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ORIGINAL RESEARCH

Morphological alterations of upper gastrointestinal tract in patients with new onset-dermatomyositis: correlation with demographic, clinical and laboratory features

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OBJECTIVE: To endoscopically assess the upper digestive tract of adult patients with newly diagnosed dermatomyositis; to correlate possible changes in the gastrointestinal tract with demographic, clinical and laboratory features in this population.
METHOD: A cross-sectional study evaluating 65 newly diagnosed dermatomyositis cases from 2004 to 2015 was carried out. We excluded patients with clinically amyopathic dermatomyositis, overlap dermatomyositis, polymyositis, liver diseases, prior gastric surgery, upper gastrointestinal tract symptoms (except for upper dysphagia), systemic infections, alcohol consumption and smoking.
RESULTS: Mean age of patients was 44.9 years, with disease duration of four months. Endoscopic findings were observed in 70.8% of patients. (1) Esophageal disease/gastric distress was documented in 18.5% of patients: erosive distal esophagitis (16.9%) and non-erosive distal esophagitis distal (1.5%); (2) gastric distress in 63.1% of cases: antral gastritis (42.3%) and pangastritis (27.8%); (3) duodenal involvement in 15.4% of patients: bulbar duodenitis (10.9%) and duodenal ulcers (7.7%). There were no neoplasic lesions. On multivariate analysis, erosive distal esophagitis was less associated with older patients. Males had a higher prevalence of erosive gastritis. Enanthematous pangastritis was less associated with lesions with "V-neck" sign lesions.
CONCLUSIONS: This study provides the first estimates of the prevalence of high endoscopic findings in adult patients with newly diagnosed dermatomyositis. The results may be relevant to guide conduct in digestive disorders with upper digestive endoscopy, and point to the need for pharmacological prevention of digestive tract lesions in these patients. Further studies are needed to validate this data and evaluate patients with dyspeptic symptoms.

KEYWORDS: Dermatomyositis, dyspepsia, gastrointestinal endoscopy, myositis.

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INTRODUCTION

Dermatomyositis (DM) is a rare systemic autoimmune disease characterized by the presence of proximal, symmetrical and progressive muscle weakness of limbs and the presence of typical skin lesions, such as heliotrope rash and/or Gottron's papules.[1-5] In addition, patients with DM may present with constitutional symptoms as well as joint, cardiac, pulmonary and gastrointestinal tract involvement.[1-6]

DM is an immune-mediated microangiopathy which affects both the skin and skeletal muscles diagnosed by confirming the presence of inflammatory infiltrate composed of B lymphocytes, macrophages and CD4+ lymphocytes, especially in the perivascular region of muscle tissue biopsy.[3-5,7]

In the case of upper gastrointestinal tract involvement, patients with DM may be asymptomatic or present a variety of symptoms such as dysphagia,

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regurgitation, heartburn, nausea, vomiting, abdominal distension and pain in the upper abdominal region.[8-13]

Despite this diversity of digestive symptoms, there are currently no studies analyzing the possible anatomical alterations found in the upper gastrointestinal tract of patients with DM. In cases of juvenile DM, vascular abnormalities in gastroduodenal mucosa, as well as bioelectric activity of gastric muscles, have been described.[14-17] Although serious, the presence of vascular disease of the gastrointestinal tract in juvenile DM is rare.[18]

Thus, the primary objective of this study was to evaluate the upper digestive endoscopy (UDE) of adult DM patients. All patients were newly-diagnosed DM and had no upper digestive tract symptoms (except high dysphagia). Secondarily, we correlated gastrointestinal tract changes with demographic, clinical and laboratory data in this sample.

MATERIALS AND METHODS

This retrospective, cross-sectional, single-center study consecutively evaluated 65 adult patients that met at least four of the five criteria of Bohan and Peter, including mandatorily, typical cutaneous lesions (heliotrope rash and/or Gottron's papules).[4]

The patients were initially admitted to our tertiary service from January 2004 to January 2015 for investigation of symmetrical and proximal progressive muscle weakness of limbs associated with classic skin lesions (heliotrope rash and/or Gottron's papules) and elevated muscle enzymes (e.g. creatine phosphokinase and aldolase) with no apparent cause. As part of the internal service protocol, these patients were also submitted to UDE to rule out any neoplasia lesions. To characterize DM, patients underwent electromyography and muscle biopsy (vastus lateralis muscle). In this investigation, these patients were defined as new-onset DM and subsequently included in the study.

