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Light-Chain Amyloidosis Revealed By Peripheral Neuropathy

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Abstract:
Amyloidosis is a condition characterised by extracellular deposition of fibrillar proteins arranged in beta-pleated sheets, the formation of which is irreversible, thus impairing the proper functioning of various tissues. There are several types of amyloidosis, depending on the specific protein involved: Amyloid light-chain (AL)amyloidosis, Serum amyloid A protein (AA) amyloidosis, hereditary amyloidosis, senile amyloidosis and haemodialysis amyloidosis. AL amyloidosis is secondary to the synthesis of a light or exceptionally heavy chain of isolated monoclonal immunoglobulins.
Various symptoms can reveal the disease, including the disease, in particular renal, cardiac, neurological, osteoarticular, digestive, pulmonary and skin involvement.
We describe the observation of a 67-year-old patient with AL systemic amyloidosis which was revealed by peripheral neurological involvement, namely carpal tunnel syndrome and demyelising polyradiculoneuropathy with dysautonomia and macroglossia, confirmed by lingual biopsy. In front of immunoelectrophoresis of serum proteins "Typage par néphélémétrie Laser", which revealed the presence of an IgA class monoclonal component with a Kappa light chain Immunoelectrophoresis of serum proteins "Typage par néphélémétrie Laser", which revealed the presence of an IgA class monoclonal component with a Kappa light chain , a bone marrow biopsy was carried out, coming back in favor of B lymphocytic lymphoma.
This being said, amyloidosis should be systematically suspected in any patient with carpal tunnel syndrome accompanied by dysautonomia and pain, and a B-cell haemopathy should be sought, in particular Myeloma and non-Hodjkin's lymphoma.

Keywords: *AL amyloidosis, Carpal tunnel syndrome, Macroglossia, Kappa light chain, Myeloma*

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I. Introduction

Amyloidosis constitutes a large group of different diseases characterized by an extracellular deposition of fibrillar aggregates that derive from several naive proteins able to self-assemble, with an abnormal ordered antiparallel β-sheet structure. This dynamic growth of misfolding proteins generates insoluble and toxic amasses that may deposit in tissues in bundles[1,2].Moreover, the accumulation of pathologic proteins is largely related to a reduction of the folding stability and to a high tendency to achieve one or more conformation [1].

Deposition of amyloid fibrils may conduct to an impairment of organs and tissues, since any structure may be involved, including the heart, kidney, and nervous system.

Amyloid aggregates may be related to a mutant protein as in hereditary amyloidosis, or in immunoglobulin light chain (AL) amyloidosis; may be a consequence of a prolonged plasmatic excess of a normal protein, as in reactive systemic (AA) amyloidosis or β2-microglobulin (β2-M); or may be a consequence of the senescence process for wild-type transthyretin amyloidosis (ATTR-wt) also termed senile systemic amyloidosis [3].

The main sub-type of systemic amyloidosis is considered the “light-chain” (AL) amyloidosis, that is characterized by amyloid deposition of misfolded monoclonal immunoglobulin light chains, which polymerize as amyloid fibrils [4]. Then, the most common sub-type is the “reactive amyloidosis” (AA amyloidosis), related to several inflammatory disorders such as chronic infections or rheumatoid arthritis. Amyloidogenic activity is reported only for a slight percentage of immunoglobulin light chains. Variability of light chains in amino acid sequences is correlated to the plasma cell differentiation maturation process; thus, pathogenesis is related to a mutation of the genes encoding for the light chains as well as the occurrence of somatic mutations [1].

AL amyloidosis may present alone or associated with Waldenstrom’s macroglobulinemia or multiple myeloma [5], although studies regarding myeloma reported the occurrence of amyloidosis in only 12 to 15% of cases.

II. Case description

A 65-year-old patient, with no particular general history and no family history of amyloidosis, presented with tingling paresthesias in the first 3 fingers of both hands, which had been evolving for 3 years, with atrophy of the thenar eminence in both hands. The evolution was marked by the appearance 6 months later of gluteal muscle contractures, hampering his walking and gardening activities. 1 year later, a tongue hypertrophy appeared, interfering with eating and speaking, as well as a penis and scrotal hypertrophy. This was followed 1 year later by electric discharge-type pain on the posterior face of the deltoid, the posterior face of the thighs and the appearance of vesico-sphincter disorders with overflow urination and incomplete bladder emptying, as well as multiple adenopathies.

On admission, the neurological examination revealed :
- Limited lingual mobility with macroglossia and indurations on the lateral edges of the tongue (Cf. Figure 1).
-Hypertrophy of the shoulder girdle muscles (Deltoid muscles, upper trapezius) (Cf.Figure2) with thermoalgesic hypoesthesia of the first 3 fingers on both sides with positive Phalen's sign and radial reflex abolished on both sides.
-Hypertrophy of the pelvic girdle muscles (gluteal muscles) (Cf.Figure3) with patellar and achilles hyporeflexia.

