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# Autoimmune necrotizing myopathy in an octogenarian: a case report

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Autoimmune necrotizing myopathy (ANM) is a rare form of immune-mediated myopathy, with less than 200 cases reported worldwide. Its mean age of presentation is of 64 years and only 8 cases of octogenarians have been described so far. We present the case of NAM in an 82 year-old male patient who consulted with a 3-month painless subacute proximal upper and lower limb weakness that led him to prostration. He had been taking statins for two years as secondary stroke prevention. His work-up showed high CK levels, a pathological EMG and a muscular biopsy compatible with necrotizing myopathy. ANM is an infrequent pathology that has statin use as a known risk factor. In turn, statin prescription has been significantly boosted by the 2013 American Heart Association's cholesterol treatment guidelines. Unlike younger patients, a mild motor morbidity in older people can significantly worsen their risk of falls, which is consecutively associated with functional decline, hospitalization and death. We estimate that given the worldwide population ageing and the statinization process currently ongoing, geriatric cases will increase in frequency and we believe that due to their extreme frailty statin indication and close follow-up should be mindfully considered in octogenarians.

**Key words**: Autoimmune necrotizing myopathy, Statinization, Population ageing, Geriatric patients, Octogenarians

## INTRODUCTION

Autoimmune necrotizing myopathy (ANM) belongs to the infrequent group of immune-mediated myopathies [1], of which it approximately represents a 10% [2]. It was first acknowledged as a distinct entity in 2004 [3] and 4 series of patients have been since published, with the largest being of 100 cases [4-8]. ANM affects men and woman in an equal fashion with a mean age of presentation of 64 years [4 8]. Statin use is the main known risk factor for its development, although approximately 33% of the cases occur without a prior exposure to them [9]. In that regard, the 2013 ACC/AHA atherosclerotic cardiovascular prevention guidelines [10] introduced both a new classification method and therapeutic algorithm for blood cholesterol treatment which determined that an estimated 1 billion people worldwide have an indication of statin therapy [11]. In addition, global population ageing is also an ongoing trend [12] that associated with the massive use of statins (statinization [11]) will probably result in older affected patients who not necessarily have the same therapeutic response and resilience of younger ones [13]. So far, there are only eight reported cases of ANM in octogenarian patients [4 6 7 9 14-16] and here we present the case of an 82-year-old patient along with a small review of the currently available literature of ANM focusing in the elderly.

## CASE REPORT

An 82-year-old patient was evaluated in our hospital due to a painless subacute mobility restriction that had

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started 3 months prior to the consult and evolved in the following two months to an inability to walk. He had a history of Chagas disease, acute myocardial infarction, hypertension, alcohol and tobacco abuse, mild cognitive impairment and ischemic stroke without clinical sequelae. He had been taking 10 mg of atorvastatin daily for the past two years and was also treated with carvedilol, enalapril and finasteride. On physical examination he had four limb proximal weakness (Medical Research Council Scale -MRCS-: 3) with no strength limitation in distal muscles (MRCS: 5). He had absent deep tendon reflexes and distal hypopalesthesia. His body mass index was 17. Laboratory findings included CK levels of 3996 U/L, aldolase of 40 U/L, LDH of 898 U/L, AST 282 of U/L, negative HIV and VDRL and normal ionogram, calcium and TSH levels. His EMG showed a chronic polyneuropathy as well as myopathic motor unit potentials in proximal upper and lower limb muscles and spontaneous muscular discharges both in proximal and distal muscles (Fig. 1). A deltoid biopsy was performed which revealed necrotic muscle fibers associated to a macophagic infiltrate (CD 68+), without lymphocytes, amyloid deposits, fiber vacuolization or vasculitis; compatible with a necrotizing myositis (Fig. 2). We were only able to perform anti-SRP testing, for which he was negative. He was started on prednisone 1 mg/kg/day and weekly methrotexate 15 mg, with a slow but steady normalization of his CK levels with no clinical amelioration at two months but with mild strength improvement in his upper limbs (MRCS: 4) at the three month follow-up.

