Myopathy as a rare presentation of AL amyloidosis

C. Meert, MD[1], S. Vanderschueren, MD, PhD[2], K. Poesen, MD, PhD[3], R. Sciot, MD, PhD[4], S. Pans, MD[5], M. Delforge, MD, PhD[1]

SUMMARY

Amyloid myopathy is a rare manifestation of amyloid light chain amyloidosis. We present a case of a 41-year old male with multiple myeloma with muscle hypertrophy, muscle weakness and enlargement of the submandibular glands as the only presenting clinical symptoms, illustrating the sheer difficulty of diagnosing amyloid light chain amyloidosis in patients with mainly soft tissue involvement. Even if there is a clinical suspicion, it is often hard to verify as Congo red stain and immunohistochemistry on muscle biopsy are not always reliable. After bortezomib-based induction treatment followed by autologous stem cell transplantation with high dose melphalan conditioning, he achieved complete haematological remission as well as a significant clinical response. We would like to highlight the importance of early diagnosis and treatment, as progression to more extensive visceral involvement can lead to rapid occurrence of organ failure and death.

(BELG J HEMATOL 2017;8(3):113-7)

INTRODUCTION

Symptoms in amyloid light chain (AL) amyloidosis are caused by deposition of insoluble fibrillar aggregates derived from immunoglobulin light-chains secreted by a monoclonal population of plasma cells. Depending on the organs involved, specific symptoms and signs will develop that often include the heart, kidneys, liver, gastro-intestinal tract and/or peripheral nervous system. In a minority of cases there is also involvement of the musculoskeletal system, causing muscle weakness and enlargement (amyloid myopathy), disorder of the joints (arthropathy) and lesions of the bone (osteopathy). In this article we report a case to illustrate the clinical presentation, diagnostic challenges and therapeutic approach of amyloid myopathy.

CASE REPORT

A 41-year old patient was admitted to the emergency department. He worked as an airline pilot, was previously in good general condition with a medical history of mouth ulcers treated with vitamin B supplements, an appendectomy and a negative investigation for weight loss nine years earlier. Over the last couple of months, he had the impression of gradually developing painless swelling of joints and muscles combined with prolonged morning stiffness and decreased mobility due to muscle weakness. He also complained of swelling of the tongue, again especially in the morning. During that first admission, swelling of muscles and tongue were not obvious on physical examination. Several lab tests were performed: erythrocyte sedimentation rate

[1]Division of Haematology, KU Leuven, Leuven, Belgium, [2]Research Department of Microbiology and Immunology, Laboratory for Clinical Infectious and Inflammatory diseases, KU Leuven, Leuven, Belgium, [3]Laboratory for Molecular Neurobiomarker Research, KU Leuven, Leuven, Belgium, [4]Translational Cell and Tissue Research, KU Leuven, Leuven, Belgium, [5]Department of Radiology, University Hospital of Leuven, Leuven, Belgium. Please send all correspondence to: M. Delforge, MD, PhD, KU Leuven, Division of Haematology, UZ Herestraat 49, bus 7003 36, 3000 Leuven, Belgium, tel: 0032 16 34 68 80, email: michel.delforge@uzleuven.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: AL amyloidosis, amyloid myopathy, autologous stem cell transplantation, muscle pseudohypertrophy.

