

Chloroquine diphosphate: a risk factor for herpes zoster in patients with dermatomyositis/polymyositis

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OBJECTIVES: Herpes zoster has been widely described in the context of different systemic autoimmune diseases but not dermatomyositis/polymyositis. Therefore, we analyzed the prevalence, risk factors and herpes zoster outcomes in this population.

METHOD: A retrospective cohort study of herpes zoster infections in dermatomyositis/polymyositis patients was performed. The patients were followed at a tertiary center from 1991 to 2012. For the control group, each patient with herpes zoster was paired with two patients without herpes zoster. Patients were matched by gender and the type of myositis, age at myositis onset and disease duration.

RESULTS: Of 230 patients, 24 (10.4%) had a histories of herpes zoster (19 with dermatomyositis and five with polymyositis, two-thirds female). The mean age of the patients with herpes zoster was 44.6 ± 16.8 years. No difference between the groups was found regarding cumulative clinical manifestations. Disease activity, autoantibody, muscle and leukogram parameters were also comparable between the groups. No differences in immunosuppressive (alone or in association with other immunosuppressive therapies) or glucocorticoid (current use, medium dose and cumulative dose in the last two months) therapies were found between patients with and without herpes zoster. However, a higher proportion of patients in the herpes zoster group received chloroquine diphosphate compared to the control group. All of the patients received acyclovir; 58.3% of patients had postherpetic neuralgia and no cases of recurrence were reported. Furthermore, individuals who were taking high prednisone doses at the time of the herpes zoster diagnosis had reduced levels of postherpetic neuralgia.

CONCLUSIONS: These data suggest that chloroquine diphosphate could predispose patients with dermatomyositis/polymyositis to developing herpes zoster, particularly women and dermatomyositis patients.

KEYWORDS: Antimalarial; Chloroquine Diphosphate; Dermatomyositis; Herpes Zoster; Inflammatory Myopathies; Polymyositis; Risk Factors.

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INTRODUCTION

Idiopathic inflammatory myopathies encompass a heterogeneous group of systemic autoimmune diseases, including polymyositis (PM), which is characterized by symmetrical proximal and progressive muscle weakness of the limbs and dermatomyositis (DM), which, in addition to muscle involvement, includes skin abnormalities, such as heliotrope and Gottron's papules (1,2).

Viral infections, such as herpes zoster (HZ), have been increasingly reported in individuals with systemic

autoimmune diseases. Among patients with systemic lupus erythematosus, for instance, there is an HZ prevalence of 4.5% (3) and an incidence of 6.4–58.7 events/1,000 patient-years (3,4). Corticosteroids (3) and immunosuppressive agents (4–6), disease activity (5–8) and the presence of anti-Sm autoantibodies (8) number among the possible risk factors for HZ in this population. The incidence of HZ in rheumatoid arthritis is 9.96 cases/1,000 patient-years (9), and the risk factors in this cohort include older age (>45 years old), the presence of cancer, chronic lung disease, corticosteroid usage (10), exposure to immunosuppressive (10) and immunobiological therapies (11) and immune system dysregulation (12).

Through a few epidemiological studies, HZ in DM/PM has been investigated within the context of other opportunistic infections or by examining a few myositis cases with HZ (13–15). Thus, Fardet et al. (13) analyzed the incidence, risk factors, and severity of HZ in 121 patients with DM. However, these authors evaluated HZ and herpes simplex

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in DM patients with and without malignancy. Marie et al. (14) assessed several opportunistic and severe infections in 279 patients with DM/PM for a period of 13 years, but they found only three cases of HZ. Nagaoka et al. (15) analyzed the incidence of HZ in 22 patients with DM/PM over a period of 10 years. Five patients had histories of this viral infection, which predominantly occurred in the remission stage of the disease, showing no relationship with drug therapies.

Due to the dearth of publications on the topic, the aim of this study was to analyze the prevalence, risk factors and outcomes of HZ in our cohort of DM/PM patients.