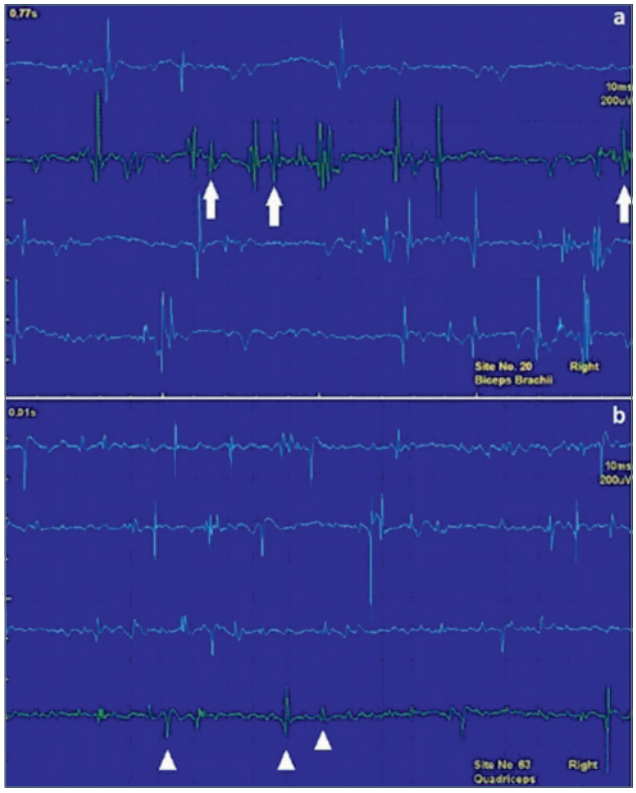


**Figure 1.** Electromyography of the right biceps (a) and quadriceps (b). (a) myopathic motor unit action potentials (white arrows) with reduced interference pattern at maximal effort. (b) spontaneous muscular activity (arrowheads: positive sharp waves and fibrillations) at rest.

## DISCUSSION

ANM is a 15-year-old entity characterized by subacute or chronic proximal generalized weakness associated with elevated CK levels [4 7-9 14], frequent myalgia [4 5 9], exceptional diyphagia [1 17] or extra-muscular involvement [2] and a characteristic non inflammatory muscular biopsy with abundant necrosis [4 5 8 14 18]. Its physiopathology is unknown [9 18 19] and it has been associated with HIV infection, connective tissue diseases, malignancy and the use of statins regardless of the type or time of exposure [4 5 7 9 14 17]. Two antibodies have been described in association with ANM: anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (Anti-HMGCR) and anti-signal recognition particle (Anti-SRP) [20]. Anti-HMGR antibodies are usually present in patients with a history of statin use [6 8 21] who have developed ANM or other inflammatory myopathies [22]. Anti-SRP antibodies are also not exclusive of ANM but are less frequently linked to statin exposure [7]. ANM has a worse prognosis than the other immunomediated myopathies, with frequent

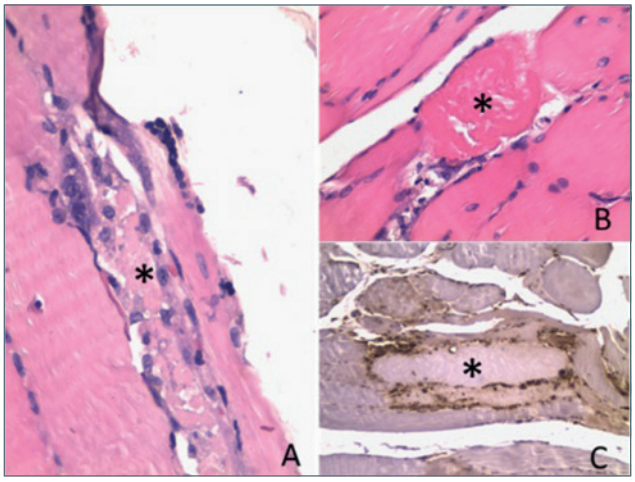


**Figure 2.** Deltoid muscle biopsy showing a myofiber necrosis (*) with fragmented eosinophilic cytoplasm, surrounded by a macrophage infiltration. A- Hematoxylin-eosin stain X100. B- Hematoxilin-eosin stain X400. C- CD68 peroxidase-immunohistochemistry marking macrophages. X100.

relapses [4] and disabling morbidity [2]. Initial treatment is with corticosteroids or intravenous gammaglobulin [9], early associated to a steroid sparing agent such as methrotexate, azathioprine, mycophenolate mofetil, tacrolimus or rituximab [2 19].