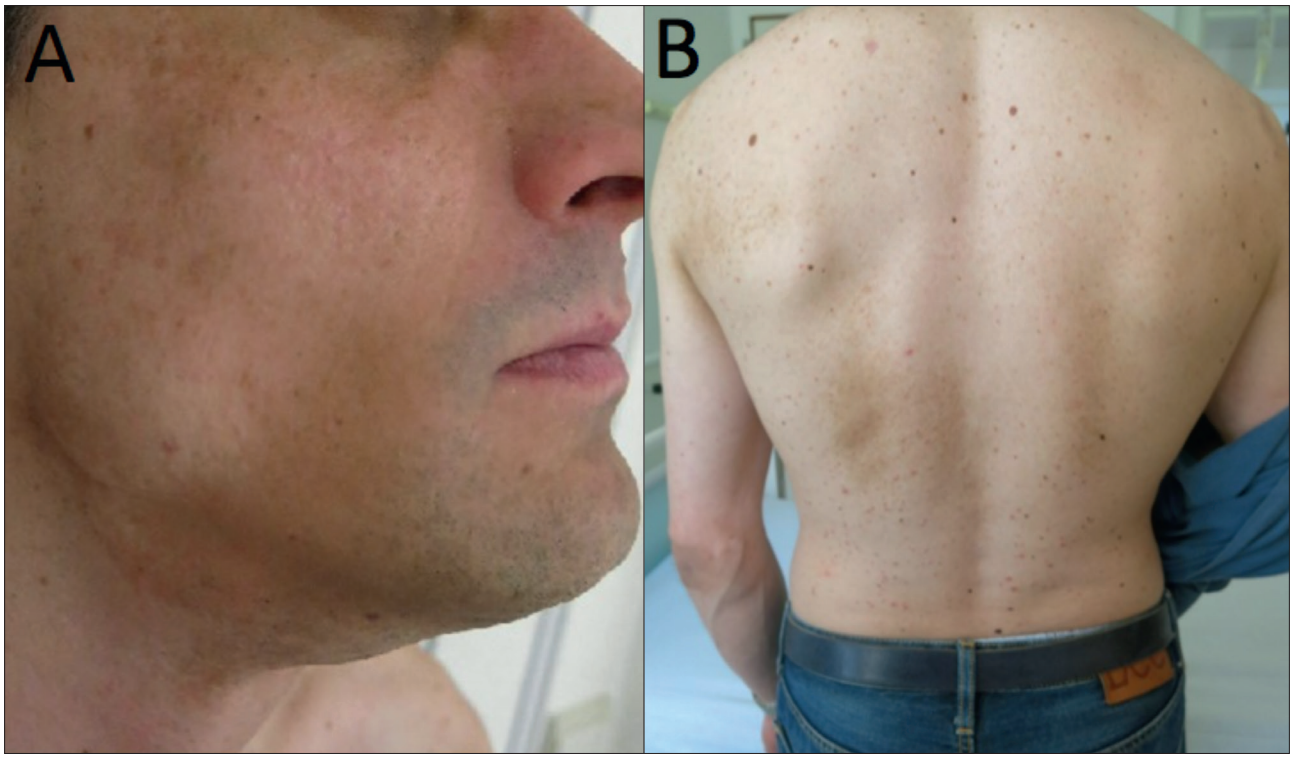

FIGURE 1. (A) Hypertrophy of the interscapular musculature. **(B)** Painless enlargement of the submandibular glands.

and C-reactive protein were not raised. Screening for rheumatic disorders and vasculitis, including anti-nuclear antibody test, rheumatoid factor, anti-citrullinated peptide antibody and anti-neutrophil cytoplasmic antibodies were negative. Borrelia serology test was also negative. Thyroid function was normal. No diagnosis could be made at that time and regular follow-up was planned.

Over the following months his symptoms gradually worsened. Due to his profession as a pilot, he visited different hospitals where he underwent several radiological examinations, including CT and ultrasound of the neck, chest X-ray and bone scintigraphy. However, these examinations did not reveal any abnormality. When he attended our internal medicine outpatient clinic, he had developed noticeable swelling of the musculature of both forearms and upper and lower legs with induration of the skin, as well as painless enlargement of the submandibular glands. A differential diagnosis between early scleroderma, HIV-related or familial forms of lipodystrophy, polymyositis, dermatomyositis, sarcoidosis, eosinophilic fasciitis and sialadenosis was made. Nail fold capillaroscopy was reported negative. EMG showed changes compatible with mild non-inflammatory myopathy. As there appeared to be no direct threat to organ function, it was decided to merely follow-up on this patient with regular clinical visits for the time being.

A month later he presented at the emergency department once more, describing sudden onset of painful swelling of the hands. Spotted hyperpigmentation of the skin had appeared around the face, arm pits, elbows and shoulder blades. At this time he had also developed considerable swelling of the interscapular muscles (*Figure 1*). There were no signs of peripheral neuropathy. Because of these symptoms a trial of steroids was given which stabilised but did not significantly improve the symptomatic burden. An MRI of the right upper leg showed sturdy appearance of the muscles, absence of any muscle oedema and symmetric inflammation of the posterior fascia. Histopathological examination of muscle tissue was consistent with mild inflammatory myopathy as there was some lymphocytic infiltration. A hypogammaglobulinemia was further investigated with serum protein electrophoresis, immunofixation and urine analysis. When the presence of monoclonal kappa light chains in serum and Bence Jones proteinuria was discovered, the patient was referred to the haematology department where further diagnostic work up regarding this paraprotein was initiated. Bone marrow biopsy confirmed an increase in plasma cells with kappa light chain restriction and amyloid deposition in the

