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LETTER TO THE EDITOR

SUCCESSFUL "SALVAGE" THERAPY OF INTRAVENOUS CYCLOPHOSPHAMIDE FOR REFRACTORY POLYMYOSITIS IN AN ELDERLY PATIENT: CASE REPORT

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Dermatomyositis and polymyositis may affect children and adults and are now widely recognized as major causes of disability which, thanks to the introduction of immunosuppressive drugs, is often treatable, at least to some extent. Few data exist regarding polymyositis in elderly patients. We describe a case of refractory life-threatening polymyositis in an elderly patient, successfully treated with intravenous cyclophosphamide.

Idiopathic inflammatory myopathies are usually regarded as a heterogeneous group of autoimmune rheumatic diseases defined by criteria which incorporate clinical features, serological abnormalities, electromyographic changes and typical histological appearances (1-2).

Although there has never been an adequate double-blind controlled trial of corticosteroids, it seems certain that these drugs, in spite of all their side-effects, have substantially improved the outcome of patients with inflammatory muscle disease. Nevertheless, neither steroids alone nor steroids in conjunction with a variety of other immunosuppressive drugs, including azathioprine, methotrexate, cyclosporin, cyclophosphamide and mycophenolate, have the capacity to induce full remission in every case. Likewise, other modalities, including intravenous immunoglobulin, total body irradiation and thoracic drainage, have either not been adequately assessed in double-blind controlled trials or have been shown to be of limited benefit in trials of modest duration. In more resistant cases of polymyositis or dermatomyositis it may be necessary to use cyclophosphamide, cyclosporin or the promising newer immunosuppressive agents mycophenolate mofetil or tacrolimus to achieve disease control (3-4).

MATERIALS AND METHODS

Polymyositis tends to present between 30 and 60 years old, and age seems to be an important predictive factor. Marie et al (5) reported that complete remission from polymyositis/ dermatomyositis was less frequent and the mortality rate was higher in elderly patients than in younger patients. Nevertheless, to our knowledge few data exist on the clinical course and response to treatment in patients > 70 years old. We therefore report a case of refractory polymyositis in an elderly patient.

A.L., male, 75 years old, suffering from hypertension and who had previously undergone surgical treatment for rectal adenocarcinoma with terminal ileostomy, in February 2004 referred the onset of a lilac-coloured rash over eyelids, a cutaneous erythema involving upper chest and upper back and progressive symmetrical proximal muscle weakness of the upper and lower limbs. He was admitted to the hospital and was diagnosed with dermatopolymiositis according to Bohan and Peter criteria (1). He was treated with oral prednisone (75 mg/daily) with a rapid clinical improvement. After seven

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months the steroid dosage was progressively reduced. In November 2005 he suffered from a clinical relapse and was hospitalized; he was treated with high dose methylprednisolone i.v with poor benefit and progressive clinical worsening and bed restriction. From December 2005 he began to suffer from dysphagia, firstly for liquids and then for solids; he was therefore transferred to our Division of Internal Medicine. On admission he was in poor clinical condition, vigilant, well-oriented, apyretic, eupnoic at rest, restricted to bed due to the complete immobility of upper and lower limbs and was suffering from complete dysphagia and diffuse polymyalgias; his A.D.L. index score (6) was 0. On physical examination, an erithematous-desquamative rash was present on the face, hands and upper chest and back, inspiratory crackles were heard on both lower lung fields, while heart sounds were normal.

Initial laboratory studies showed elevated levels of muscle enzymes, including creatinine kinase (CK) and lactate dehydrogenase (LDH) (Table I; Fig. 1 and 2). The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) levels were high. The rheumatoid factor was negative and the antinuclear antibody titre was 1: 320 with a cytoplasmic pattern. Anti-SRP and Anti M2 antibody was positive (Table I). Other chemistry profiles showed a neutrophil leucocytosis and a mild increase of creatinine levels (Table I). The arterial blood gas analysis without O_2 supplementation showed $PaCO_2$ of 23.2 mmHg, PaO_2 of 65.7 mmHg, and O_2 saturation of 92.2%. To examine the possibility of cancer recurrence, our patient underwent a chest radiograph that revealed only a subcentrimetric nodule (unchanged in comparison with a previous radiogram of one year earlier) on the upper pulmonary lobe, a high resolution chest CT scan that confirmed the non-cancerous nature of this nodule, an abdominal CT and a colonscopy that both excluded a rectal cancer recurrence or metastasis.

