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# Spontaneous pneumomediastinum in dermatomyositis: a case series and literature review

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**OBJECTIVES:** To describe a case series of spontaneous pneumomediastinum in dermatomyositis and to review the literature.
**METHODS:** This was a retrospective single-center case series, reporting 9 patients with pneumomediastinum and defined dermatomyositis, followed from 2005 to 2017.
**RESULTS**: Median age of patients: 33 years; cutaneous and pulmonary involvement in all cases; constitutional symptoms in 88.8% of patients; involvement of the joints in 11.1%, gastrointestinal tract in 44.4%, and muscles in 77.7%; subcutaneous emphysema was observed in 55.5% and pneumothorax in 11.1%, respectively. Muscle weakness was observed in 77.7% of cases and with a median level of serum creatine phosphokinase of 124U/L. Drawing on results for our literature review, the overall analysis showed that the risk factors associated with spontaneous pneumomediastinum were: (a) a history of interstitial pneumopathy; (b) normal or low levels of muscle enzymes; (c) previous use of systemic glucocorticoid; (d) over 50% of patients had subcutaneous emphysema; (e) high mortality as a consequence of severity of the interstitial lung disease.
**CONCLUSIONS**: Our case series revealed that pneumomediastinum is a rare complication in dermatomyositis that occurs in patients with a history of interstitial pneumopathy and may be accompanied by subcutaneous emphysema and pneumothorax.

**KEYWORDS:** Dermatomyositis; myositis; pneumomediastinum; pneumopathy.

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## INTRODUCTION

Dermatomyositis (DM) is a systemic autoimmune myopathy, classically characterized by the presence of progressive, symmetrical, predominantly proximal muscular weakness of the limbs, as well as typical cutaneous lesions such as heliotrope and Gottron's papules.[1-3] In addition, DM may present with cardiac, pulmonary and gastrointestinal involvement.[1-3]

Spontaneous pneumomediastinum is an uncommon complication in DM, with a high mortality rate.[4-16] Given the rarity of this event, most of the literature available is limited to case reports.[4-49] Despite this limitation, the following factors are believed to be related to the progression of pneumomediastinum in DM: previous presence of interstitial pneumopathy,[4,7,8,12,39] younger patients,[36] presence of cutaneous vasculopathy,[8,9,24] normal or slightly increased serum levels of muscle enzymes,[4,10,39] and prior use of glucocorticoids.[10,12,23,39]

Therefore, the objectives of the present study were to describe a series of cases of spontaneous pneumomediastinum in DM from our tertiary service center and to review the literature.

## MATERIALS AND METHODS

**Case series.** This was a retrospective single-center case series, reporting 9 patients with defined DM, according to the Bohan and Peter criteria,[2] or with clinically amyopathic DM according to the Gerami et al. criteria.[50] All patients were from the same tertiary center, between 2005 and 2017.

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The study was approved by the local Ethics Committee.

The exclusion criteria used were: patients with DM concomitant with other associated systemic autoimmune diseases (overlaps); occurrence of neoplasms, pulmonary infections (i.e., tuberculosis, aspergilloma) or chronic obstructive pulmonary disease.

The following data on the eligible patients were evaluated from electronic medical records, with pre-standardized and parameterized information related to the initial diagnostic investigation and follow-up of patients exhibiting clinical/laboratory-confirmed activity:

- Demographic data: current age; age at disease diagnosis; time between diagnosis and symptoms onset; sex; ethnicity
- Clinical manifestations: constitutional symptoms (fever and weight loss); heliotrope; Gottron's sign/papules; facial rash; "V-neck" sign; "shawl" sign; periungual hyperemia; vasculitis; calcinosis; ulcers; mechanic's hands; muscle weakness in upper and lower limbs (muscle strength determined according to the Medical Research Council recommendations[51]), joint involvement, gastrointestinal tract (high dysphagia, vasculitis) and pulmonary involvement (dyspnea: moderate to mild exertion, accompanied by abnormalities on pulmonary images); and cutaneous crackling (subcutaneous emphysema)
- Abnormalities on pulmonary computer tomography images: interstitial pneumopathy, pulmonary fibrosis, pneumothorax, subcutaneous emphysema and pneumomediastinum

Serum levels of muscle enzymes in blood samples collected routinely for medical consultation: creatine phosphokinase (reference value: 32 - 294 U/L) and aldolase (1.0 - 7.5 U/L), determined by the automated kinetic method.