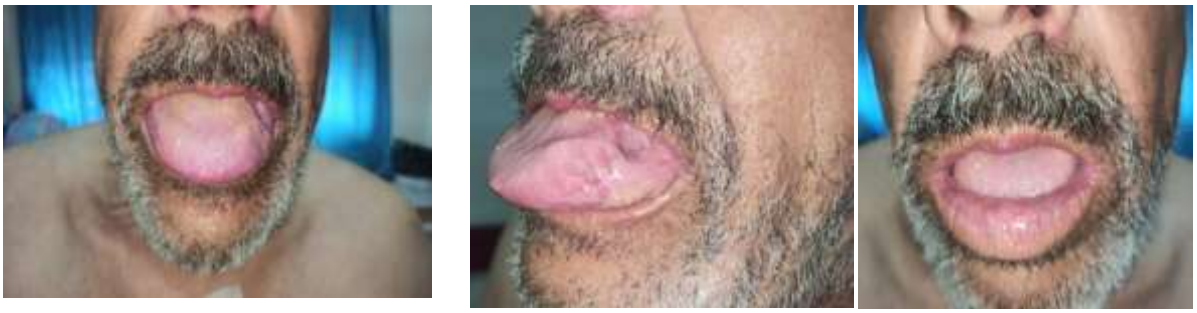

Figure 1(a-b-c): Macroglossia and indurations on the lateral edges of the tongue

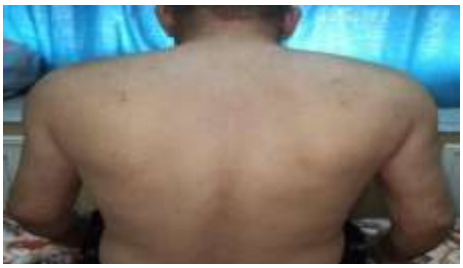

Figure 2: Hypertrophy of the shoulder girdle muscles

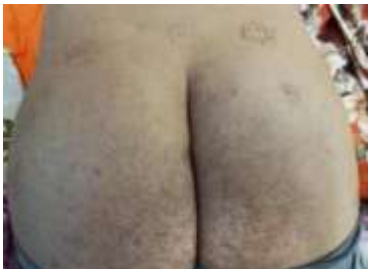

Figure 3: Hypertrophy of the pelvic girdle muscles

Somatic examination revealed:
-Right corneal opacity(Cf. Figure 4).
-Submandibular adenopathy, 4cm oval, long axis, mobile, not fixed to the deep plane, with no sign of inflammation opposite.
-Joint stiffness with limited joint amplitudes in both knees (flessum knees) and Halus Valgus, and scrotal hypertrophy.
-Hypertension with a BP of 135/80 mmHg and 160/80 mmHg after 3 min of orthostatism.

Figure 4: Right corneal opacity

The patient presents with vegetative manifestations such as constipation, diarrhoea, oesophagitis, premature satiety, erectile dysfunction, as well as vesicosphincter disorders such as dysuria, incomplete emptying, overflow micturition with the notion of lunette erythema.

Electro neuronomyographic (ENMG) examination revealed signs of extremely severe bilateral median nerve damage in the wrist (Carpal tunnel syndrome).

In the lower limbs, ENMG revealed a peripheral, sensory-motor, symmetrical, demyelinating neurogenic disorder, with prolonged F-wave latency in the external popliteal sciatic (SPE) and internal popliteal sciatic (SPI) nerves on both sides, and a slowing of the conduction velocity of the motor nerves and the right sural nerve.

Cytochemical study of the Cerebrospinal fluid (CSF) showed no abnormalities.

Standard laboratory work-up revealed renal failure, with urea 0.48 g/l, microalbuminuria 31 mg/l, creatinemia 17.53 mg/l and 24h proteinuria 614,56 mg.

Inflammatory panel: SV h1: 75 then SV h2: 101.

Thyroid function tests (TSH us, FT4, anti-TPO antibodies) were unremarkable.

Vitamin B12 low at 141 pg/ml (N: 200-1100 pg/ml)

Homocysteine elevated to 19.72 umol/l (N: 5.46-16.24 umol/l).

Lingual biopsy revealed squamous mucosa overlying conjunctivo-vascular and muscular chorion, with extracellular eosinophilic deposits stained congo red and showing birefringence in polarized light. All consistent with amyloidosis.

On the basis of the data from the lingual biopsy and protein electrophoresis, the patient was referred to the haematology department for specialist management. The diagnosis of multiple myeloma was raised and a more detailed work-up was carried out:

Immunoelectrophoresis of serum proteins "Typage par néphélémétrie Laser", which revealed the presence of an IgA class monoclonal component with a Kappa light chain and a collapse of polyclonal immunoglobulins. Serum alpha heavy chains were negative.

A kappa/lambda ratio value was 75.32 H (0.26-1.65).

Presence of a urinary Bence Jones protein of the KAPPA free light chain type, by immunofixation of urinary proteins.

A bone marrow biopsy showed diffuse infiltration by a malignant lymphoid tumour proliferation made up of small to medium-sized cells and a slightly densified reticulin framework.

Immunohistochemistry showed a mixed population of CD20+ lymphoid and CD138+ plasma cells

Bone marrow biopsy showed bone marrow infiltration by B lymphocytic lymphoma.