Exclusion criteria: patients with polymyositis, amyopathic DM, DM associated with other systemic autoimmune diseases, liver disease, previous gastric surgery, cancer, upper gastrointestinal tract symptoms (except high dysphagia), systemic infections, history of alcohol abuse and smoking.

Demographic, clinical, laboratory and therapeutic data were obtained from a review of electronic medical records, containing previously standardized and parameterized data. The laboratory tests presented in this study were performed at the time of UDE. The following parameters were analyzed: constitutional symptoms, skin changes (heliotrope, Gottron's papules, ulcers, photosensitivity, "V-neck" sign, "shawl" sign, calcinosis, ulcers and vasculitis - skin biopsy: histopathological analysis with perivascular lymphocytic infiltrate), articular involvement (arthralgia and / or arthritis), high dysphagia, pulmonary involvement (dyspnea and computed tomography scan with evidence of interstitial lung disease and/or lung disease in "ground-glass" abnormality), muscle strength of limbs (grade 0: no muscle contraction; grade I: trace of contraction; grade II: normal amplitude movements but incapable of countering the action of gravity; grade III: normal amplitude movements against gravity; grade IV: full mobility against gravity and degree of resistance; grade V: complete mobility against strong resistance against the action of gravity).[19] Serum creatine phosphokinase levels (normal range: 24 - 173 IU/L) and aldolase (1.0 - 7.5 IU/L) were determined by the automated kinetic method. Autoantibodies against cellular components (antinuclear antibodies - ANA) were determined by indirect immunofluorescence using Hep-2 cells as a substrate. Analyses of the anti-Mi-2 and anti-Jo-1 were performed by using commercial solid-phase immunoblotting kit, a qualitative immunoassay line for detection of human immunoglobulin G autoantibodies against specific myositis antigens in serum (Euroimmun, Lübeck, Germany). In order to increase the specificity of the method, the manufacturer's protocol was followed. Reaction positivity was defined according to a previously published study.[20]

Information on the UDE was obtained from electronic reports issued by the endoscopy service of the institution. Furthermore, the Los Angeles ratings were used to define gastroesophageal reflux disease,[21] while the current Sydney classification was employed for endoscopic findings of the gastric mucosa.[22] This study was approved by the institutional ethics committee.

Statistical analysis. The Kolmogorov-Smirnov test was used to evaluate the distribution of each continuous variable. The data are expressed as: mean ± standard deviation (SD) or median (25^{th} - 75^{th} interquartile) for continuous variables, and frequencies (%) for categorical variables. Comparisons between the different parameters were made using Student's *t*-test or the Mann-Whitney test for continuous variables. Pearson's chi-squared test or Fisher's exact test was used to evaluate the categorical variables. The measurements (univariate and multivariate) were expressed as an odds ratio (OR) with 95% confidence interval (CI) by using a non-conditional logistic model. For gastrointestinal tract data in patients with new onset-dermatomyositis values of $p < 0.05$ were considered significant. All of the analyses were performed with the SPSS 15.0 statistics software (Chicago, USA).

RESULTS

A total of 65 consecutive DM patients were included in the study, with 75.4% female gender and 76.9% white ethnicity. The mean age of patients was 44.9 ± 15.5 years, with a median duration of symptoms attributed to DM of four months (Table 1).

Table 1 - General data from 65 patients with new-onset dermatomyositis

Age (years)	44.9 ± 15.5
Female gender	49 (75.4)
Black ethnicity	15 (23.1)
Disease duration (months)	4.0 [2.0-8.0]
Constitutional symptoms	40 (61.5)
Cutaneous involvement	
Heliotrope rash	58 (89.2)
Gottron's papules	57 (87.7)
Photosensitivity	42 (64.6)
"V-neck" sign	29 (44.6)
"Shawl" sign	14 (21.5)
Vasculitis	14 (21.5)
Ulcers	6 (9.2)
Calcinosis	1 (1.5)
Pulmonary involvement	24 (36.9)
Joint involvement (arthralgia and/or arthritis)	20 (30.8)
Upper dysphagia	37 (56.9)
Muscle involvement	65 (100.0)
Upper limbs (muscle strength)	
Grade V	4 (6.2)
Grade IV	37 (56.9)
Grade III	24 (36.9)
Lower limbs (muscle strength)	
Grade V	4 (6.2)
Grade IV	36 (55.4)
Grade III	25 (38.4)
Antinuclear factor	32 (49.2)
Anti-Mi-2 autoantibody	6 (9.2)
Anti-Jo-1 autoantibody	3 (4.6)
Creatine phosphokinase (U/L)	1247 [276-9000]
Aldolase (U/L)	23.0 [7.0-61.0]
Medications*	
Prednisolone	30 (46.2)
Non-steroidal anti-inflammatory drugs	2 (3.1)
Gastric protector**	22 (33.8)

