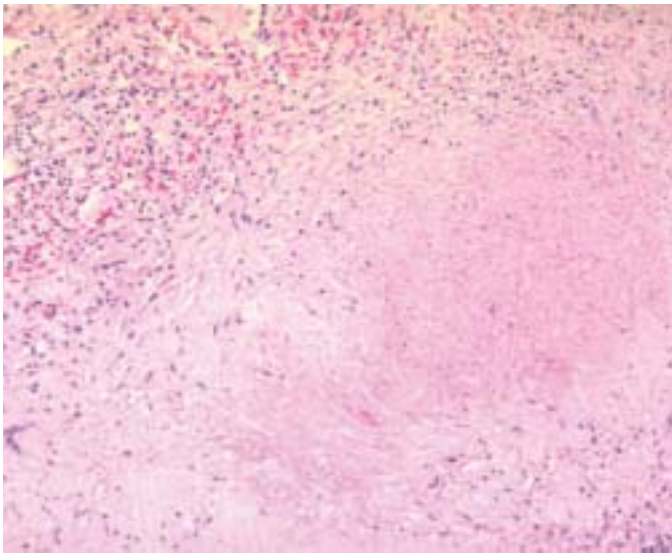


Figure 4 Lung showing a caseating granuloma with a Langhans type multinucleated giant cell (H&E).

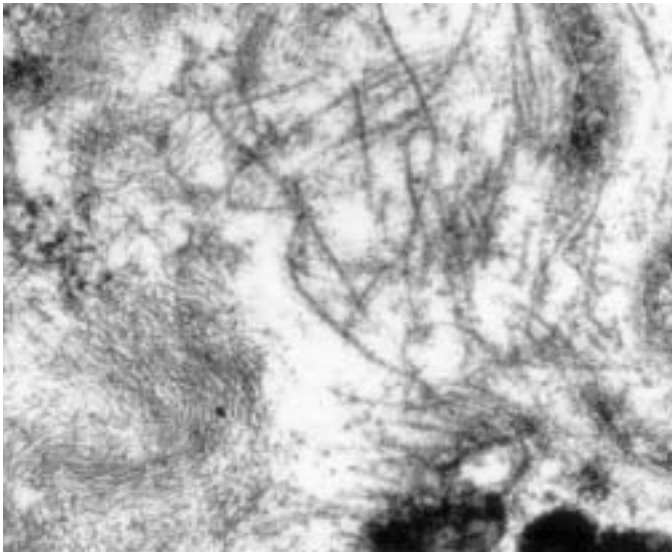


Figure 5 Electron microscopy from the muscle biopsy demonstrating haphazardly arranged amyloid fibres.

The patient had very extensive amyloid deposition in the diaphragm and intercostal muscles causing type II respiratory failure, amyloid deposition in the tongue and oesophagus caused his bulbar symptoms, and amyloid deposition in the heart was responsible for his arrhythmia and cardiac failure. Although the distribution of amyloidosis was more characteristic of AL-type (apart from completely sparing the kidneys), the presence of miliary tuberculosis might have suggested secondary (SAA) amyloidosis. However, the consistently negative SAA immunostaining suggests that in this case the miliary tuberculosis was probably a reactivation of a previous infection as a result of the steroid treatment. Miliary tuberculosis was the primary cause of death.

This is an unusual case of systemic amyloidosis, probably AL-type, with predominant bulbar and respiratory symptoms due to extensive skeletal muscle involvement.

GENERAL DISCUSSION

Dr Mary Reilly: There was no brainstem disease and all the bulbar signs and symptoms were related to local infiltration of the tongue and other muscles. This finding, together with the pattern of organ involvement and the rapidity of the disease course would be atypical for TTR-related amyloidosis and much more in keeping with AL amyloid.

Professor Kerry Mills: Although the skeletal muscle EMG was essentially normal, the EMG of the tongue was very unusual in that it showed no spontaneous activity. The diaphragmatic EMG report was misleading. It is important to remember that the failure to produce a diaphragmatic response does not necessarily mean that there is neurogenic paralysis. The diaphragm was so infiltrated that there was no EMG response to maximal phrenic nerve stimulation.

Professor Richard Hughes: We all failed to palpate the tongue. It looked normal in size on the floor of the mouth and appeared spastic when the patient attempted to move it.

Dr Istvan Bodi: The tongue was not objectively enlarged at post-mortem but histologically there was muscle atrophy and extensive amyloid deposition.

Dr Phillip Barnes: Was there evidence of eye muscle involvement at post-mortem? What was the cause of his marked restriction of upgaze?

