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Alemtuzumab (Campath-1H) for Treatment of Refractory Polymyositis

To the Editor:

We describe a 48-year-old woman with polymyositis refractory to conventional therapy who responded to alemtuzumab (Campath-1H). This humanized lymphocytotoxic monoclonal antibody recognizes the cell-surface glycoprotein CD52, abundantly expressed by B and T lymphocytes, monocytes, and natural killer cells.

Our patient presented in 1996 with seropositive, antinuclear antibody-negative, nonerosive rheumatoid arthritis, which was treated with sulfasalazine 2 g daily. In 1998 she developed generalized muscle pains; investigations showed creatine kinase (CK) was > 5000 U/l, anti-Jo-1 antibody was positive; muscle biopsy and electromyography confirmed an inflammatory myopathy. There was no evidence from this or subsequent biopsies to suggest an inclusion body myositis. She was initially treated with prednisolone 45 mg daily and azathioprine 150 mg daily but these failed to control her myositis. Over the next 8 years various other agents were prescribed, singly and in combination, and prednisolone was continued (Table 1).

Despite these regimes her CK always remained above 3000 U/l and she became progressively weaker. Prior to treatment with alemtuzumab in 2006, she required a wheelchair and assistance to rise from sitting. Muscle power was 3/5 MRC grade in the proximal lower limbs, 4- or 4/5 in the upper limb and distal muscle groups. She became increasingly breathless and hypoxic (pO₂ 7.7 kPa inspiring room air), with reduced alveolar diffusing capacity (KCO 1.09; predicted 1.51). Further investigations revealed significant pulmonary arterial hypertension (PAH) at right-heart catheterization with mean pulmonary artery pressure 44 mm Hg (normal 10-17 mm Hg), pulmonary vascular resistance 10.09 Wood units (normal 2-4 Wood units), and pulmonary artery wedge pressure 8 mm Hg (normal 5-13 mm Hg). A high resolution computerized tomography chest scan showed interstitial fibrosis with a nonspecific interstitial pneumonia pattern. In addition there was respiratory muscle weakness (sniff nasal inspiratory pressure 21

Table 1. Drug therapy used prior to alemtuzumab therapy. Prednisolone was continued at varying doses; medications listed were also used in combination. Methotrexate was avoided because of patient's respiratory disease.

Drug Therapy	Duration, mo	Reason for Cessation
Azathioprine 150 mg	3	Inefficacy
Cyclosporine 200 mg	34	Inefficacy
Intravenous immunoglobulin 0.5 mg/kg (monthly)	3	Inefficacy
Chlorambucil 2 mg daily	12	Inefficacy
Adalimumab 40 mg alternate weeks	3	Inefficacy
Adalimumab 40 mg weekly	3	Inefficacy
Mycophenolate mofetil 2 g	24	Inefficacy
Tacrolimus 2 mg daily	12	Inefficacy
IV cyclophosphamide 15 mg/kg; methylprednisolone 700 mg, 6 pulses at 3 weekly intervals	18	Inefficacy