RESULTS

Our patient was treated with intravenous (IV) pulse methylprednisolone (1000 mg/day for 3 consecutive days) with no clinical benefit and successively high dose IV immunoglobulins were added at 0.4 g/kg/day for five days, with partial lowering of muscle enzyme levels (Table I; Fig. 1 and 2), but no clinical improvement. On the tenth day of hospital stay, owing to the progressive dysphagia worsening, parenteral nutrition was started and the arterial blood gas analysis without O2 supplementation showed $PaCO_2$ of 38.5 mmHg, PaO_2 of 51 mmHg, and O_2 saturation of 82.2%, suggestive of a severe respiratory failure (Fig. 3). On this basis a "salvage" therapy with a single IV bolus of cyclophosphamide was started with an early and appreciable clinical improvement with amelioration of dysphagia and recovery of autonomous feeding, remittal of dyspnoea and myalgias, progressive amelioration of arterial blood gas values (see graph 3), and progressive lowering of biochemical markers of disease activity (CK, LDH, ESR, CRP, leucocytosis) (Table I; Fig. 1 and 2).

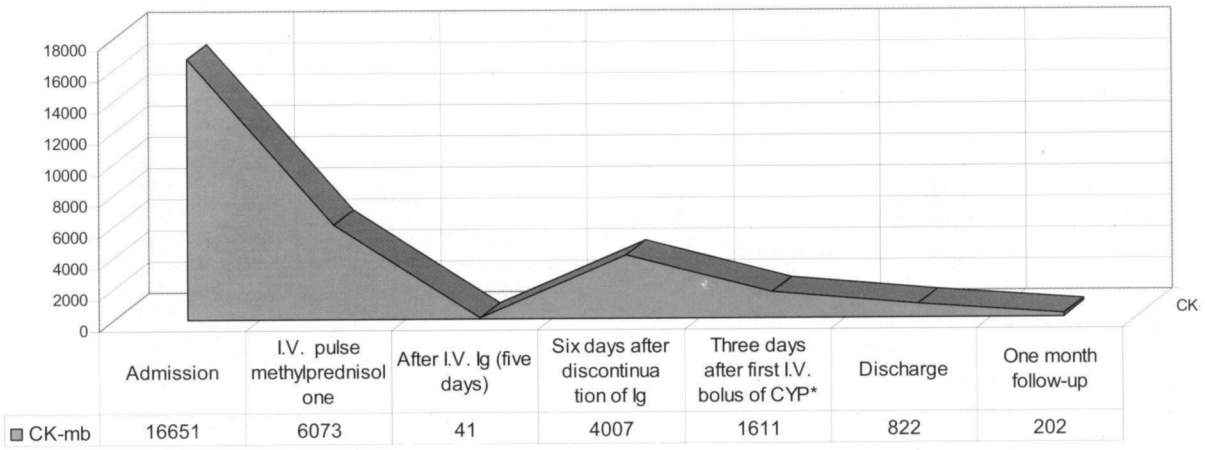
The patient was discharged on the 23rd day with an almost full clinical remission of the indexes of clinical activity of the disease (Table I; Fig. 1 and 2) and with an A.D.L. (Index of indipendence in activity of Daily Living) score of 2. Oral prednisone (50 mg /day) and methotrexate i.m. (15 mg/weekly) were added, and subsequently monthly IV pulse cyclophosphamide (1,4 g) (500 mg/m^2) was continued. After two months the patient was well, with an A.D.L. score of 3 and normal levels of biochemical markers of disease.

DISCUSSION

Dermathomiosytis can be a difficult disease to treat. Systemic corticosteroids are the first choice of treatment. About a quarter of patients either fail to respond or develop steroid related toxicity. Second line agents are then added, either alone or in combination with steroids. Failure of the disease to respond to second-line agents can then be a problem.