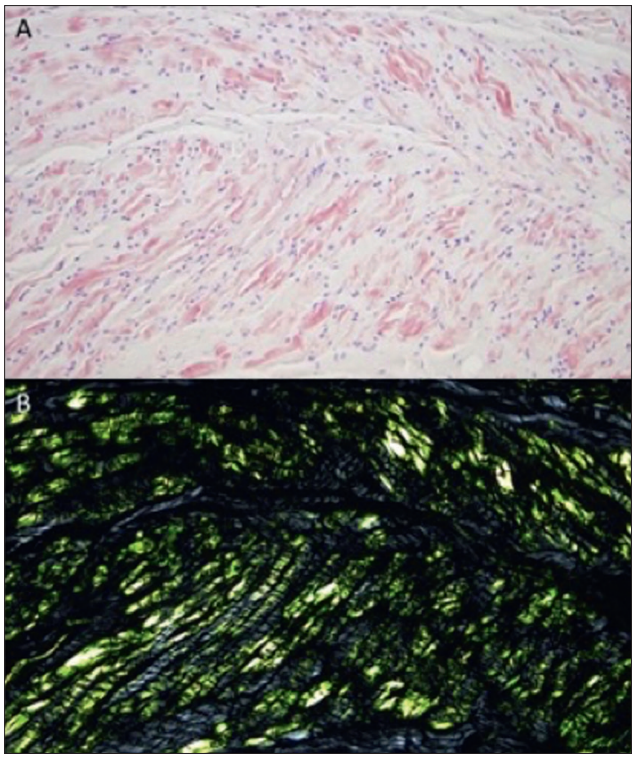

FIGURE 2. (A) Congo red stain revealing amyloid deposits on muscle biopsy. **(B)** Focal apple green birefringence when viewed under polarized light.

vascular walls. MRI whole body revealed several small lesions with high cellular density in the chest wall and lumbar spine, compatible with skeletal lesions caused by myeloma. Congo red stain on the muscle biopsy performed earlier revealed the presence of amyloid deposits showing focal apple green birefringence when viewed under polarised light (*Figure 2*). The diagnosis of light chain kappa multiple myeloma with secondary AL amyloidosis was made with the skeletal muscles and submandibular glands as primary target organs for amyloid infiltration in this patient.

As the heart is frequently affected in AL amyloidosis secondary to myeloma and cardiac amyloidosis being the most important prognostic factor, a cardiac ultrasound and MRI were performed showing no signs of cardiac involvement. Troponin and pro-brain natriuretic peptide were within the normal range. Liver and kidneys appeared to be spared as well. The kappa serum free light chain concentration was 686 mg/L (normal range 3.30 - 19.40). Lambda free light chain was 1.30 mg/L (normal range 5.70 - 26.30), while the ratio of kappa/lambda chain was high at 528 (normal range 0.30 - 1.20).

Induction chemotherapy in the form of bortezomib-cyclophosphamide- dexamethasone was initiated shortly after diagnosis. Serum free light chains normalised after two cycles. After four cycles there was a slight but transient increase in serum free light chains, even though a complete cytological and molecular remission was confirmed in bone marrow. Subsequently the patient underwent autologous peripheral blood stem cell transplantation following conditioning with high dose melphalan. As consolidation therapy, two cycles of bortezomib-dexamethasone were given afterwards. The patient has been in complete remission biochemically, no clonal plasma cells have been detectable by multiparameter flow cytometry and MRI with diffusion weighted imaging has shown no signs of disease recurrence since. From a clinical perspective, there was a significant decrease in muscle hypertrophy, stiffness and fatigue and increase in quality of life. One year after autologous stem cell transplantation he was allowed to start working again. However, he remains in close follow-up and attends the day clinic on a monthly basis for immunoglobulin infusions as a protective measure against infections because of persistent hypogammaglobulinemia.