■ MATERIALS AND METHODS

Study population, clinical assessment and data collection. Between January 1991 and January 2012, 230 consecutive patients with DM or PM and who fulfilled at least four of the five Bohan and Peter (2) criteria were followed at a tertiary hospital. Twenty-four subjects (10.4%) in this group had histories of HZ. Of the remaining patients without HZ, a control group of 48 patients (two controls for every HZ patient) was formed and matched by gender, disease type (DM or PM), age at the onset of myositis and disease duration. The study was approved by the local Research Ethics Committee.

Demographics, drug therapy and clinical and laboratory data were retrospectively obtained through a systematic review of all patient medical records. Drug therapy and laboratory data were based on the time of the DM/PM diagnosis and the season in which the HZ event occurred, while the clinical manifestations considered were those presenting during the follow-up of these patients.

Constitutional symptoms, skin changes (e.g., heliotrope, Gottron's papules, ulcers, photosensitive, calcinosis, and vasculitis), joint involvement (arthralgia and/or arthritis), and gastrointestinal (dysphagia) and respiratory (dyspnea on moderate exertion) manifestations were analyzed.

Creatine kinase (normal range 24–173 IU/L) and aldolase (1.0–7.5 IU/L) were determined using an automated kinetic assay. Leukocyte count, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase were also assessed. The erythrocyte sedimentation rate and C-reactive protein levels were evaluated using the Westergren and nephelometry methods, respectively. Autoantibodies against cellular components were determined with indirect immunofluorescence using Hep-2 cells as the substrate. Autoantibody anti-Jo-1 was determined using the Western blotting method.

All of the patients were first started on corticosteroids (prednisone 1 mg/kg/day, administered orally), which were tapered gradually according to clinical and laboratory stability. In cases of high disease severity (dysphagia with risk of aspiration pneumonia, cutaneous vasculitis, or being refractory to oral corticosteroids), intravenous corticosteroids were administered (methyl prednisolone 1 g/day for three consecutive days). The following drugs were used alone or in combination for corticosteroid sparing: azathioprine (2–3 mg/kg/day), methotrexate (20–25 mg/week), cyclosporine (2–3 mg/kg/day), mycophenolate mofetil (2–3 g/day), leflunomide (20 mg/day), cyclophosphamide (0.5–1.0 g/m² of body surface), intravenous human immunoglobulin (1 g/kg/day for two consecutive days) and chloroquine diphosphate (3–4 mg/kg/day).

Herpes zoster information

HZ infection was clinically defined by the appearance of the typical vesicular eruption distributed in a dermatome. The potential complications of HZ, which were listed on the protocol form, included postherpetic neuralgia (persistence of pain for more than one month after the disappearance of the rash) (16) and cutaneous dissemination (vesicular lesions outside the primary and adjacent dermatomes) (17). All of the lesions were initially evaluated by rheumatologists and then by dermatologists from our service.

The disease status at the time of the HZ diagnosis was defined as (a) partial clinical response (evidence of disease activity within the last 6 months of disease); (b) complete clinical response (6-month continuous period with no evidence of disease activity while still receiving myositis therapy); and (c) clinical remission (6-month continuous period with no evidence of disease activity and no myositis therapy) (17). Disease activity was defined as an increase in muscle enzyme sera levels, with clinical evidence of limb muscle weakness at two consecutive medical evaluations.

Statistical analysis

Continuous variables are expressed as the means \pm standard deviations (SDs), as medians with interquartile ranges (IQRs), or as percentages for categorical variables. Student's t-test or the Mann-Whitney U-test for continuous variables was employed to evaluate the differences between the DM/PM groups. The 95% confidence intervals (95% CI) were calculated using binomial distribution. All of the variables that significantly differed statistically in the univariate analysis (comparison between patients with and without HZ episodes or with and without neurological sequelae) were selected for adjustment. The sex- and age-adjusted odds ratios (ORs) and 95% CIs were calculated using an unconditional logistic model, and $p < 0.05$ was considered statistically significant.

■ RESULTS

Demographic and clinical features of patients with and without herpes zoster

Over a 21-year follow-up period, 24 (10.4%) of 230 patients had HZ (19 DM cases and 5 PM cases, 3.8:1), and two-thirds were female. The clinical and demographic features of these patients are shown in Table 1. In general, these characteristics were comparable between the groups with and without HZ, except for a higher prevalence of DM in the group with HZ compared to the patients without HZ ($p = 0.046$).

