Long Standing DADS Variant of CIDP Preceding AL amyloidosis: A sentinel event or serendipitous association?

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Introduction

Diagnosis, treatment and long-term term monitoring of patients with chronic inflammatory neuropathies can be difficult with many pitfalls. This is particularly true when patients on immunomodulatory therapy (IMT) worsen as the worsening could be due to a relapse, emergence of an associated or unrelated disorder or due to an error in the primary diagnosis. Primary amyloidosis (AL) is often called the 'great imitator' due to its indolent and multisystemic presentation and is often the least considered amongst the heterogeneous spectrum of paraproteinemic neuropathies.[1] When a paraproteinemia is encountered during evaluation of neuropathy, failing to think beyond MGUS can delay the diagnosis of AL until so advanced that treatment is ineffective.[2] Here we present a case of a patient with idiopathic distal acquired demyelinating symmetric neuropathy (DADS-I) who succumbed to AL after two decades. We explore the association of AL neuropathy with DADS, both paraprotein-related neuropathies.

Case Report

A 35-year-old dentist presented with a two-year history of insidious numbness and paresthesia over the toes, feet and fingertips. These symptoms progressed to include unsteadiness of gait, loss of distal dexterity and hand tremors preventing him from performing his job. He did not have pain, autonomic symptoms or any constitutional complaints. His family history was notable for an unusual sensorimotor polyneuropathy in his father who also had IgG paraproteinemia and an elevated CSF protein. The neurological examination showed mild distal weakness with MRC grade 4+/5 power in ankle dorsiflexion and 4/5 of intrinsic hand and foot muscles. He had diffuse areflexia, impaired large and small fiber sensation distally and a positive Romberg test. He also had postural tremor of both hands persisting on intentional movements. The nerve conduction studies during the first visit revealed a demyelinating severe sensorimotor polyneuropathy. (Table 1)

Prior investigations showed a CSF protein of 128gm/L and normal laboratory tests including CBC, ESR, renal function, vitamin B12, glycosylated hemoglobin, 2-hour glucose tolerance test, serum protein electrophoresis, serum immunoelectrophoresis, levels of IgG, IgA and IgM, and anti MAG level. A sural nerve biopsy reviewed with a neuropathologist showed an inflammatory neuropathy with marked loss of myelinated nerve fibers, hypermyelinated fibres, scattered CD45+ lymphocytes and occasional CD68+ macrophages consistent with CIDP. Congo red staining did not reveal any amyloid deposition.

A diagnosis of CIDP was made and he was started on prednisone and propranolol for tremor. He stopped progressing, his balance normalized and his dexterity improved although not back to normal and he had to change his career. Whenever steroid tapering was attempted, he had worsening of symptoms and function. Low dose prednisone was continued and IVIG added. He remained on this maintenance therapy and was doing well clinically and electrically. The nerve conduction studies done in eleven years from the baseline were somewhat improved compared to baseline. (Table 1) Any attempts at increasing IVIG intervals or reducing dosage was met with worsening symptoms. Trials of cyclophosphamide, azathioprine and rituximab as steroid-sparing agents failed. After 18 years, the patient deteriorated despite maintenance steroid and IVIG and was re-investigated. (Table 2) Laboratory testing showed a monoclonal peak of IgG lambda with M protein level of 10gm/L with a second value about 8 months later of 11gm/L. Within six months, he developed progressive pedal edema and was diagnosed with nephrotic syndrome. Renal biopsy showed mild to moderate mesangial expansion by pale staining material which was also found in vessel walls and which stained positive with Congo red stain, and immunofluorescent microscopy showed IgG lambda deposits. With a positive family history of neuropathy, genetic studies were performed for an autosomal dominant hereditary amyloidosis and no pathogenic variants were found in (transthyretin) TTR, fibrinogen alpha chain (FGA), lysozyme (LYZ) and ApoA1 genes. He was treated with cyclophosphamide and bortezomib and later lenalidomide

Table 1. Motor nerve conduction studies during the course of illness

	Latency			Velocity (m/s)			Amplitude (mv)		
Time in years	0	11	18	0	11	18	0	11	18
Median nerve APB Wrist	6.7	5.9	5.4				9.6	12.3	8.2
Elbow	15.8	15.7	16.2	27	27	24	5.6	7.3	4.3
Axilla	18.8	19.2	19.4	33	36	30	4.9	7.2	4.1
Peroneal nerve EDB Ankle	10.0	8.8	10.3				1.5	1.8	0.2
Fibular head	28.2	25.3	25.3	17	18	20	0.2	1.2	0.1
Popliteal fossa	32.3	30.2	29.7	20	20	20	0.3	1.1	0.1
Peroneal nerve TA Fibular head	*	5.4	6.0				*	12.0	5.2
Popliteal fossa	*	8.8	9.5				*	11.6	4.9

