

# Experience with cyclophosphamide in the treatment of a young woman with refractory dermatomyositis

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Dermatomyositis is an idiopathic inflammatory myopathy characterized by the presence of rash and moderate-to-severe muscle weakness secondary to inflammation of the muscle. It can be a difficult condition to treat. Systemic corticosteroids are the first choice of treatment. However, about a quarter of patients either fail to respond to steroids or develop steroid-related toxicity. Second-line agents such as azathioprine and methotrexate are then added either alone, or in combination with corticosteroids. Failure of the disease to respond to second-line agents can then be a problem and this is often referred to as “refractory dermatomyositis”. Unfortunately, there is neither agreement nor well-established guidelines on the best regimen or combination of immunosuppressive agents in the case of refractory dermatomyositis.

## CASE REPORT

A 22-year-old woman was admitted to hospital for complaint of progressive muscle weakness that had been worsening since one week before admission.

Three months before the admission, she had complained of mild muscle weakness and generalized fatigue. There were no fever, joint aches, difficulty in climbing stairs or arising from a seated position, difficulty in raising her arms, rash, dyspnea, or swallowing problems. The patient consulted a general practitioner and was given several tablets of vitamins; the complaints did not improve. She then consumed traditional herbs, but the symptoms continue to worsen.

For the one month before admission, she was no longer able to climb stairs normally, and noticed a progressive loss of body weight (approximately 9 kg in 3 months). At the same time, a rash appeared over her cheeks and forehead, and she experienced swallowing difficulty.

One week before the admission, the patient reported her inability to arise from supine position and was unable to raise her arms without any help. She also developed a high fever with productive cough and purulent sputum. She had not consumed any over the counter drugs. There was no complaint of abdominal pain or dysphonia. The patient then consulted a neurologist and was then referred to a rheumatologist.

Physical examination showed Glasgow coma scale of 15; the patient was moderately ill with

pulse rate of 96 beats/min, regular, respiratory rate of 22 breaths/min, and body temperature of 38.1°C. She was thin, with a body weight of 43 kg, height of 162 cm, and body mass index of 16.3 kg/m<sup>2</sup>. She had muscle atrophy. There was rash over her cheeks and forehead. Chest auscultation revealed vesicular breath sound with diffuse rales; there was no wheezing. Her cardiac and abdominal physical examinations were unremarkable. There was no lymph node enlargement. Neurological examination of her proximal and distal arm and leg muscles strength scored 3 out of 5, with the impression of paresis of the ninth and tenth cranial nerve and decreased oromotor movement.

Her laboratory tests showed high erythrocyte sedimentation rate at 70 mm/hr, with haemoglobin of 11.7 g/dL, leukocyte count of  $12 \times 10^3/\text{mm}^3$  (neutrophils 91%), and platelet count of  $385 \times 10^3/\text{mm}^3$ . The titer of aspartate transaminase (AST), alanine transaminase (ALT), and creatine kinase (CK) were high at 1,059 U/L, 390 U/L, and 21,093 U/L, respectively. Her hepatitis A, B, and C seromarkers were negative, with  $\gamma$ -glutamyl transferase ( $\gamma$ -GT) of 37 U/L. Her C-reactive protein (CRP) titer was 12 mg/L, calcium was 9.4 mg/dL, and phosphate was 3.3 mg/dL. The immunology panel showed CD4+ level of 301 cells/ $\mu\text{L}$ , positive antinuclear antibody (ANA) with negative ANA profile (including anti Jo-1), and normal titer of total IgE, IgA, IgM, IgG, IgM anticardiolipin antibody (ACA), IgG ACA, thyroxine (T4), and sensitive thyroid stimulating hormone (sTSH).

Her chest X-ray showed presence of infiltrates consistent with pneumonia. Sputum culture revealed *Pseudomonas sp.* sensitive to ceftazidime, ciprofloxacin, piperacilin/tazobactam, cefoperazone/sulbactam, doripenem, cefepime, ceftiprome, meropenem, imipenem, levofloxacin, and gatifloxacin. Abdominal ultrasound was normal. Electromyography (EMG) and nerve conduction tests revealed diffuse myogenic lesions over her upper and lower extremities with normal motor and sensory nerve conduction velocity, consistent with clinical myositis. Her fiber optic endoscopic evaluation of swallowing (FEES) study with nasopharyngolaryngoscope revealed oropharyngeal phase of neurogenic dysphagia with silent aspiration and high risk for respiratory tract aspiration.