Data expressed as mean ± standard deviation, median (interquartile range 25%-75%) or percentage (%). * At time of upper digestive endoscopy; ** Proton pump inhibitor (omeprazole) or anti-H2 blocker (ranitidine).

Constitutional symptoms were present in 61.5% of patients at diagnosis; dermatologic manifestations such as heliotrope, Gottron's papules and photosensitivity were common, with a prevalence of 89.2%, 87.7% and 64.6%, respectively (Table 1).

Pulmonary involvement, articular problems, and high dysphagia were present in 36.9%, 30.8% and 56.9% of patients, respectively.

All but four of the patients had some degree of objective muscle weakness.

Approximately half of patients tested ANA positive (Table 1). Anti-Mi-2 and anti-Jo-1 were found in 6 (9.2%) and 3 (4.6%) patients, respectively. Median levels of serum creatine kinase and aldolase were 1,247 U/L and 23.0 U/L, respectively (Table 1).

At the time of the UDE, 46.2% of patients were in use of prednisone (0.5 - 1.0 mg/kg/day) and 3.1% had been using non-steroidal anti-inflammatory drugs for at least one week.

Approximately one third of patients had been using a gastric protector (omeprazole or ranitidine) for at least one week.

About 70% of patients presented endoscopic changes of the upper digestive tract (esophagus, stomach and/or duodenum). Of these, 47.7% exhibited changes in one of the upper digestive tract areas, 20.0% in two areas and 3.1% concomitantly in all three areas (esophagus, stomach and duodenum).

Table 2 shows endoscopic findings for the upper gastrointestinal tract of patients. Esophageal involvement was documented in 18.5% of patients, distal non-erosive esophagitis in 1.5% of cases, and distal erosive esophagitis in 16.9%. In the latter group, 9 patients were Grade A and 2 patients Grade B, according to the Los Angeles classification. Gastric changes were identified in 63.1% of patients and were primarily characterized by the presence of antral gastritis (42.3%), followed by pangastritis (27.8%). There were no cases of corpus or severe gastritis, according to the Sydney classification. Endoscopy results revealed that 15.4% had duodenal involvement, 10.9% bulbar duodenitis and 7.7% duodenal ulcer.

An additional analysis showed through univariate analysis, that there was no correlation between the endoscopic findings mentioned in Table 2 (distal esophagitis, antral gastritis, pangastritis, duodenal ulcer and bulbar duodenitis) and all data of patients showed in Table 1 (demographic, clinical, laboratory and medications) ($P > 0.05$), except for those variables shown in Table 3 (erosive distal esophagitis, erosive antral gastritis, enanthematous antral gastritis and enanthematous pangastritis). Furthermore, these last variables proved also significant on multivariate linear regression analysis (Table 3). Thus, there was a lower likelihood of erosive distal esophagitis with higher patient age, lower likelihood of enanthematous pangastritis in patients presenting skin lesions with the "V-neck" sign, and a greater likelihood of enanthematous and erosive antral pangastritis in male and black patients, respectively.

Table 2 - Percentage of patients with new-onset dermatomyositis by type of endoscopic change in upper gastrointestinal tract.

Region			Number of patients (%)
B Esophageal involvement			12 (18.5)
Distal esophagitis	Erosive	Mild	11 (16.9)
		Moderate	0
	Non-erosive	Mild	1 (1.5)
		Moderate	0
Gastric involvement			44 (63.1)
Antral gastritis	Enanthematous	Mild	3 (4.9)
		Moderate	4 (6.6)
	Erosive	Mild	13 (20.0)
		Moderate	4 (6.2)
	Atrophic		3 (4.6)
Pangastritis	Enanthematous	Mild	10 (15.4)
		Moderate	2 (3.1)
	Erosive	Mild	3 (4.6)
		Moderate	2 (3.1)
	Atrophic		1 (1.6)
Duodenal involvement			10 (15.4)
Duodenal ulcer	Healed		5 (7.7)
Bulbar duodenitis	Enanthematous	Mild	4 (6.2)
		Moderate	0
	Erosive	Mild	1 (1.6)
		Moderate	2 (3.1)
Concomitant involvement of:			46 (70.8)
One area (esophagus, stomach or duodenum)			31 (47.7)
Two areas (esophagus, stomach and/or duodenum)			13 (20.0)
Three areas (esophagus, stomach and duodenum)			2 (3.1)

Table 3 - Univariate and multivariate analysis of endoscopic findings of upper gastrointestinal tract in new-onset dermatomyositis.