The mean age of the patients with HZ was 44.6 ± 16.8 years (range 21 to 84 years). Demographic and clinical variables of the 24 patients in the HZ group were compared with those of the 48 randomly selected and matched patients without HZ, as shown in Table 2. No differences were detected between the two groups regarding the cumulative clinical manifestations (Table 2). Furthermore, the two groups were comparable in terms of current disease status, laboratory parameters (initial and current) and autoantibodies (Table 3).

All of the HZ patients initially received intravenous acyclovir (30 mg/kg/day).

There was no difference between DM/PM with and without HZ with regard to glucocorticoid therapy (current use, medium dose and cumulative dose over the two



Table 1 - Comparison of the general demographic and clinical features of the dermatomyositis/polymyositis patients with and without herpes zoster.

	HZ (+)	HZ (-)	p-value
	(n = 24)	(n = 206)	
DM:PM ratio	19:5	113:87	0.046
Sex at disease onset ± SD (years)	43.8 ± 16.8	42.2 ± 14.2	0.123
Gender - female (%)	7 (71)	157 (97)	1.000
Time between disease diagnosis and symptoms (IQR) (mo)	5.0 (2.0-9.0)	3.0 (2.0-6.0)	0.264
Cumulative clinical manifestations			
Constitutional symptoms (%)	15 (63)	105 (51)	0.521
Bedrest (%)	3 (13)	55 (27)	0.212
Articular: arthralgia/arthritis (%)	12 (50)	88 (43)	0.521
Gastrointestinal tract: dysphagia (%)	8 (34)	74 (36)	1.000
Pulmonary: dyspnea (%)	5 (21)	56 (27)	0.766

DM: dermatomyositis; HZ: herpes zoster; IQR: interquartile range; PM: polymyositis; SD: standard deviation.

previous months). Similarly, immunosuppressive therapy use was similar in both groups (Table 4). However, the patients using chloroquine diphosphate had a 5.98-fold (95% CI, 1.66-22.26) greater risk of developing HZ compared to the patients who did not receive chloroquine diphosphate treatment.

Clinical evaluation and dermatome locations of herpes zoster

Table 5 shows the dermatome locations of HZ, as well as the clinical evaluations. Six cases had simultaneous involvement of two dermatomes. Neurological sequelae occurred in 14 (58.3%) of 24 patients, and no cases of HZ recurrence were reported. The duration of the neurological symptoms was 8.2 ± 4.4 years.

The demographics, disease status and clinical and laboratory features were comparable in the patients with and without postherpetic neuralgia. However, the latter group used a higher prednisone dose at the time of the HZ diagnosis (median 40 mg/day [range 5-70]) than the former

group (median 15 mg/day [range 0-40], p = 0.018, with OR of 0.93 and 95% CI of 0.86-0.99).

DISCUSSION

The present study identified chloroquine diphosphate as the primary risk factor for HZ in DM/PM. In our population, we noted a high HZ prevalence that predominantly affected women and individuals with DM.

An important aspect of this retrospective study's design was its large cohort of HZ cases and associated risk factors in the patients with DM and PM, which are both considered rare systemic autoimmune diseases. Additionally, the study and control groups were matched by age because there is a known HZ cluster disparity between young and elderly subjects. Moreover, gender, disease type (DM or PM), age at diagnosis and disease duration were also controlled for by sample matching to avoid a confounding bias.

Despite enrolling large samples, many authors have found few HZ cases in their DM/PM populations.

Table 2 - Demographic and clinical features of selected patients with dermatomyositis/polymyositis according to the presence of herpes zoster.