APB- abductor pollicis brevis, EDB- extensor digitorum brevis, TA- tibialis anterior, * not done

without response. He underwent autologous bone marrow transplantation in, but his condition was complicated by cardiomyopathy and bilateral pulmonary emboli. At the last clinic visit, he had mild distal motor weakness, sluggish to absent reflexes and significant loss of sensation affecting ambulation and was wheelchair-bound. He had subsequent worsening with sepsis, progressive cardiac and renal dysfunction and succumbed to his illness within 2 years of the neurological deterioration. Figure 1 outlines his disease course and treatment.

Discussion

The current report highlights a case of DADS-I variant of CIDP initially responsive to IMT for almost two decades. Late in the course, paraproteinemia was detected and was confirmed to be due to AL. This case raises several complex questions about the long-term monitoring of inflammatory and paraproteinemia associated neuropathies.

The cornerstone in the evaluation of neuropathy is the appropriate classification of the syndrome based on clinical phenotype, nerve conduction studies and laboratory investigation. Since the initial description by Katz et al in early 2000 of the distinct distal sensory predominant neuropathy associated with M protein, the spectrum of paraproteinemic neuropathy has expanded.[3,4] . SPEP and SIEP are usually ordered and if a paraproteinemia is detected, both physician and patient are often reassured that the diagnosis is MGUS and paraproteinemic neuropathy. However, another plasma cell dyscrasia which is often missed is AL. Amyloidosis refers to a group of conditions in which misfolded insoluble protein fibrils with unique beta pleated structure and staining properties accumulate in the extracellular tissue, and can either be localized or systemic, acquired or inherited.[5] AL or primary systemic amyloidosis arises due to the deposition of monoclonal immunoglobulin light chain which in turn is produced by a clonal plasma cell expansion. In fact AL is a plasma cell dyscrasia along the same lines as multiple myeloma (MM), and the pathogenic mechanism which leads the clonal expansion down the path to MM or to systemic amyloidosis remains unknown.[6,7] Peripheral neuropathy is seen in 17 to 35% of AL patients and is not a common presenting symptom, but when it is, the diagnosis of AL is significantly delayed.[8–10] While the commonest neuropathic presentation is sensory predominant neuropathy with autonomic symptoms resembling hereditary transthyretin amyloidosis, presentations including cranial neuropathies, lumbosacral plexopathies, mononeuropathies and CIDP have been described.[11–16]

However, it does not appear that our patient had AL presenting as a DADS variant of CIDP at onset. The patient had a phenotype most suggestive of DADS and never had any autonomic symptoms. In addition, the absence of amyloid deposits but rather features consistent with CIDP in the nerve biopsy, a positive response both clinically and electrically with IMT and a duration of illness spread over two decades do not appear to be consistent with a CIDP-like presentation of AL. The diagnosis of AL in this case was made after reinvestigation prompted by clinical deterioration after many years of stability on IMT.

When evaluating and monitoring patients with paraproteinemia, besides progression to MM it has to be borne in mind that all forms of MGUS can potentially progress to AL. [17] In a series from the Mayo Clinic, 9% of