Dr Istvan Bodi: Unfortunately the eye muscles were not examined but the restriction of upgaze might have been due to amyloid infiltration of the extra-ocular muscles.

Dr Mary Reilly's clinical diagnosis

Amyloid, probably AL type.

Dr Istvan Bodi's pathological diagnosis

Despite initial results suggesting this might be systemic TTR-related amyloidosis, the clinical phenotype and the negative TTR staining make AL-amyloidosis the most likely diagnosis. Steroid induced reactivation of pulmonary tuberculosis was the primary cause of death.

COMMENT

Amyloidosis is a disorder of protein folding in which normally soluble proteins are deposited as abnormal insoluble fibrils that progressively

disrupt tissue structure and organ function. Amyloid is classified according to the chemical composition of its fibrillary components (Kazatchkine *et al.* 1993). More than 20 different proteins have been identified that can be deposited as amyloid in man. They share the common characteristic of forming beta pleated sheets and it is this that gives them the characteristic green birefringence when stained with Congo Red and viewed under polarized light. In addition, amyloid deposits always contain the non-fibrillary pentraxin plasma protein- serum amyloid p component (SAP). This protein undergoes specific calcium-dependent binding to amyloid fibrils stabilizing them and reducing their clearance. Radiolabelled SAP is used as a tracer *in vivo* to quantitatively image amyloid deposition.

Amyloidogenic protein is deposited as amyloid in three different clinical settings:

- It is deposited when there is an abundance of a structurally normal precursor protein as can occur in chronic disease (e.g. tuberculosis) where an excess of AA amyloid is produced – this is secondary amyloidosis.
- It is deposited when a normal but intrinsically amyloidogenic protein has been present in normal quantities for a long time – in senile systemic amyloidosis normal structure transthyretin (TTR) is deposited in the heart and other organs (Westermark *et al.* 1990).
- However, the most common cause of clinical amyloidosis is when a mutated protein with an abnormal structure is deposited as amyloid. This occurs in patients with acquired plasma cell dyscrasias when monoclonal immunoglobulin light chain AL amyloid is produced (primary systemic amyloid), and in autosomal dominant inherited amyloidosis syndromes including familial amyloid polyneuropathy (Reilly & King 1993), and familial amyloid cardiomyopathy (Kisilevsky *et al.* 1996) in which mutations in the TTR gene result in abnormal TTR protein which is deposited as amyloid.

In a study of 6305 autopsies, 43 with systemic amyloidosis were identified, 50% had AA amyloid, 25% TTR amyloid, and 23% AL amyloid. AL amyloid was associated with myeloma in 50% of cases but in the rest no plasma cell dyscrasia was identified. At post-mortem, AA and AL amyloid most frequently affected the kidneys and TTR amyloid most frequently affected heart and lungs (Strege *et al.* 1998). However, symptomatic respiratory involvement is most commonly seen in AL-amyloid. Respiratory involvement

with amyloidosis most commonly involves the transbronchial tree and lung parenchyma. In a recent review of 16 cases with thoracic involvement by amyloidosis only one had hereditary amyloid of TTR type on immunohistochemistry (Shah *et al.* 2002).

Our patient had no family history of amyloidosis and his age, the rapid progression of his disease and the distribution of amyloid, despite the lack of renal involvement, makes AL-amyloid the most likely diagnosis. We did not find evidence of a monoclonal light chain in our patient on serum electrophoresis but there is no record of Bence Jones protein analysis and we did not perform a bone marrow biopsy. Immunostaining of the bone marrow for lambda and kappa isotypes is reported to demonstrate a dominant clonal population of plasma cells in the majority of cases of AL-amyloidosis where urine immunofixation is negative (less than 10% of cases) (Comenzo 2000). However, post-mortem bone marrow samples in our case did not show evidence of a plasma cell dyscrasia. Extensive immunostaining of post-mortem amyloid-laden tissue was also negative for kappa and lambda light chains. However, stains using commercial polyclonal antisera to kappa and lambda light chains are positive in only half the cases of AL amyloidosis. This is probably because the pathological light chain fragments are commonly derived from the variable domain and do not contain epitopes that are recognized by the commercially available antibodies which themselves are mainly directed against constant domain determinants.

Amyloidosis is one category of a growing number of diseases that are caused by abnormal protein folding and deposition. Medical treatments aimed at stabilizing the native protein, inhibiting fibril formation, reversing amyloid folding and dissociating SAP to accelerate fibril clearance are under investigation (Pepys 2001).

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