For the analysis of myositis-specific autoantibodies, the serum samples collected at the time of the initial investigation of the disease from patients exhibiting clinical-laboratory activity were aliquoted and stored at -20ºC. The identification of the anti-Mi-2 autoantibodies was carried out with the Myositis Profile Euroline Blot test kit (Euroimmun, Lübeck, Germany) using the manufacturer's protocol. Positivity of the reaction was defined according to previous studies.[52] Identification of the anti-MDA-5 autoantibody was performed by the Enzyme-Linked Immunosorbent Assay (ELISA) method, using the recombinant MDA-5 protein and the anti-MDA-5 monoclonal antibody (MyBioSource, CA, USA). The positivity of the reaction was defined according to previous studies.[53]

Disease activity was defined as the presence of clinical manifestations (i.e., cutaneous lesions and/or muscular changes: objective muscular weakness of limbs) and biochemical changes (increase in serum muscle enzymes), without an apparent cause. Complete clinical response was defined as a period of 6 consecutive months without evidence of disease activity, and with the use of glucocorticoids and/or immunosuppressants. Clinical remission was defined as a period of 6 consecutive months without evidence of disease activity, and without glucocorticoid and immunosuppressant use over the period.

**Literature Review.** We conducted literature searches in electronic databases. The search was carried out in December 2017, based on the descriptors with the following keywords in English, Spanish, Portuguese, French or Italian: "DM", "pneumomediastinum", "mediastinal emphysema". The keywords were combined with the Boolean operators "AND" and "OR" and adapted for each database as required. In addition, the reference list of each retrieved article was reviewed manually. The following inclusion criteria were adopted: no chronological limit, original articles, case reports, and case series. We excluded abstracts of conferences, monographies, theses and dissertations, articles related to other myopathies (i.e., muscular dystrophies, metabolic myopathies, and neuromuscular diseases) and letters to the Editor with commentaries from a review. In addition, for articles reporting pneumomediastinum in other myopathies and collagenopathies, only patients with DM were considered in the analysis. The search led to the retrieval of 46 articles with case reports.[4-49]

**Statistical analysis**. The Kolmogorov-Smirnov test was used to evaluate the distribution of each of the continuous variables. The results were presented as mean ± standard deviation for continuous variables and number (%) for categorical variables. The median (minimum - maximum) values were calculated for continuous variables that did not have a normal distribution.

## RESULTS

We evaluated 9 DM patients with pneumomediastinum. The general characteristics of the patients are shown in Table 1. Two of these patients had clinically amyopathic DM (# 8 and # 9).

The median age of patients was 33.0 (20.0 - 57.0) years, with predominance of males and Caucasians. The median time between diagnosis and symptom onset was 3.0 (2.0 - 24.0) months. The median follow-up time was 7.0 (0.2 - 15.0) years.

Constitutional symptoms were present in 8 (88.8%) of the patients. Cutaneous involvement was present in all cases, involvement of joints in 1 (11.1%), gastrointestinal tract in 4 (44.4%), pulmonary in 9 (100%) and muscles in 7 (77.7%) patients. Subcutaneous emphysema was observed in 5 (55.5%) and pneumothorax in 1 (11.1%) patient, respectively.

The most prevalent skin lesions were cuticle hypertrophy and periungual hyperemia (100%), followed by Gottron's papules (88.8%), heliotrope (88.8%), facial

**Table 1.** Demographic, clinical, laboratory, and disease progression features and complementary exams of the 9 patients with dermatomyositis and pneumomediastinum.

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| Age (years) | 46 | 20 | 39 | 57 | 31 | 28 | 27 | 33 | 45 |
| Sex | M | F | F | F | M | M | M | M | M |
| Ethnicity | C | C | AB | C | C | C | AB | AB | C |
| Time: diagnosis - symptoms (months) | 24 | 2 | 3 | 8 | 4 | 3 | 3 | 2 | 2 |
| Follow-up time (years) | 15 | 7 | 8 | 0.2 | 8 | 2 | 8 | 0.2 | 1.5 |
| Constitutional symptoms | + | + | | + | + | + | + | + | + |
| Cutaneous involvement | | | | | | | | | |
| Heliotrope | + | + | | + | + | + | + | + | + |
| Gottron's sign or papules | + | + | + | + | + | + | + | + | |
| Facial rash | + | + | | + | + | + | + | + | + |
| "V-neck" sign | + | + | | + | | + | | + | + |
| Shawl Sign | | + | | + | | + | | | |
| Periungual hypertrophy | + | + | + | + | + | + | + | + | + |
| Vasculitis | + | + | | + | | | + | | + |
| Ulcers | + | + | | + | + | | + | | |
| Calcinosis | | | | | + | | | | |
| Joint involvement | + | | | | | | | | |
| Gastrointestinal tract involvement | | + | | + | | + | + | | |
| Pulmonary involvement | | | | | | | | | |
| Dyspnea | + | + | + | + | + | + | + | + | + |
| Interstitial pneumopathy | + | + | + | + | + | + | + | + | + |
| Pulmonary fibrosis | + | | + | + | + | | + | | |
| Muscular strength | | | | | | | | | |
| Upper limbs | IV | III | IV | IV | IV | IV | III | V | V |
| Lower limbs | IV | III | IV | IV | IV | IV | III | V | V |
| Initial CPK (U/L) | 170 | 3031 | 674 | 41 | 120 | 65 | 190 | 124 | 120 |

CPK: creatine phosphokinase; F: female; M: male; C: Caucasian; AB: Afro-Brazilian
All patients were anti-MDA-5 and anti-Mi-2 negative.

rash (88.8%), vasculitis (55.5%), digitalis ulcers (33.3%), and calcinosis (11.1%).