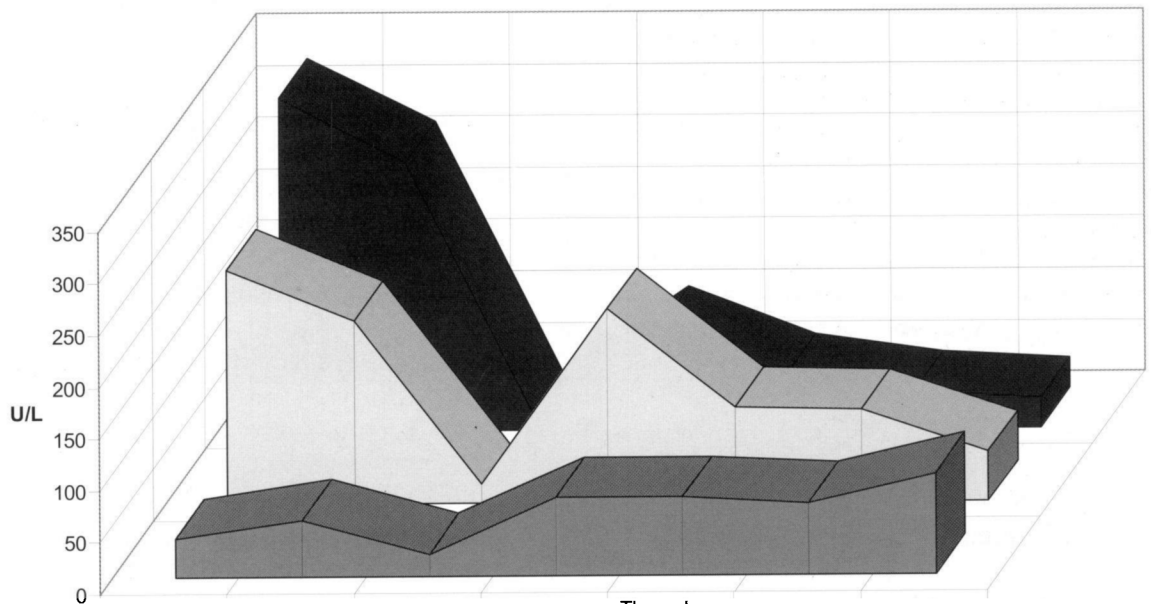
In our patient, steroids and intravenous immunoglobulin (IVIG) failed and only intravenous cyclophosphamide (CYP) obtained a clinical improvement.

Intravenous pulse cyclophosphamide treatment is widely used in the management of autoimmune connective tissue diseases and has resulted in a dramatic improvement in patient outcome. Currently, intravenous doses of cyclophosphamide, calculated on a surface area basis (0.75 gr/m^2), have tended to be high (in the order of 750–1250 mg) and the infection rate has consequently been high, in some series up to 25% (7-8). Over the past 10 years, in an attempt to reduce the incidence of infections and other adverse effects, some authors (8-9) have treated patients with severe connective diseases using a less aggressive



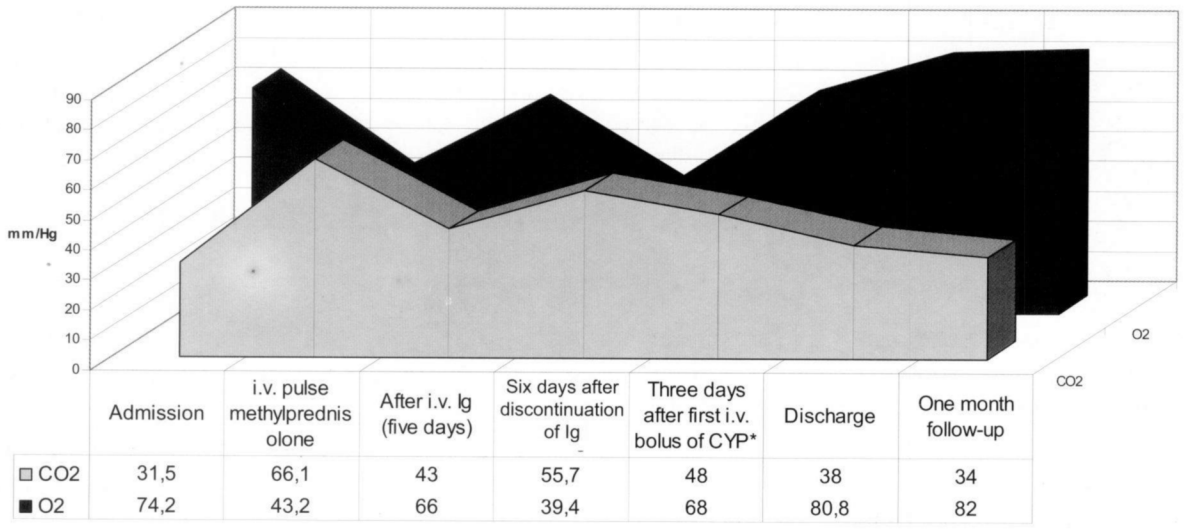
	Admission	I.V. pulse methylprednisolone	After I.V. Ig (five days)	Six days after discontinuation of Ig	Three days after first I.V. bolus of CYP*	Discharge	One month follow-up
CK-mb	16651	6073	41	4007	1611	822	202

Fig. 1. *Trends of creatine kinase plasma levels. *CYP: cyclophosphamide; IV: intravenous*



	Admission	I.V. pulse of methilprednisolone	After i.v. Ig (five days)	Six days after discontinuation of Ig	Three days after first i.v.bolus of CYP*	Discharge	One month follow-up
ALT	37	55	22	76	76	70	98
AST	227	177	19	188	92	89	48
CK-mb	322	260	17	99	53	36	29