DISCUSSION

Soft tissue involvement in AL amyloidosis might not be as rare as originally believed. In one series soft tissue, bone and joint manifestations were identified in 42.9% of 191 cases. In 9.4% it was the dominant organ system involved.[1] The most common manifestations were submandibular gland enlargement (31.9%), macroglossia (23.0%), carpal tunnel syndrome (13.1%), and amyloid arthropathy (3.7%). Enlargement of the skeletal muscles was found to be far less common (1.6%). The clinical finding of muscle enlargement is described as 'pseudohypertrophy' because muscle fibre diameter is not increased, but there is an increase in the number of fibers. Hence histology is much more consistent with hyperplasia rather than hypertrophy. The underlying pathogenesis is largely unknown, although it has been proven that immunoglobulin light chains or an associated factor can have a growth-promoting effect on myoblasts in vitro.[2] A prominent role in the process for myogenic progenitor or satellite cells that can maintain the capacity to stimulate adult muscle growth, repair and regeneration has been suggested.[3,4]

As our case already implies, diagnosing AL amyloidosis with a presentation of mainly soft tissue involvement can be quite challenging given that symptoms are mostly gradual in onset, aspecific and difficult to diffe-

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Amyloid myopathy is characterised by proximal weakness and painless muscle enlargement defined as pseudohypertrophy.**
2. **As serum and urine protein electrophoresis and even Congo red staining on muscle biopsy can be repeatedly negative, specific testing such as determination of serum free light chains, bone marrow, subcutaneous fat and/or rectal biopsy should be requested in cases with a high index of suspicion based on the patient's symptoms and clinical signs.**
3. **The mainstay of treatment currently consists of peripheral stem cell transplantation following high dose melphalan for patients who are eligible.**
4. **For patients who are not eligible for ASCT, the treatment of choice is a bortezomib-based regimen. Immunomodulatory drugs like lenalidomide have been used successfully as well.**

rentiate from other systemic diseases involving the musculoskeletal system. A delayed diagnosis can have dire consequences because it often leads to more extensive organ involvement that worsens prognosis and might compromise long-term outcome. Moreover, standard serum and urine protein electrophoresis can be repeatedly negative and muscle biopsy amyloid deposits were not recognised on initial biopsy in 19 out of 79 published cases.[5] Congo red staining is highly sensitive for detecting amyloid, but unfortunately the technique is prone to sampling error. Therefore, if there is a high index of suspicion based on clinical signs and symptoms, specific testing such as determination of serum free light chains, bone marrow aspiration for detection of clonal plasma cells, and subcutaneous fat and/or rectal biopsy for Congo red staining should be requested promptly.

Additionally timely diagnosis can save patients from cardiac or renal events which remain the major causes of death in AL amyloidosis. The mainstay of treatment consists of drugs targeting the monoclonal plasma cells including the proteasome inhibitor bortezomib and autologous hematopoietic stem cell transplantation (ASCT) following high dose melphalan in eligible patients. As induction chemotherapy, a combination of bortezomib and an alkylating agent like cyclophosphamide with dexamethasone (VCD) is commonly used. There is however a significant treatment-related mortality in patients with extensive organ, especially cardiac, involvement.[6,7] In addition to severe cardiac involvement, exclusion criteria for ASCT include advanced age, systolic blood pressure <100 mmHg, severe gastro-intestinal involvement, inadequate liver function, and severe autonomic neuropathy.[8] As less than a quarter of patients are eligible for ASCT, newer agents like proteasome inhibitors and immunomodulatory drugs have been tried and successfully used in the treatment of AL amyloidosis. A recommended frontline regimen is VCD, able to achieve haematological responses in 62% of 230 analysed cases. In 43% at least a very good partial response (VGPR) was obtained.[9] In a retrospective comparison of VCD versus cyclophosphamidethalidomide-dexamethasone (CTD), higher rates of VGPR were obtained and progression-free survival was longer. There was however no benefit on overall survival.[10] Lenalidomide in combination with dexamethasone and cyclophosphamide (RCD) has been shown to be effective in newly diagnosed and relapsed AL amyloidosis, obtaining haematological responses in 46% of newly diagnosed cases (VPRG in 25% and complete response in 18%) that seem to be durable as well. As there is a potential risk for more cardiac toxicities, it is recommended to start treatment with lower starting doses (e.g. 15 mg/d) compared to patients with myeloma.[11] New proteasome inhibitors like carfilzomib and ixazomib are currently under investigation for treatment of relapsed AL amyloidosis and have shown promising results.[12]

CONCLUSIONS

AL amyloidosis can cause muscle weakness and enlargement defined as pseudohypertrophy in a minority of patients. Early recognition is crucial as it can save patients from more extensive organ involvement before treatment can be initiated. The mainstay of treatment currently consists of peripheral stem cell transplantation for eligible patients or bortezomib-based regimens. If a significant suppression of the malignant plasma cell clone can be obtained, many patients can benefit from a long-term survival.

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