Regarding pulmonary involvement, all patients had dyspnea associated with the presence of interstitial pneumopathy. In addition, 4 of the 9 patients also had pulmonary fibrosis.

With the exception of two patients (# 8 and # 9), all had limb muscle weakness, with a median serum CPK level of 124 (93 - 432) U/L.

Anti-Mi-2 and anti-MDA-5 autoantibodies were absent in all cases.

At discharge, all patients received oral prednisone. Pulse therapy with methylprednisolone (1 g / day, for 3 consecutive days) and human intravenous immunoglobulin (2 g / kg, divided over 2 consecutive days) were administered in 4 and 6 of the 9 patients, respectively. During outpatient follow-up, patients received several types of immunosuppressant drugs (Table 2).

At study endpoint, two patients exhibited disease activity and died (pneumomediastinum complications: pulmonary infection and acute respiratory failure). Four patients had complete clinical response and three had complete remission of the disease.

Clinical features and mortality factors are displayed in Tables A and B in Annex 1.

## DISCUSSION

In the present study, 9 consecutive patients with DM and pneumomediastinum were evaluated. All cases were associated with the presence of interstitial pneumopathy.

**Table 2.** Drug treatment and clinical progression of the 9 patients with dermatomyositis and pneumomediastinum.

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| Glucocorticoid | | | | | | | | | |
| Pulse therapy with methylprednisolone | + | | + | | + | | | | + |
| Previous prednisone | + | + | + | + | + | + | + | + | + |
| Current prednisone (mg/day) | 5.0 | 0.0 | 0.0 | 60.0 | 0.0 | 0.0 | 0.0 | 60.0 | 7.5 |
| Human intravenous immunoglobulin | + | + | | | + | + | + | | + |
| Previous Immunosuppressants | | | | | | | | | |
| Azathioprine | + | + | + | | + | + | + | + | |
| Methotrexate | + | + | | | + | + | + | | |
| Cyclosporine | + | | | | + | + | + | | + |
| Leflunomide | | | | | + | | | | |
| Cyclophosphamide | + | | + | | | | | | + |
| Current immunosuppressants | | | | | | | | | |
| Azathioprine | + | | + | | | | | + | |
| Methotrexate | | | | | | + | | | |
| Cyclosporine | + | | | | | | | | + |
| Leflunomide | | | | | | | | | |
| Cyclophosphamide | | | | | | | | | |
| Current disease status | | | | | | | | | |
| Disease activity | | | | + | | | | + | |
| Complete clinical response | + | | + | | | + | | | + |
| Clinical remission | | + | | | + | | + | | |
| Death | | | | + | | | | + | |

Given that pneumomediastinum in DM is an uncommon event in a rare disease, the studies available in the literature are limited to single case reports. In contrast, a series of 9 patients with DM and pneumomediastinum is reported in the present study. In addition, a systematic review of the literature was performed, analyzing the possible risk factors associated with pneumomediastinum and its prognosis.

In DM, spontaneous pneumomediastinum has been found in patients with history of interstitial pneumopathy[4-11,13-20,24-49] and may occur simultaneously with subcutaneous emphysema[4,6-10,12-15,17,19-21,23,25-40] and pneumothorax.[4-6,9,10,13,25,26,28,29,34,35,42,46] In our series, all cases had a history of interstitial pneumopathy, 55.5% had subcutaneous emphysema and 11.1% pneumothorax, at the time of the diagnosis of spontaneous pneumomediastinum.

Reported risk factors for pneumomediastinum in patients with DM are as follows: a) history of interstitial pneumopathy;[4,7,12,28,39] b) young patients;[36] c) cutaneous vasculopathy;[8,24,39] d) normal or low levels of muscle enzymes;[4,10,39] e) prior use of systemic glucocorticoids;[10,12,23,39] and f) presence of anti-MDA-5.[5]

For the risk factors reported in the literature, 100% of our cases had a history of interstitial pneumopathy, 77.7% were patients younger than 30 years old, 33.3% had cutaneous vasculopathy, 77.7% had normal or low levels (less than twice the upper limit of normal) of muscle enzymes, 77.7% prior use of systemic glucocorticoids and no patients had the anti-MDA-5 autoantibody.