	HZ (+)	HZ (-)	p-value
	(n = 24)	(n = 48)	
DM: PM ratio	19:5	38:10	1.000
Age at disease onset ± SD (years)	43.8 ± 16.8	44.1 ± 15.3	0.935
Gender - female (%)	7 (71)	14 (71)	1.000
Time between disease diagnosis and symptoms (IQR) (mo)	5.0 (2.0-9.0)	3.0 (3.0-8.5)*	0.855
Time between HZ and disease diagnosis (IQR) (mo)	13.0 (6.0-31.0)	9.5 (5.9-19.0)	0.190
Cumulative clinical manifestations			
Constitutional symptoms (%)	15 (63)	24 (50)	0.393
Bedrest (%)	3 (13)	11 (23)	0.290
Cutaneous			
Heliotrope (%)	19 (79)	33 (69)	0.158
Gottron's papules (%)	19 (79)	34 (71)	1.000
Vasculitis (%)	6 (25)	6 (13)	0.325
Calcinosis (%)	3 (13)	1 (2)	0.140
Ulcers (%)	3 (13)	6 (13)	0.269
Photosensitive (%)	12 (50)	20 (42)	1.000
Articular: arthralgia/arthritis (%)	12 (50)	16 (33)	0.171
Gastrointestinal tract: dysphagia (%)	8 (34)	22 (46)	0.310
Pulmonary: dyspnea (%)	5 (21)	12 (25)	0.766

*Comparable period for patients who developed herpes zoster.

DM: dermatomyositis; HZ: herpes zoster; IQR: interquartile range; PM: polymyositis; SD: standard deviation.



Table 3 - Disease status and laboratory features of patients with dermatomyositis/polymyositis according to the presence of herpes zoster.

	HZ (+) (n = 24)	HZ (-) (n = 48)	p-value
Disease status			
Complete clinical response	2 (8)	6 (13)	0.596
Partial clinical response	20 (83)	37 (77)	0.538
Clinical remission	2 (8)	7 (15)	0.450
Laboratory features			
Creatine kinase (U/L)			
At diagnosis	761.1 (254.0–4300.0)	3031.0 (148.0–9015.0)	0.449
At HZ event	178.5 (82.5–672.0)	14.0 (10.5–60.8)*	0.304
Aldolase (U/L)			
At diagnosis	14.0 (7.5–49.5)	14.0 (10.5–60.8)	0.583
At HZ event	6.3 (4.6–9.9)	5.6 (4.9–8.2)*	0.594
Aspartate aminotransferase (U/L)			
At diagnosis	86.5 (42.0–238.0)	82.0 (39.0–184.0)	0.898
At HZ event	45.9 ± 46.5	51.9 ± 59.2*	0.641
Alanine aminotransferase (U/L)			
At diagnosis	63.5 (32.0–120.0)	63.0 (29.0–177.0)	0.685
At HZ event	42.4 ± 36.4	64.5 ± 118.3*	0.241
Lactate dehydrogenase (U/L)			
At diagnosis	639.0 (390.0–1506.0)	714.0 (456.0–1109.0)	0.605
At HZ event	813.0 (386.5–736.0)	576.0 (450.0–623.0)*	0.926
At HZ event			
Leukocytes (mm ³)	7689.9 ± 3662.7	7161.5 ± 3129.0*	0.550
Neutrophils (mm ³)	5875.0 ± 3112.1	4874.3 ± 2,759.0*	0.193
Lymphocytes (mm ³)	1554.2 ± 960.5	1523.6 ± 955.8*	0.900
C-reactive protein (mg/dL)	4.9 (1.5–14.7)	2.1 (1.0–9.3)*	0.080
ESR (mm/1 st hour)	18.4 ± 12.2	21.4 ± 19.6*	0.448
Antinuclear factor (%)			
	15 (63)	28 (58)	0.734
Anti-Jo-1 antibody (%)			
	3 (13)	1 (2)	0.069

*Comparable period for patients who developed herpes zoster. Results expressed as the means ± standard deviation or as median (interquartile ratios). ESR: erythrocyte sedimentation rate; HZ: herpes zoster; SD: standard deviation.

Notably, Marie et al. (14) identified only three individuals with HZ in 279 cases and Yu et al. (18) detected two subjects with HZ among 192 cases of DM/PM, whereas Fardet et al. (13) found 16 HZ cases among 121 DM patients. In the present study, we evaluated 24 (10.4%) HZ cases among 230 patients who were clinically diagnosed with DM/PM over a 21-year follow-up period. Therefore, a considerable number of infected patients were identified in this population.