A diagnosis of dermatomyositis, oropharyngeal phase of neurogenic dysphagia with silent aspiration, and community acquired pneumonia with differential diagnosis of aspiration pneumonia was made. We gave the patient a total of 2100 kkal of soft diet via nasogastric tube and intravenous fluid 1500 mL/day. We began treatment with intravenous methylprednisolone 125 mg b.i.d for three consecutive days, tapered down to 125 mg q.d., 62.5 mg q.d., and 16 mg t.i.d. We also administered azathioprine 50 mg t.i.d., ceftazidime 1 gram t.i.d., and a tablet containing combination of calcium hydrogen phosphate 500 mg and cholecalciferol 133 IU t.i.d. The patient was also referred for physiotherapy program.

After a month of hospitalization with those medications, the rash, fever, and cough resolved. Serial chest X-ray confirmed the improvement of lung condition. However, there was no improvement in her swallowing problem. Furthermore, there was declining muscle strength to grade 1 out of 5 for her proximal arm and leg muscles, and 3 out of 5 for her distal limb muscles. She underwent comparative FEES study, with disappointing result. There was also re-increment of CK titer values, as were shown in table 1; thus, we decided to add methotrexate 10 mg/week to her medications.

Due to the clinical deterioration despite the administration of corticosteroid and two immunosuppressive agents, we decided to offer to the patient and her family the administration of intravenous cyclophosphamide. The drug's potential side effects were discussed. The patient and her family consented to receive cyclophosphamide. We gave her intravenous cyclophosphamide 500 mg two-weekly. The administration of methylprednisolone was continued according to the previously planned dose, but we discontinued both azathioprine and methotrexate.

After the second administration of intravenous cyclophosphamide (table 1), the patient showed improvement of muscle strength and decreased levels of AST, ALT, and CK. Her muscle test showed that the score of proximal arm and leg muscles strength were 2 and 2, respectively, and the score of her distal arm and leg muscles strength were 3 and 3, respectively. After the third course of the two-weekly injections, the patient was discharged from hospital. The plan was for her to receive six consecutive monthly injections of intravenous cyclophosphamide 500 mg.

After the nine serial cyclophosphamide injection within 6 months, her muscle test showed that the proximal arm and leg muscles strength were 4 and 4 respectively and her distal arm and leg muscles strength were normal. The AST, ALT, and CK improved at 20 IU/L, 30 IU/L, and 270 IU/L respectively. She was then switched to mycophenolate mofetil 500 mg b.i.d. and methylprednisolone 12 mg q.d. Repeated FEES showed improved swallowing reflexes. The patient was also started to regain her ability to walk.

## DISCUSSION

Idiopathic inflammatory myopathies (IIM) are heterogeneous potentially debilitating—and sometimes life-threatening—diseases characterized by muscle inflammation with subsequent weakness. On the basis of well-defined clinical, demographic, histological, and immunopathological criteria, the inflammatory myopathies form three major and discrete groups, i.e. polymyositis, dermatomyositis, and sporadic inclusion-body myositis.<sup>1,2</sup>

An epidemiological study from Canada in 2009 revealed that the prevalence of this disease was higher in women than men, and in older individuals, which is consistent with the result of previously published data from other countries. Prevalence estimates were lowest in young men and highest in older women.<sup>1,3</sup>

The clinical course is quite variable among patients with this disease. In some, the illness is brief and is followed by remission that does not require continued treatment. Other patients experience exacerbations and remissions or persistent disease activity, necessitating chronic use of immunosuppressive drugs, with the frequency of clinical and biochemical relapses varying from 34 to 60 percent in different series. Mortality is now limited to less than 10%, but long-term morbidity is still present in more than 25% of patients. Factors associated with poor survival include older age, malignancy, delayed initiation of corticosteroid treatment, pharyngeal dysphagia with aspiration pneumonia, interstitial lung disease, myocardial involvement, and complications of corticosteroid or immunosuppressive treatment.<sup>4-6</sup>

Given the rarity of IIM and the heterogeneity of the myositis syndromes, their management is difficult and has not been universally standardized. There are few well-

**Table 1** Serial evaluation of patient's aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatine kinase (CK) titer

	Adm	W1	W2	W3	W4	W5	W6	W7	W8	W9	W13	W17	W21	W25	W29	W33
AST	1,059	712	629	589	663	474	266	173	148	120	84	-	-	-	-	20
ALT	390	309	282	253	217	177	122	94	80	74	32	-	-	-	-	30
CK	21,093	10,762	8,781	7,598	11,772	4,988	2,897	1,931	1,369	967	387	-	-	-	-	270
Treatment	Methylprednisolone	-----														
	Azathioprine 3×50 mg	-----														
	MTX	-----														
					10											
					mg											
	CYP serial					1		2		3	4	5	6	7	8	9

Normal values for AST, ALT, and CK are <27 U/L, <36 U/L, and <192 U/L, respectively