This patient is one of the few octogenarians so far reported. Only eight others have been described: 4 men [4 14 16], 3 women [6 9 14] and one patient without sex specification [7]. Nazir et al. [8] with their systematic review of 100 cases and Kassardjian et al. [7] with 63 ANM patients (not included in Nazir's review) are the longest series/analysis of patients reported so far, from which is possible to speculate that even at the expense of the very probable underestimation of the total number of cases, nowadays octogenarians only reach a 5% of the ANM cases.

Our patient delayed the initial consultation since it was done when he was already bedridden in spite of having been symptomatic for three months. This might appear counterintuitive but it can be at least partially explained by his mild cognitive impairment in addition to him being an unbefriended older adult, a social situation that is becoming more and more frequent [23].

He had the typical generalized proximal weakness of myopathies but did not have myalgias, which are present in 16 to 75% of the ANMs depending on the series [4 5 9].

Over the past decade, serum antibodies have become key elements for autoimmune myositis diagnosis and have nowadays clinical defined associated syndromes [20 24]. Some of them (myositis-specific antibodies or MSA) are specific immune-mediated muscle pathology whereas the rest (myositis-associated antibodies or MAA) can also be found in connective tissue diseases [20 24]. Anti-HMGR and Anti-SRP antibodies belong to the first group and are the only antibodies associated with ANM [1]. Since testing against HMGCR is not available in our network hospitals, we could only measure anti-SRP titers, which were normal. Due to the fact that seronegative ANMs have a stronger association with malignancy [2], particularly small cell lung carcinoma and colonic carcinoma [17], we assumed the worst-case scenario and performed a whole body CT scan, which showed no present malignancy.

Our patient's initial CK levels exceeded 3000 U/L and returned to normal after two months of treatment. CK levels and antibody titers have been reported to correlate with disease activity [2 20] and precede clinical recovery in weeks or months [2 17]. Regardless, clinical improvement has been reported to be both immediate [9] or delayed [15] and therefore a better treatment response in our patient cannot be excluded. This was also the case of one of the few octogenarians so far reported [14], while the rest's recovery was total in one case [16], near complete in two [9 15], unknown due to lost of follow-up in one [4] and not specified in the remaining two [6 7]. In spite of these evolutions seeming rather benign, it is imperative to consider due to the frailty of geriatric patients even a mild locomotive disability usually has enough impact to determine a restriction in basic and instrumental activities of daily life [23], and that impact in octogenarians is even bigger [13 26].

Population ageing is noticeable through the entire world [12] and unlike younger patients, older people are prompt to metabolize drugs at more variable rates, suffer from syndromes secondary to multiple etiologies (i.e.: geriatric syndromes) [27 28] and have atypical symptoms for common pathologies [29]. In particular, upper and lower extremity weakness has been identified as an independent predisposing factor for falls in the elderly [30 31], which in turn are associated with distress, functional decline, hospitalization and death [27 28].

While in general immunomediated diseases in geriatric patients are rare [32], ANM is strongly associated with the use of statin which are being increasingly indicated since the 2013 American Heart Association guidelines of cholesterol management [10]. It suggests moderate intensity regimens as secondary prevention for cardiovascular events in individuals older than 75 years [10]. Although there is no consensus in the recommendation for primary prevention in that age group, its prescription is of common practice and will probably also multiply [31].

Our patient had a history of an ischemic neurovascular event with transitory symptoms 8-years prior to the consult and had stopped using (or was never given) statins. Nevertheless, they were re-instaurated in the previous two years for reasons that the patient could not refer. In spite of guidelines and recommendations being based on statistically inferred benefits which surpass the risks of adverse events, we believe it needs to be minded that geriatric patients do not necessarily behave like younger adults and to the best of our knowledge there have been no trials addressing statins-treatment risk-benefit among this population [11 23 31].

In conclusion, we would like to stress that although nowadays a rare entity, given the statinization process we are currently under, ANM incidence could largely increase and in the worldwide population ageing-scenario its associated morbidity could have an even bigger impact than the so far reported. Therefore, we believe that general practitioners as well as neurologists should bear in mind this entity to carefully monitor the evolution as well as to perform a thorough and individual assessment of the risk and benefits of statin use in geriatric patients.

## Conflicts of interest

The Authors declare to have no conflict of interest.

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