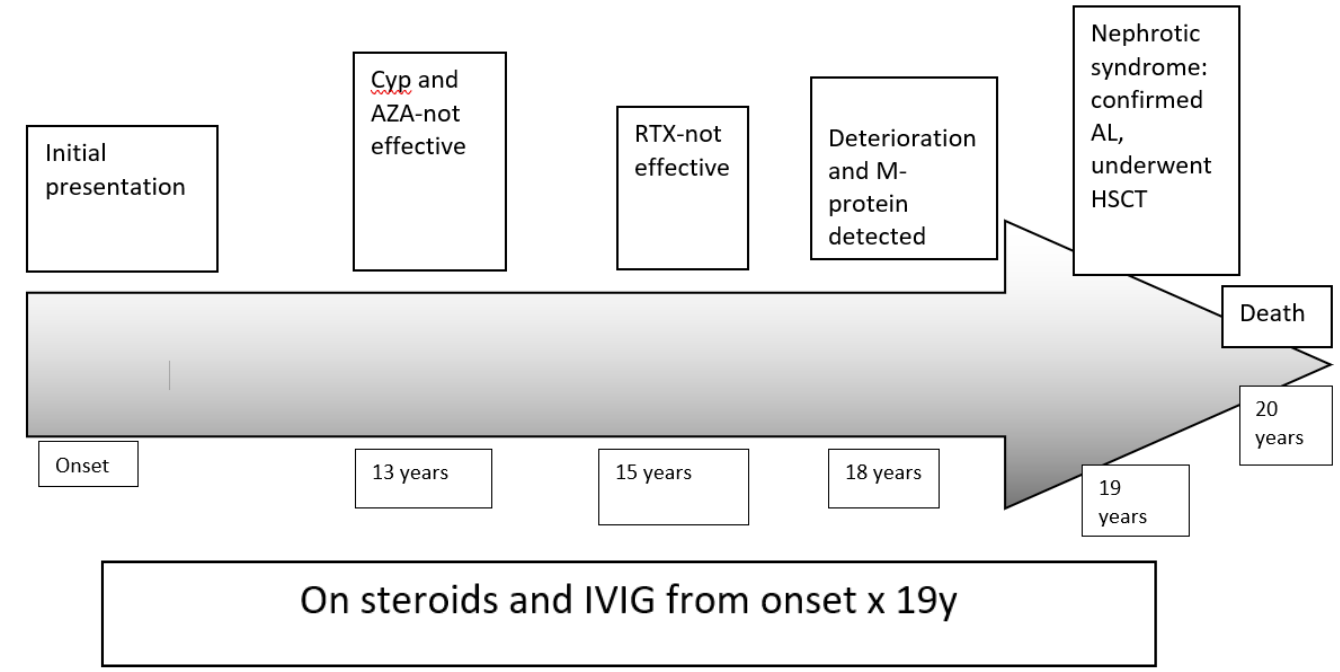

Figure 1. Timeline of disease course

all patients with a monoclonal gammopathy were ultimately proven to have light chain amyloidosis.[18] Features that demand special attention include predominantly axonal polyneuropathy, bilateral CTS, debilitating symptoms and rapid neuropathy progression. Many AL characteristic systemic symptoms and signs, such as periorbital purpura, macroglossia and shoulder pad signs, are seen only in a minority of AL patients.[1,5,19] Evaluation should include free light chain (FLC) assay and kappa:lambda ratio in addition to the SIEP and SPEP. Negative SPEP, SIEP and FLC in serum and urine effectively rule out AL.[5] Direct organ biopsy is rarely needed, and less invasive investigations such as abdominal fat aspiration, lip or rectal biopsy and immunohistochemistry or mass spectroscopy are useful to identify amyloid protein. Recommendations for monitoring of patients with MGUS is risk stratified based on quantity and type of M protein and FLC ratio. High risk patients need extensive evaluation including bone marrow biopsy not only to look for evidence of malignancy but also for AL.[20]

Unfortunately, our patient developed systemic manifestations of AL within a short interval from the detection of paraproteinemia, and had a rapid downhill course despite chemotherapy and bone marrow transplant. This rapid decline makes one suspect that the patient had a paraproteinemia for some time, but there was nothing to prompt re-investigation until the patient had worsening of neuropathy. Although the patient had the DADS phenotype, he had been evaluated for M protein previously with negative results. Whether initial titres were too low for detection by the then standard assays, or whether patients with DADS-I require frequent monitoring for development of paraproteinemia are questions that remain unanswered at present. Although there is no conclusive proof, the final worsening of neuropathy in this case is likely related to development AL. Interestingly, a recent large population based study showed that MGUS conferred a 2.9 fold increased risk of progression to AL when associated with peripheral neuropathy.[21] The majority of cases with MGUS-related neuropathy progressing to AL do so within the first year which is consistent with the course in our patient.

The family history of an unusual neuropathy related to paraproteinemia and its significance also remains unexplained. We found one report of a similar father-son presentation, so a rare genetic mechanism might be responsible.[22]

The diagnosis of MGUS opens a window of opportunity to the diagnosis of AL since virtually all cases of AL are preceded by MGUS. This is particularly true in the setting of a neuropathic presentation since there is increased risk of progression of MGUS to AL with such an association. Since

an M protein is associated with 50-70% of DADS cases, it may be worthwhile to monitor all DADS patients for AL frequently, even if the initial testing is negative. The need for FLC and kappa:lambda ratio along with the assessments SPEP and SIEP in serum and urine in screening and monitoring MGUS patients has to be stressed. Finally, when a patient with CIDP who is doing well on IMT fails, the novel development of MGUS or AL should be considered.

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