Adm, admission; W, week from admission day; MTX, oral methotrexate; CYP, intravenous cyclophosphamide

controlled clinical trials concerning IIM and many of the reported studies have not adequately differentiated muscle weakness, as secondary to disease activity (implying ongoing inflammation), damage (signifying permanent damage), and the patients' own perception of their disease, to evaluate the efficacy of treatment regimen. Moreover, some patients are refractory to first and second-line treatment, requiring a more potent immunosuppressive drug.<sup>4,5,7,8</sup>

The diagnosis of dermatomyositis was constructed based on diagnostic criteria suggested by Bohan and Peter in 1975. Muscle histology, included as part of the criteria, remains the gold standard for confirming the diagnosis of IIM, when typical changes (infiltrates of mononuclear inflammatory cells, regenerating and degenerating muscle fibers) are present in a muscle biopsy. However, because the disease is patchy in distribution, sampling error precludes 100% sensitivity. A muscle biopsy can look normal despite clinically evident muscle weakness. Furthermore, the changes in some biopsies may be too nonspecific and the degree of histopathological feature is not correlated with the degree of muscle weakness. Our patient fulfilled four out of five criteria of Bohan and Peter diagnosis criteria, i.e. symmetrical proximal muscle weakness, elevation of serum level of skeletal muscle enzymes, abnormal EMG, and typical skin rash of dermatomyositis, which is consistent with diagnosis of definite dermatomyositis although muscle biopsy was not done in our patient.<sup>4,9</sup>

Swallowing difficulty in our patient, as was confirmed by FEES study, is a common comorbidity found in patients with dermatomyositis, which brings serious implications. The dysphagia associated with these myopathies primarily affects the skeletal muscle-activated oropharyngeal phase of swallowing. It may precede weakness of the extremities or even present as the sole symptom. Dysphagia is associated with nutritional deficits (reflected by our patient's progressive loss of body weight), aspiration pneumonia, decreased quality of life, and poor prognosis. In their research, McCann LJ et al failed to show any correlation between swallow score and objective measures of muscle strength and function or general disease activity and function. They concluded that in the absence of a more accurate assessment method to determine which patients are most at risk of swallow dysfunction and aspiration, all patients with active dermatomyositis should be referred for swallow assessment.<sup>10,11</sup>

Dermatomyositis can be a difficult condition to treat. Systemic corticosteroids are the first choice of treatment. Most patients at least partially respond to corticosteroids and a complete lack of response should prompt a reconsideration of that diagnosis.<sup>7</sup> However, about a quarter of patients either fail to respond to steroids or develop steroid-related toxicity. Second-line agents should then be added either alone, or in combination with corticosteroids. Failure of the disease to respond to second-line agents, and side effects of these drugs, can be a problem.<sup>7,12</sup>

It has not been clearly defined which dermatomyositis cases should be categorized in the group of refractory dermatomyositis. Several studies apply this terminology to cases that do not respond to second-line immunosuppressive agents, while others apply it to cases that not respond to

corticosteroids.<sup>7,12</sup> Our patient showed at least partial response to corticosteroid, as can be seen in the minimal improvement of the clinical condition (rash) and laboratory results in the first four weeks; however, there was failure in reaching a complete response despite addition of azathioprine and metotrexate. She was thus considered a case of refractory dermatomyositis.

As previously mentioned, there is unfortunately neither agreement nor well established guidelines on the best regimen or combination of immunosuppressive agents for refractory dermatomyositis. The choice depends on the severity of the disease, extramuscular manifestations, personal experience, and the relevant relative efficacy-safety profile ratio of the drug.<sup>8</sup> Several immunosuppressive agents, either reported by individual case reports or case series, have been used as treatment of choice in refractory dermatomyositis cases. There is not yet head-to-head comparative trial of the different immunosuppressive agents in the management of refractory dermatomyositis. For simplifying the approach, we can refer to a therapy classification for dermatomyositis that was developed by Miller. This classification categorized those agents into three major classes. First-line therapies include methotrexate, instead of corticosteroids and other adjunctive treatment (physical therapy, hydroxychloroquine, topical therapies for skin rashes, photoprotective measures, calcium and vitamin D for bone protection). Second-line therapies include azathioprine, cyclosporine, intravenous immunoglobulin (IVIG), or combinations of these agents. Third-line therapies include mycophenolate mofetil, tacrolimus, cyclophosphamide, rituximab, anti-tumor necrosis factor agents, as well as other biologicals (e.g. anakinra, alemtuzumab) and stem cell therapy. As a general rule, for patients with severe, refractory, or corticosteroid-dependent disease, combinations of second-line therapies or newer third-line therapies are frequently used.<sup>7-9,13</sup> In our case, disappointing result with the second-line therapy (azathioprine) necessitated the use of a third-line agent. The third line agent we chose was cyclophosphamide.