Based on other systemic autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, the major risk factors for developing HZ include older age, use of corticosteroids and immunosuppressive agents, disease activity, female sex, cancer, lung disease and impaired cellular immunity (3–12,19–21).

In our population, HZ predominantly affected adults with a mean age of 44 years (range 21 to 84 years), with no tendency toward affecting older individuals. Moreover, to avoid analysis bias, individuals with neoplasias were excluded.

In contrast with other systemic autoimmune diseases, in which impaired cellular immunity is considered a risk factor for HZ development (12), humoral immunity function might be considered relevant in inflammatory myopathies because the prevalence of HZ was higher in the DM patients compared to the PM patients. From an immunopathological standpoint, CD8 (+) lymphocyte and macrophage infiltrations are primarily found in PM muscle fibers (22), whereas

in DM, B cells play important roles in the pathogenesis of the disease through the presence of autoantibodies, immune complex deposition in the dermoepidermal junction of skin lesions and the presence of B cells in inflamed muscles and perivascular areas (23,24). Additionally, deposition of complement and immunoglobulin in the perifascicular endothelium can lead to ischemia and muscle atrophy, underlining the importance of humoral immunity (25). Thus, disturbances in humoral immunity might increase HZ reactivation, as we found a higher prevalence of HZ in the DM patients compared to the PM patients.

Nagaoka et al. (15) analyzed five HZ cases among 22 DM/PM patients and noted that the infection affected more patients without disease activity; they found no correlation over time with corticosteroid use. Our results showed that HZ prevalence was independent of disease status and clinical and laboratory features, including cutaneous manifestations. Moreover, daily and/or cumulative dosages of corticosteroid and/or intravenous pulse methylprednisolone did not increase the risk for HZ development in our population. Likewise, using immunosuppressive therapy (methotrexate, azathioprine, mycophenolate mofetil, leflunomide and cyclophosphamide)—either alone or in combination—was not associated with HZ.

However, patients using chloroquine diphosphate had a fivefold greater risk of developing HZ compared to patients not receiving chloroquine diphosphate treatment.



Table 4 - Drug use features of patients with dermatomyositis/polymyositis according to the presence of herpes zoster.

	HZ (+) (n = 24)	HZ (-) (n = 48)	p-value
Corticosteroid			
Using (%)	21 (87.5)	37 (77.1)	0.292
Mean ± SD (mg/day)	26.5 ± 20.0	30.3 ± 27.1	0.515
≥20 mg/day	14 (58.3)	26 (54.2)	0.805
Cumulative dose* (g)	1.5 ± 1.2	1.5 ± 1.4	0.928
Immunosuppressives			
Azathioprine (%)	12 (50.0)	18 (37.5)	0.310
Mean ± SD (mg/kg/day)	2.4 ± 0.2	2.4 ± 0.3	0.721
Methotrexate (%)	6 (25.0)	19 (39.6)	0.220
Mean ± SD (mg/week)	23.0 ± 2.7	22.5 ± 2.6	0.727
Cyclosporine (%)	1 (4.2)	1 (2.1)	0.612
Mean ± SD (mg/kg/day)	2.0	2.0	1.000
IVIg (%)	1 (4.2)	3 (6.3)	0.716
Mean ± SD (g/kg)	2.0	2.0	1.000
Leflunomide (%)	1 (4.2)	0	0.154
Mean ± SD (mg/day)	20.0	-	-
Cyclophosphamide (%)	4 (4.2)	2 (2.1)	0.612
Mean ± SD (g/m ² body surface)	0.8 ± 0.2	0.7 ± 0.3	0.795
Mycophenolate mofetil (%)	1 (4.2)	0	0.154
Mean ± SD (g/day)	3.0	-	-
Chloroquine diphosphate (%)	9 (37.5)	5 (10.4)	0.006
Mean ± SD (mg/day)	3.2 ± 0.2	3.3 ± 0.3	0.814
Corticosteroid + immunosuppressive (%)			
Using (%)	17 (70.8)	31 (64.6)	0.592
Number of immunosuppressives			
One (%)	16 (66.7)	28 (58.3)	0.494
Two (%)	1 (4.2)	9 (18.8)	0.154
Three (%)	1(4.2)	0	0.131

HZ: herpes zoster; IVIG: intravenous immunoglobulin; SD: standard deviation; Cumulative dose: past two months.