Endoscopic findings	Parameters	Univariate		Multivariate	
		OR	95%CI	OR	95%CI
Erosive distal esophagitis	Age	0.95	0.91-0.99	0.94	0.88-0.99
Erosive antral gastritis	Male gender	4.45	1.22-16.16	4.78	1.35-16.96
Enanthematous antral gastritis	Black ethnicity	5.70	1.03-31.70	5.52	1.02-29.97
Enanthematous pangastritis	"V-neck" sign	0.21	0.04-0.99	0.08	0.007-0.91

OR: Odds ratio; CI: confidence interval.

Moreover, endoscopic changes did not correlate ($p > 0.05$) with all parameters showed in the Table 1, including drug therapy (prednisone, nonsteroidal anti-inflammatory and/or gastric protector).

No neoplasia lesions were identified in this study.

DISCUSSION

The present study found that approximately 70% of adult patients with newly-diagnosed DM without upper gastrointestinal tract symptoms (except high dysphagia) had endoscopic changes in the upper digestive tract.

Although DM is a rare disease and strict exclusion criteria were employed in the present study, this analysis included a sample of 65 patients with defined DM. Information on patients was based on previously standardized and parameterized data, ensuring reliable study data. Endoscopic examinations were performed at the same service adopting the same standardization of reports, thereby reducing inter-examiner variability. In addition,

as UDE examinations were performed in newly-diagnosed patients, the cases were evaluated at the same time and at a similar phase, rendering the sample more homogeneous for subsequent analysis.

We included only cases without upper gastrointestinal tract symptoms that were newly-diagnosed and therefore in a fully active phase of the disease. The objective was to exclude or reduce many parameters that can influence the endoscopic examination, such as drug therapy (glucocorticoids, immunosuppressives, nonsteroidal anti-inflammatory drugs, gastric protectors).

Although well-documented in juvenile DM,[14-18] there are currently no descriptions of endoscopic findings of the upper digestive tract in adult patients with DM.

Approximately 70% of our patients had endoscopic changes in at least one area of the upper digestive tract. Gastric involvement occurred in approximately two-thirds of the patients analyzed, while changes in the esophagus and duodenum were present in 18.5% and 15.4% of cases, respectively.

In the case of esophageal involvement, the majority of patients had an erosive distal esophagitis picture, corresponding to 16.9% of all our cases, and therefore comparable to the rate reported in the literature of 12.0 - 17.3%.[23,24] In addition, the frequency of erosive distal esophagitis decreased with patient age. Further studies are warranted to evaluate this possible inverse relationship between esophageal injury and age.

Gastric changes were present in two thirds of patients with DM. Erosive antral gastritis and erosive pangastritis accounted for half of all gastric changes. The presence of this erosive gastritis is not associated with the use of medications, especially nonsteroidal anti-inflammatory drugs. At the time of UDE, half of the patients were in use of non-steroidal anti-inflammatory drugs or prednisone. Nevertheless, the use of these medications, as well as gastric protectors, had no impact on endoscopic findings, suggesting that the changes observed were inherent to DM. Because DM is a vascular disease, in which vascular depletion leads to tissue ischemia, the subsequent compensatory stimulus may result in neoangiogenesis. This phenomenon is clearly demonstrated on nailfold capillaroscopy, which discloses capillary ectasia, micro-hemorrhages, vessel bushes, and areas of capillary dropout. One hypothesis for the present findings is that such vascular changes also occur within the wall of the gastrointestinal tract.

Male gender and black ethnicity were factors associated with a higher frequency of erosive antral gastritis and enanthematous antral gastritis, respectively. A hypothesis for these associations, although not explored in the present study, is that male patients may have a higher frequency of *Helicobacter pylori*, which is strongly associated with higher prevalence of gastritis in the antral region.[25-27]

Unlike other skin lesions analyzed in this study, only the presence of the cutaneous type "V-neck" sign injury was associated with UDE findings. In this case, there was an inverse relationship between presence of the injury and enanthematous pangastritis. Further studies are needed to confirm this association between the two parameters and to assess a possible cause-consequence relationship.