Although it has been effective in other autoimmune diseases, cyclophosphamide has had variable results in patients with IIM. A number of reports have described the use of cyclophosphamide in dermatomyositis patients, but the numbers have been too small to draw any conclusions and certainly no controlled trial evidence exists. There may be a strong case for its use in patients with dermatomyositis, particularly when associated with vasculitis, interstitial lung disease, and involvement of respiratory or bulbar muscles.<sup>5,8,14,15</sup>

Retrospective analysis of 12 juvenile dermatomyositis patients treated with intravenous cyclophosphamide in various doses by Riley P et al<sup>5</sup> in 2004 concluded that treatment with intravenous cyclophosphamide appeared to have resulted in major clinical benefit with no evidence of serious short-term toxicity. Skin, muscular, and extramuscular features of the disease improved and this improvement persisted following the discontinuation of treatment. There were no major short-term side effects resulting from the administration of this agent, as reflected from other researches of cyclophosphamide use for various autoimmune diseases. The three main long-

term concerns for any patient after cyclophosphamide administration are malignancy, infertility, and gonadal failure. Reported malignancies, with peak incidence at seven years after the therapy, have been observed in those who received more than 50 g cumulative dose of cyclophosphamide. Premature ovarian failure is relatively common when cyclophosphamide is administered to women over 30 years of age, but very rare in those under 20 years and only with very high dose. A study conducted by Wang et al revealed that only 4% of younger than 21 year female lupus patients receiving oral cyclophosphamide with cumulative dose over 40 g suffered premature ovarian failure.<sup>16</sup> Martin-Suarez et al<sup>17</sup> revealed that none of the patients suffered ovarian failure associated with low dose (500 mg weekly) intravenous pulses of cyclophosphamide as treatment for various severe connective tissue diseases. Martin et al<sup>18</sup> in their study reviewing the side effects of intravenous cyclophosphamide pulse therapy in a group of 75 patients suffering from various autoimmune disorders who received a total of 451 intravenous cyclophosphamide pulses, given on monthly basis with mean follow-up period  $26.7 \pm 22.1$  months found that infection was the most common side effect but rarely required in-patient treatment with no premature ovarian failure observed in the 25 female patients at risk.

Those risk and benefit data support the decision to choose cyclophosphamide as the third line immunosuppressive agent to be administered to our patient. There are also several other agents that could possibly be chosen, e.g. IVIG and rituximab. We decided to reserve the use of these agents due to financial consideration, in case of persistent refractory condition in our patient after cyclophosphamide treatment. Fortunately, our patient showed improvement of both clinical and laboratory parameters, obviating the need to administer additional agents. No specific short-term adverse effect was observed; however, continuous long-term monitoring of potential adverse effects is needed.

Continuous efforts are being undertaken to achieve the best possible treatment for patients with IIM, but more specific immunotherapy still awaits a precise understanding of target antigen molecules and the immunopathological process

responsible for these disorders. However, the availability of new agents coupled with the development of validated reliable assessment tools to evaluate disease activity and damage offers the realistic prospect of more effective treatments.<sup>8</sup>

Administration of immunosuppressive agents is only a small part in the big picture of holistic management of dermatomyositis cases. Other important parts of therapy include general rehabilitative measures, proper management of potential lung complications (i.e. aspiration pneumonia due to esophageal dysfunction and ventilatory insufficiency), as well as infection management, since several predisposing factors increase the patients' risk of developing infections. These factors include upper oesophageal involvement, thoracic muscle myopathy, use of immunosuppressive drugs and immune system dysfunction due to the disease itself. The literature indicates that, not only do patients have a high rate of infectious complication (up to 33%), but infection is also implicated in 46% of deaths in this patient group, which makes it a significant prognostic factor. Close follow-up of dermatomyositis patients with risk factors for developing major infections is mandatory.<sup>19,20</sup>

## SUMMARY

We report here a case of a young woman with refractory dermatomyositis who was treated with cyclophosphamide because the patient did not show good response despite administration of methylprednisolone, azathioprine, and methotrexate, which is consistent with a case definition of refractory dermatomyositis. Published literature suggested that treatment with intravenous cyclophosphamide appears to result in major clinical benefit with no evidence of serious short-term toxicity and considerable long-term toxicity. Our patient showed good response to cyclophosphamide, as reflected by the improvement of muscle strength and decreased level of AST, ALT, and CK after the second intravenous administration of this agent. Other important parts of therapy that should be applied include general rehabilitative measures, proper management of potential lung complications, as well as infection prevention and management.

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