Chloroquine diphosphate and its analogue, hydroxychloroquine, are used to treat various rheumatic diseases, such as rheumatoid arthritis, systemic lupus erythematosus,

sarcoidosis, dermatomyositis, Sjögren’s syndrome, chronic juvenile arthritis and psoriatic arthritis; these drugs offer clinical benefits with acceptable safety profiles (26–29). Further, these drugs have also been used to treat inflammatory myopathies, particularly for the cutaneous symptoms of DM (30–34).

Table 5 - Dermatomes and outcomes of herpes zoster.

Case	Localization	HZ evaluation with neurological sequelae
1	Left dorsal area	Yes
2	Nose, left lower limb (L5)	No
3	Face, left lower limb (L5)	No
4	Thoracic area, left upper limb	No
5	Lower right limb (tibial nerve)	Yes
6	Left dorsal (T11)	Yes
7	Left upper limb	Yes
8	Dorsal area	Yes
9	Left upper limb	Yes
10	Dorsal area	No
11	Dorsal area	No
12	Dorsal area, left lower limb	Yes
13	Right dorsal area (T11)	Yes
14	Left thoracic area	Yes
15	Left thoracic area, abdomen	Yes
16	Trigeminal nerve	Yes
17	Right lower limb	No
18	Gluteus (S1 and S2)	No
19	Left thoracic area	Yes
20	Left thoracic area	Yes
21	Left lower limb (S1)	No
22	Trunk	No
23	Right thoracic area	No
24	Left thoracic area (T4)	Yes

HZ: herpes zoster.

Chloroquine might also have antiviral activity (35). As a lysosomotropic weak base, it impairs the replication of some viruses by reducing the efficiency of endosome-mediated virus entry or by inhibiting low-pH-dependent proteases in trans-Golgi vesicles (35). Its antiviral activity against the human immunodeficiency virus (36) and the SARS coronavirus has also been demonstrated (37,38). However, chloroquine has also been shown to increase symptom severity and mortality (e.g., following Semliki Forest virus and encephalomyocarditis virus infection, as well as increasing viral titers in various organs) (39). Our results clearly showed that chloroquine was a risk factor for HZ development in subjects with DM/PM, independent of disease status, therapy and demographic features.

Regarding the clinical evaluation, at least half of our patients had neurological sequelae. Six patients had simultaneous involvement of two dermatomes, while no cases of HZ recurrence were reported. Postherpetic neuralgia can result in severe pain such that patients are often unable to wear clothing that comes in contact with the lesions or be exposed to wind because of high skin sensitivity in regions such as the thorax and face. The incidence of postherpetic neuralgia rises from 10% among individuals of all ages to as high as 40% among those aged



50 years and older (40). A large prospective study identified four independent predictors of postherpetic neuralgia: older age, severe, acute pain, severe rash and a shorter duration of rash before consultation (41). Although controversial, short-term use of corticosteroids can reduce the pain severity and improve patient quality of life in the acute phase (42). Note that high prednisone doses at the time of HZ diagnosis were found to decrease the incidence of postherpetic neuralgia in our patients.

In conclusion, our data showed a high prevalence of HZ in the DM/PM population studied and confirmed that chloroquine diphosphate is a risk factor for HZ development in this population, particularly women and DM patients. Further research is necessary to evaluate the possible molecular mechanism underlying the higher HZ prevalence in DM subjects compared to PM patient populations.

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AUTHOR CONTRIBUTIONS

Cunha GF participated in the data collection and writing of the manuscript. Souza FH participated in the writing of the manuscript. Levy-Neto M participated in the manuscript revision. Shinjo SK contributed to the study design and participated in the data collection and manuscript revision.

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