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Long-term efficacy of alemtuzumab in polymyositis

Sr, We present a PM patient refractory to standard therapy, who showed effective clinical remission after a single treatment cycle with alemtuzumab for >3 years of follow-up. This is, to our knowledge, the first report of long-term efficacy of alemtuzumab in the treatment of PM.

This Caucasian male patient was born in 1957. PM manifested at the age of 52 with progressive symmetrical muscle weakness and myalgia of proximal limb muscle-ture starting in 2009. At first consultation the patient showed a positive Gower’s sign and maximum walking distance was reduced to 500 m. The diagnosis of PM was established in May 2009 and was based on typical clinical presentation, elevated creatine kinase (CK) levels (3237 U/l), myopathic changes in the electromyogram and muscle biopsy showing endomysial CD8+ T cell infiltration (Fig. 1A). Ro-52 autoantibodies were positive; other myositis-specific autoantibodies (anti-Jo-1, anti-Mi-2 or anti-SRP) could not be detected. Therapy with oral prednisolone (80 mg/day) in combination with azathioprine (start dose 50 mg/day, end dose 225 mg/day) was initiated, significantly ameliorating muscle weakness and myalgia. Azathioprine therapy had to be withdrawn in August 2009 due to extremely elevated liver enzymes. Under subsequent therapy with ciclosporin (200 mg/day), it was not possible to further taper the prednisolone dose (<40 mg/day). The disease course showed sustained progression, as CK levels were still considerably elevated. Thus we started i.v. cyclophosphamide (monthly cycles at 2 × 1000 mg, followed by 2 × 1300 mg), which was not able to slow disease progress, decrease CK level or spare corticosteroid therapy. Walking distance further deteriorated to 150 m. A combination therapy of IVIG (start dose 5 × 40 g/day, followed by monthly cycles of 3 × 30 g/day) and MTX (start dose 7.5 mg/day, end dose 30 mg/day) was initiated in September 2010. After an initial favourable response, the disease progressed further despite increasing MTX doses to 30 mg/day, with CK levels increasing to 5242 U/l, and the patient reported significant deterioration of muscle strength. IVIG and MTX were subsequently withdrawn. After giving informed consent, the patient received alemtuzumab (one cycle at 5 × 30 mg) under premedication with clemastine, ranitidine, paracetamol, ondansetron and i.v. methylprednisolone (250 mg/day) in May 2011 (Fig. 1B). Alemtuzumab led to a rapid and long-lasting depletion of T cells, B cells and NK cells (supplementary Fig. S1, available at Rheumatology Online). At first application, the patient suffered from infusion-related reactions with fever and chills, while subsequent infusions were well tolerated. Afterwards the patient received famciclovir, fluconazole and cotrimoxazole for infection prophylaxis until CD4+ T cells reached >200 cells/µl. Approximately 12 weeks later the patient noticed an improvement in muscle strength, which was confirmed on physical examination and was slightly preceded by a continuous decrease in CK level. In addition, constant improvement of walking distance and prednisolone tapering to 7.5 mg/day was achieved. Until the beginning of July 2014 the disease course remained stable, when the patient reported progressive myalgia and deterioration of walking distance. No severe adverse events have been observed so far. We decided to administer another cycle of alemtuzumab.

Current therapeutic options of PM consist of corticosteroids, IVIG and immunosuppressants such as AZA or MTX [1]. These therapies are mainly non-specific, have various adverse effects and often show limited efficacy. Monoclonal antibodies are emerging as new therapeutic strategies for autoimmune myopathies, however, to date only limited evidence exists for their use [2]. Alemtuzumab is a monoclonal anti-CD52 antibody leading to rapid, long-lasting depletion of immune cells, but not of haematopoietic stem cells. After depletion, the reconstitution of immune cells follows a certain pattern, with T cells being the last to recover after years [3]. Here, anti-CD52 treatment was
initiated under the rationale that CD8+ T cells are critically involved in the progressive destruction of muscle cells in PM and are found clonally expanded in the muscle of PM patients [4].

In our standard therapy-refractory patient, we observed a stable disease course with constant improvement of muscle strength lasting for ~3 years, adding to previous reports providing short-term observations of alemtuzumab efficacy in PM [5, 6]. It should be kept in mind, however, that interpretation of our data is limited by previous immunosuppressive medication.

The high incidence of secondary autoimmunity (~30%) in alemtuzumab-treated patients should always be considered in therapeutic decisions [7]. Thorough surveillance is needed to prevent serious adverse events after alemtuzumab infusion.

In conclusion, we present the first long-term follow-up case of adult PM effectively treated with alemtuzumab. Therefore alemtuzumab might be a new, promising alternative in long-term PM therapy. However, randomized and controlled trials are required to draw definite conclusions.
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Supplementary data

Supplementary data are available at Rheumatology Online.

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The GTF2I rs117026326 polymorphism is associated with anti-SSA-positive primary Sjögren’s syndrome

Sirl, Primary SS (pSS) represents a systemic autoimmune disease mainly targeting exocrine glands and manifesting as dryness of the mouth (xerostomia) and eyes (xerophthalmia) [1]. It is characterized by lymphocytic infiltration in these glands and by the presence of a panel of circulating autoantibodies. Among these, those directed against SSA and SSB are the most abundant [1]. As is common for autoimmune diseases, the pathogenesis of pSS involves genetic predisposition as well as environmental factors. Determining the genetic basis of pSS will provide an important research tool for exploring the pathogenesis of the disease.

In a recent study published in Nature Genetics, Li et al. [2] reported the first genome-wide association study for pSS. In addition to the HLA locus, three non-HLA susceptibility loci, GTF2I, STAT4 and TNFAIP3, were identified in their study [2]. Unexpectedly, the locus indicating the strongest susceptibility was not the HLA locus but the GTF2I rs117026326 C/T polymorphism, with the T allele as the risk allele (OR 2.20, \( P = 1.31 \times 10^{-53} \)) for pSS. Moreover, the latter locus has not been reported so far to be associated with any other autoimmune diseases [3, 4], indicating a potential pSS-specific genetic predisposition. The discovery of the GTF2I rs117026326 polymorphism as a strong and disease-specific susceptibility locus provides a hint regarding pSS-specific pathogenesis. Therefore, confirmation of disease relevance and a more detailed analysis of this locus will help considerably in exploring the pathogenesis of pSS.

The GTF2I rs117026326 polymorphism was reported to be associated with pSS in Han Chinese but not in Caucasians [2, 5], suggesting an ethnic-specific