Magnetic resonance imaging (MRI) of the spinal cord and brain were without abnormalities.

Cardiac ultrasound revealed left ventricular hypertrophy.

Natriuretic peptide tests measuring BNP or NT-proBNP levels were: 215.4pg/ml (N< 125).

Overall, this was a lymphoplasmacytic lymphoma, revealed by peripheral neurogenic involvement in the context of systemic amyloidosis in a 65-year-old patient with no specific pathological history. Following the decision of the multidisciplinary team, the patient was started on Vincristine.

III. Discussion

Primary systemic AL amyloidosis is a hematological disorder associated with clonal plasma cell (or B lymphoid) proliferation resulting in monoclonal immunoglobulin light chain. In most cases, amyloidogenic monoclonal immunoglobulin can be detected in serum and/or urine, either by immunofixation or serum free light chain assay. These proteins will form fibrillar deposits in various organs, eventually leading to organ dysfunction and death [1].AL amyloidosis can affect all organs. The viscera most frequently affected by AL amyloidosis are the heart, kidneys, liver, gastrointestinal tract and peripheral nerves [6, 7].

In our case, peripheral neuropathy was the initial symptom and the main reason for medical consultation . Peripheral neuropathy is a common manifestation of AL amyloidosis, and the incidence of peripheral neuropathy in AL amyloidosis varies from 9.6 to 35% [8–10].

In our patient, peripheral neurogenic involvement manifested as carpal tunnel syndrome and length-dependent demyelinating sensory-motor radiculoneuropathy.

It should be noted that the typical pattern of amyloid neuropathy is symmetrical, length-dependent, lower-limb predominant, slowly progressing axonal polyneuropathy, with severe pain [8]. The involvement of small nerve fibers is more severe than that of large nerve fibers. Over time, both motor and sensory fibers and both large and small fibers become involved [11].In other studies, some patients also presented with lumbosacral radiculopathy and multiple mononeuropathy [8]. This reminds us that there are different types of peripheral nerve involvement in AL amyloidosis.

Autonomic neuropathy is a particularly severe complication that manifests with gastroparesis, diarrhea or constipation, impotence and severe postural hypotension [12]. Carpal tunnel syndrome is also common in AL amyloidosis [3].

Peripheral nerve involvement in AL amyloidosis is not well recognized due to a lack of awareness. When the initial symptoms present as peripheral neuropathy, there is often a delay in the diagnosis [13, 14]. In elderly males with neuropathy accompanied by pain and autonomic dysfunction, especially those with fatigue, the diagnosis of AL amyloidosis should be considered.

To make a definite diagnosis of AL amyloidosis, the presence of monoclonal protein is necessary. Our patient had kappa light chains. In AL amyloidosis, lambda light chains are more frequent than kappa light chains by about 3:1 [15].

If peripheral neuropathy presents as the initial symptom, peripheral nerve biopsy can help to make correct diagnosis. Gillmore et al. suggested that when possible, a biopsy should be taken from an apparently affected organ to achieve the highest sensitivity and specificity [16] , as was the case with our patient whose tongue biopsy had revealed squamous mucosa overlying conjunctivo-vascular and muscular chorion, with extracellular eosinophilic deposits stained congo red and showing birefringence in polarized light. All consistent with amyloidosis.

AL amyloidosis may be isolated (the so-called primary AL form) or associated with a B-cell haemopathy (myeloma, MGUS "monoclonal gammapathy of undetermined significance", Waldenström disease, secretory B-cell lymphoma).

AL amyloidosis is most often associated with an underlying plasma cell neoplasm, but is rarely caused by a B-cell non-Hodgkin lymphoma (NHL). When associated with NHL, there is often an IgM paraprotein present. This is known as IgM-related AL amyloidosis (IgM AL), and represents a distinct clinical entity with unique diagnostic and management considerations. Approximately 5-7% of patients diagnosed with AL amyloidosis will have IgM-associated disease [17]. When compared with non-IgM AL, IgM AL more commonly has soft tissue, lung and peripheral nerve involvement. Importantly, cardiac involvement has been shown to be less common in IgM AL (32-45% IgM AL vs. 70% with non-IgM AL) [18].

Most patients with multiple myeloma, who developed amyloidosis had a kappa/lambda ratio < 1:2, suggesting that lambda chains are associated with an increased risk of developing this complication [19].

The management of patients with amyloidosis is complex and depends on the associated systemic involvement [20].

Therapeutic choices depend on the patient's age, general condition and the extent of the disease [21].Prognosis depends on the degree of organ damage, ranging from several years to less than 6 months in patients with severe cardiomyopathy [10].

The prognosis of patients with AL amyloidosis associated with NHL remains uncertain. Our patient had no cardiac involvement, giving him a much poorer prognosis.

IV. Conclusion

As systemic amyloidosis is a potentially fatal disease, systemic involvement must be ruled out in the case of localized amyloidosis, to better adapt the therapeutic strategy. AL amyloidosis with underlying B-cell NHL is important to recognize due to its unique diagnostic and treatment considerations.

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