Fig. 2. *Creatine kinase mb, aspartate and alanine aminotransferase plasma levels. *CYP: cyclophosphamide; IV: intravenous*



	Admission	i.v. pulse methylprednisolone	After i.v. Ig (five days)	Six days after discontinuation of Ig	Three days after first i.v. bolus of CYP*	Discharge	One month follow-up
□ CO2	31,5	66,1	43	55,7	48	38	34
■ O2	74,2	43,2	66	39,4	68	80,8	82

Fig. 3. *Trends of arterial oxygen and carbon dioxide concentration. *CYP: cyclophosphamide; IV: intravenous*

Table I. *Laboratory findings during hospitalization and after follow-up. *CYP: cyclophosphamide*

	Admission	Intravenous pulse methylprednisolone	After intravenous Ig (five days)	15° days (Three days after first bolus of CYP)	Discharge	One month follow-up
Urea (mg/dl)	*196*	*121*	*138*	*150*	*62*	*58*
Creatinine (mg/dl)	*1,54*	*0,99*	*1,54*	*1,5*	*0,82*	*0,66*
Sodium (mmol/L)	*134*					*134*
Potassium (mmol/L)	*4.64*					*3.84*
Calcium (mg/dl)	*6.86*					*8.4*
Red Blood Cells (per mm^3)	*4140000*		*4050000*			*3880000*
Haemoglobin (gr/dl)	*11.7*		*11.5*			*11.5*
Hematocrit (%)	*35.9*		*36*			*34*
Mean corpuscolar volume (fl)	*86.7*		*87.2*			*90.2*
White Blood Cells (per mm^3)	*21.390*		*13700*			*6950*
Platelet (per mm^3)	*120000*		*90000*			*87000*
Eritrocyte sedimentation rate (mm/hour)	*70*		*68*			*54*
C-reactive protein (mg/dl)	*1.57*		*1.3*			*1.00*
Oncologic markers						
Carcinoembryonic antigen (ng/ml) (v.n.<5)	*2.27*					
CA 19.9 (U/ml) (v.n.<37)	*6.99*					
TPA (ng/ml) (v.n.<92)	*100*					
Auto-Antibodies						
ANA	*Negative*					
Anti-Jo1	*Negative*					
Anti-SRP	*Positive*					
Anti-M2	*Positive*					

intravenous cyclophosphamide regimen that does not aim to induce leucopenia as a goal treatment in the induction phase of therapy. Nevertheless, the role of cyclophosphamide in inflammatory myositis is still controversial. Riley et al (9) showed that intravenous cyclophosphamide (CYP) provide major clinical benefit with no evidence of serious toxicity in the short term in juvenile dermatomyositis. Richter et al (10) showed that in 10 middle-aged patients (median age: 53.5 years) suffering from polymyositis and dermatomyositis with rapidly progressive lung disease, intravenous pulse cyclophosphamide prevented further progression in all 10 patients and led to some functional improvement, whereas Kameda et al (11) reported that also in middle-aged patients (median age: 52 years) early recognition of acute/subacute interstitial pneumonia (A/SIP) in patients with polymyositis an immediate commencement of an intensified immunosuppressive regiment, including intravenous pulse cyclophosphamide, may not be sufficient for some of those patients. Furthermore, cyclophosphamide is toxic and predisposes patients to malignancies after long-term treatment, therefore its use should be restricted to patients who are refractory to corticosteroids and other immunosuppressants such as a "salvage" treatment.

Finally, what are the reasons that led us to prefer CYP in the treatment of our elderly patient with refractory polymyositis? CYP, in our opinion, in comparison with other possible therapeutic choices such as azatioprin and rituximab, appears to be more manageable, owing to a better tolerability and easier modality of administration (pulse monthly IV). Indeed, cyclophosphamide, for its complete hepatic metabolization, has a less renal toxicity in comparison with azathioprine, so was more suitable for the treatment of our patient who had a mild renal dysfunction probably due to a reduced water intake caused by dysphagia. Moreover, our therapeutic schedule of pulse monthly IV cyclophosphamide, in an outpatient regimen, is more suitable compared to rituximab or daily azathioprine in management of a patient at high risk of nosocomial infection, such as our patient. A better cost profile also had a role in our therapeutic choices.

In conclusion, our case report could represent an interesting contribution to the clinical and therapeutic management of elderly patients with polymyositis/dermatomyositis. Our contribution is more interesting when considering that elderly subjects, more likely to have a poorer outcome in comparison with younger patients, are not often included in clinical trials with immunosuppressive agents such as cyclophosphamide, so that little information is available on this clinical issue.

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