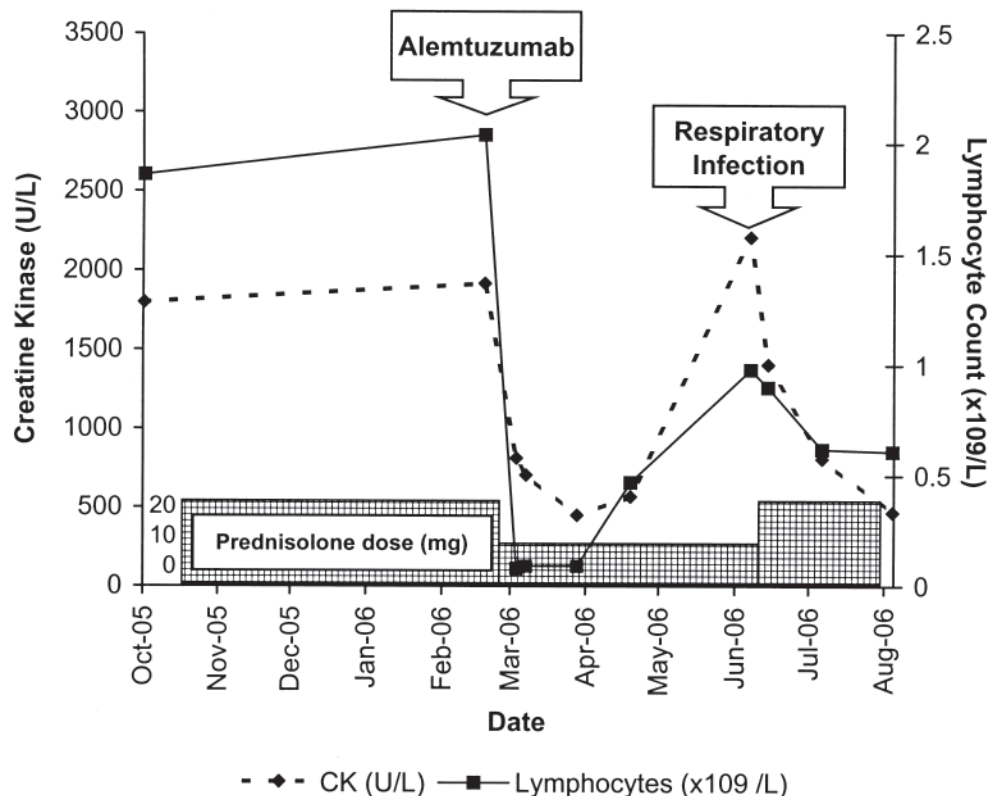


Figure 1. Changes in CK, absolute lymphocyte count, and prednisolone dose with time.

mm Hg; predicted 84 mm Hg). The PAH was considered to be out of proportion to her interstitial lung disease and she was given sildenafil, as a targeted pulmonary vasodilator for connective tissue disease-associated PAH.

In March 2006 she received 120 mg alemtuzumab intravenously over 4 days, with glucocorticoid premedication on Day 1. She experienced a "first-dose" reaction consisting of fever, rigors, and bronchospasm, but there were no other adverse effects. Following therapy she received oral cotrimoxazole, acyclovir, and nystatin for 1 month as prophylaxis against infection, and her prednisolone dose was immediately reduced to 10 mg. Her muscle power improved over a few weeks. Functionally she was now able to rise from sitting and walk independently, and there was an increase to 4–/5 MRC grade in the proximal lower limbs, and to 4 or 4+/5 in the upper limb and distal muscle groups on objective assessment. Biochemical and hematological responses are illustrated in Figure 1. A lower respiratory tract infection 3 months after receiving alemtuzumab corresponded with a clinical and biochemical relapse of her myopathy. Mycophenolate mofetil (MMF) was restarted at 1 g bd, and her prednisolone dose was increased again to 20 mg, with subsequent improvement. Unfortunately there was no improvement in respiratory function following Campath-1H and, despite treatment with sildenafil, the patient died in June 2007. The most recent CK prior to her death was 150 U/l (May 2007).

Polymyositis is an idiopathic inflammatory myopathy diagnosed by the combination of proximal muscle weakness, elevated muscle enzymes, and an invasive T cell infiltrate on muscle biopsy, in the absence of features suggestive of inclusion body myositis. There are few randomized, controlled trials to guide decisions on treatment¹. Conventionally, oral corticosteroids are used initially. Other immunosuppressive drugs are added if there is insufficient response or as steroid-sparing agents. Reports of therapies that are effective in polymyositis refractory to standard treatment are limited to case reports, case series, and uncontrolled studies².

Our patient responded to alemtuzumab when other treatments, includ-

ing cyclophosphamide and IV immunoglobulin, had failed. Autologous stem-cell transplant was considered, but would have been too hazardous due to her cardiorespiratory disease. The appearance of numerous T cells and few B cells on her muscle biopsy led us to use alemtuzumab rather than rituximab. Alemtuzumab is potentially lymphocytotoxic for both B cells and T cells and is licensed for the treatment of certain types of chronic lymphocytic leukemia. It has also been used effectively to treat refractory autoimmune and inflammatory diseases including systemic vasculitis^{3,4}, ocular inflammation⁵, multiple sclerosis⁶, and rheumatoid arthritis⁷. After administration to our patient there was a rapid decline in lymphocyte count, matched by a precipitous fall in CK. Both rose transiently at the time of a respiratory infection several weeks later, but notably, CK was subsequently controlled with MMF, which had previously proved ineffective. It also proved possible to reduce her prednisolone dose. Sadly, her pulmonary function did not improve, presumably reflecting irreversible fibrosis in the lung parenchyma and pulmonary arteries.

Our patient had previously refractory polymyositis with lymphocytic infiltrates, and her muscle disease responded rapidly to a single course of treatment with alemtuzumab. A subsequent flare of symptoms was controlled with MMF, a previously ineffective drug. We advocate further investigation of alemtuzumab in this type of setting.

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Early Callus Formation in Human Hip Fracture Treated with Internal Fixation and Teriparatide

To the Editor:

Osteoporosis is becoming a serious public health problem in Asian countries. Hip fractures represent the most significant osteoporotic fractures. Except under conditions of extremely poor health status, treatment with surgical intervention and early mobilization remains the gold standard for treating hip fractures. Recently, teriparatide, recombinant parathyroid hormone (PTH 1-34), has been approved for treatment of osteoporosis. We describe an enhanced callus formation phenomenon in a patient with hip fracture who was treated by internal fixation and daily PTH 1-34 injection.