Duodenal disease was documented in 15.4% of the cases, with duodenal ulcer present in 7.7% of the sample analyzed. Although the study was conducted at a reference center, Suzuki *et al.*[28] found a 6% prevalence of duodenal ulcer in patients with dyspeptic symptoms. This result may suggest an increased prevalence of duodenal ulcer in our patients, since the present study only included asymptomatic dyspeptic cases.

The prevalence of neoplasms in patients with newly-diagnosed DM is 8.6%,[29] where the most common primary sites in descending order are: lung, ovaries, uterus, thyroid, hematologic, colon, skin and prostate. Corroborating the results of the cited study,[28] no progressive neoplasia was found on the present UDE analysis.

Study limitations: no control group was included; only a small sample was involved, given the rarity of the disease and the strict exclusion criteria applied. Some changes, such as gastric ulcer, require a greater number of patients for prevalence analysis; no data analysis of infection by *Helicobacter pylori*, known to be linked to some gastroduodenal changes presented by patients was carried out; the cross-sectional evaluation of the patients analyzed allowed evaluation of possible associations between the parameters found but precluded deduction of possible cause-effect relationships; finally, specific muscle and cutaneous measures validated in DM were not used in the retrospective study.

SUMMARY

The estimated prevalence of gastrointestinal disorders in the study sample analyzed may be relevant to guide conduct in digestive disorders with UDE examination and points to the need for pharmacological prevention of esophageal and gastroduodenal lesions in these patients.

CONFLICT OF INTEREST

All authors declare no conflict of interest

AUTHOR CONTRIBUTION

Amorim TM: planning, reviewing literature, executing and writing the article. Furuya Junior CK: reviewing literature, executing and writing the article. Marques SB: reviewing literature, executing and writing the article. Shinjo SK: planning, reviewing literature, executing and writing the article.

ALTERAÇÕES MORFOLÓGICAS DO TRATO INTESTINAL SUPERIOR EM PORTADORES DE DERMATOMIOSITE DE INSTALAÇÃO RECENTE: CORRELAÇÕES COM CARACTERÍSTICAS DEMOGRÁFICAS, CLÍNICAS E LABORATORIAIS

OBJETIVOS: Avaliar os exames de endoscopia digestiva alta (EDA) de pacientes adultos com DM (dermatomiosite) recém-diagnosticados; correlacionar eventuais alterações do trato gastrintestinal com dados demográficos, clínicos, e medicamentosos desta população.

MÉTODO: Estudo transversal, em que foram avaliados 65 casos de DM recém-diagnosticados, no período entre 2004 a 2015. Foram excluídos casos de DM clinicamente amiopática, sobreposição com DM, hepatopatias, cirurgia gástrica prévia, sintomas do trato gastrointestinal (exceto disfagia alta), quadros infecciosos sistêmicos, etilismo e tabagismo.

RESULTADOS: A média idade dos pacientes foi de 44,9 anos, com um tempo de sintomas atribuídos a DM de quatro meses. Alterações endoscópicas foram encontradas em 70,8% dos pacientes. O acometimento esofágico/gástrico foi documentado em 18,5% dos pacientes: esofagite distal erosiva (16,9%) e esofagite distal não-erosiva (1,5%); alterações gástricas em 63,1% dos casos: gastrite antral (42,3%) e pangastrite (27,8%); o acometimento duodenal em 15,4% dos pacientes: bulboduodenite (10,9%) e úlcera duodenal (7,7%). Não foram detectadas lesões malignas. Em análise multivariada, a esofagite distal erosiva esteve menos associada a indivíduos de idade maior. Sexo masculino apresentava mais diagnóstico de gastrite erosiva. A pangastrite enantemática esteve menos associada a lesões em "V" do decote.

CONCLUSÕES: O presente estudo estima, pela primeira vez, a prevalência de alterações endoscópicas altas em pacientes adultos com DM recém-diagnosticada. Os resultados podem ser relevantes para guiar potenciais alterações digestivas com exame de EDA, bem como apontar para necessidade de prevenção medicamentosa de lesões do trato digestivo nestes pacientes.

PALAVRAS-CHAVE: Dermatomiosite, dispepsia, endoscopia gastrointestinal, miosite.

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