A 62-year-old woman with liver cirrhosis experienced sudden right groin pain when undertaking rehabilitation. Radiographs revealed a basal neck fracture (Figure 1a). The fracture was immobilized with a percutaneous cannulated screw. Due to her severe osteoporotic condition, daily PTH 20 µg injection (Eli Lilly, Indianapolis, IN, USA) with calcium 1500 mg and vitamin D 400 IU supplement were also prescribed. Protected weight-bearing with the use of double crutches was suggested for her post-operative program.

One month after surgery and PTH treatment, an external callus formation was noted around the fracture site (Figure 1b), which became more solid 3 months later (Figure 1c). The fracture line became invisible and the patient was pain-free 6 months postoperatively (Figure 1d). At 1-year followup, she had resumed previous activity (swimming, bicycle riding) without difficulty or pain.

Estrogens, bisphosphonates, and selective estrogen receptor modulators (SERM) are used in treatment of osteoporosis as inhibitors of bone resorption¹. Cao, *et al* reported that use of antiresorptive agents suppressed callus remodeling in ovariectomized rats².

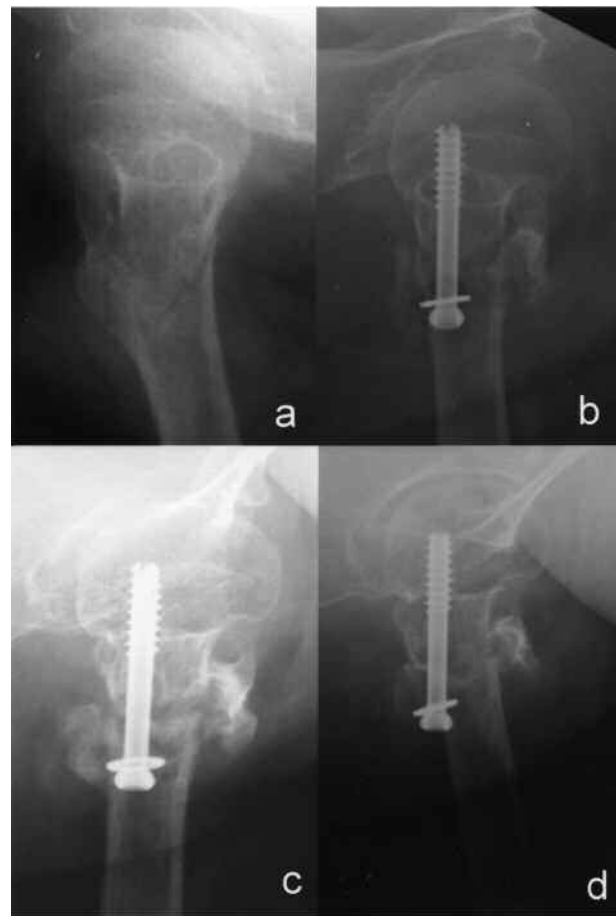


Figure 1. (a) Preoperation roentgenogram showing complete basal neck fracture. (b) One month after operation, showing callus formation. (c) Three months after operation, the amount and density of callus had increased. (d) Six months after operation, callus was consolidated and the fracture line is scarcely visible.

PTH is a calcium homeostasis regulator³. Low extracellular calcium level stimulates PTH secretion, which promotes calcium reabsorption in kidney and bone resorption⁴. Continuous infusion of PTH was reported to cause osteopenia, probably due to greater acceleration of bone resorption than bone formation; whereas intermittent PTH treatment has been shown to increase bone formation and bone mass, leading to improved compressive strength. The mechanisms of the diverse actions of the hormone on bone remain obscure, and may be caused by differences in intracellular signaling mechanisms⁵. Animal studies with intermittent PTH also showed a significant cancellous bone mass increase in ovariectomized models⁶. Skripitz and Aspenberg demonstrated that PTH treatment will increase the amount of new bone formation and implant fixation strength in normal rats^{7,8}.

We describe the first case of enhanced callus formation after daily teriparatide injection in a patient with hip fracture. Based on experience of other hip fractures treated during the same period, it is a reasonable presumption that early callus formation was due to usage of PTH. To our knowledge, enhanced callus formation by PTH in fracture has not been reported before. Intermittent PTH therapy seems to be a promising adjuvant therapy of fracture healing. Randomized controlled clinical trials are required, focused on the effect of different doses or duration of teriparatide treatment.