The pathophysiological mechanism of spontaneous pneumomediastinum in DM is unknown. Cicuttini et al.[24] suggest mechanisms of alveolar rupture secondary to interstitial pneumonitis or subpleural pulmonary infarctions resulting from vasculitis. Alveolar rupture in the peripheral alveoli causes pneumothorax, whereas rupture in the alveoli adjacent to the vessels of the threads and mediastinum leads to pneumomediastinum.[7]

In the literature, reported mortality rates among patients with pneumomediastinum in DM range from 37.5% to 52.5%.[10,31,41] In our series, pneumomediastinum-related mortality was 22.2%.

Secondly, in the present study, we performed a unified analysis of our cases together with pneumomediastinum cases in DM reported by 46 articles on PubMed published between 1986 and 2017.[4-49] This yielded a total of 81 cases, including the 9 cases in the present study.

The overall analysis of total patients with pneumomediastinum in DM revealed subcutaneous emphysema in 60.5% of cases and pneumothorax in 21.0%. In addition, 97.5% had signs of interstitial pneumopathy at the time of pneumomediastinum diagnosis (although rates of 100% have been reported in the literature), 2 patients

reported no interstitial or non-interstitial pneumopathy.[22,27] However, this evaluation was performed using simple chest X-rays and not thin-section computed tomography, where the latter exam has greater sensitivity and specificity for evaluating interstitial pneumopathy.

Based on the risk factors for pneumomediastinum described in the literature, the overall evaluation of all cases revealed: a) history of interstitial pneumopathy in 97.5% (77/79); b) young patients (< 30 years according to the WHO) in 31.5% (23/73); c) cutaneous vasculopathy (presence of Raynaud's phenomenon, digital ulcers, and digital necrosis) in 34.2% (26/76); d) normal or relatively low serum levels of muscle enzymes in 72.2% (57/79); e) prior use of glucocorticoid in 83.5% (66/79); and f) presence of anti-MDA-5 in 45.5% (10/22). Based on their presence in > 50% of patients, risk factors for pneumomediastinum in DM are: history of interstitial pneumopathy, normal or low levels of muscle enzymes, systemic use of glucocorticoid, young age and cutaneous vasculopathy. Regarding the presence of autoanti-MDA-5, (not performed in the majority of patients in previous studies), results were negative for all 9 patients in the present series. By contrast, 90.2% (10/11) positivity was reported in a study of Chinese patients [5], representing a risk factor in this group.

On the overall analysis, mortality rate was 29.2% (21/72), where deaths were associated with severity of interstitial pneumopathy and the presence of subcutaneous emphysema and pneumothorax.[4-16]

Finally, there is no established treatment for pneumomediastinum in DM, but vital support is the most important management approach. In the studies reviewed, approaches included use of systemic glucocorticoids and most currently available immunosuppressants, with different efficacy rates.[4-49] A biological agent (rituximab) was used in only one case, and considered effective. However, based on our criteria, this efficacy is questionable, because the agent was used together with methylprednisolone and cyclophosphamide, leading to improvement of the disease in the first week of treatment.[42]

The overall analysis showed that: 1) the risk factors associated with pneumomediastinum are history of interstitial pneumopathy, normal or low levels of muscle enzymes, previous use of systemic glucocorticoid, and the presence of anti-MDA-5 (in Chinese patients); 2) more than 50% of patients presented with subcutaneous emphysema; and 3) mortality risk is high and determined by the severity of the interstitial lung disease.

## SUMMARY

Pneumomediastinum is a rare complication in patients with DM associated with interstitial pneumopathy. Our case series revealed that the complication can be accompanied by subcutaneous emphysema and pneumothorax and is associated with a high mortality rate.

## AUTHOR CONTRIBUTION

P A Olivo Pallo: planning, reviewing literature, executing and writing the present article

S K Shinjo: planning, executing and writing the present article

## CONFLICT OF INTEREST

Authors declare no conflict of interest.

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## PNEUMOMEDIASTINO ESPONTÂNEO NA DERMATOMIOSITE: UMA SÉRIE DE CASOS E REVISÃO DE LITERATURA

**OBJETIVOS**: Descrever série de casos de pneumomediastino espontâneo em portadores de dermatomiosite e revisar a literatura.

**MÉTODOS**: Trata-se de série de casos, único centro, relatando 9 pacientes com pneumomediastino e dermatomiosite definida, acompanhados de 2005 a 2017.

**RESULTADOS**: A mediana da idade dos pacientes foi de 33 anos. Sintomas constitucionais estavam presentes em 88,8% dos pacientes. Houve acometimento cutâneo e pulmonar em todos os casos, acometimento das articulações em 11,1%, trato gastrointestinal em 44,4% e musculatura em 77,7% dos pacientes. Enfisema subcutâneo foi observado em 55,5% e pneumotórax em 11,1%, respectivamente. A fraqueza muscular foi observada em 77,7% dos casos, com um nível médio de creatinofosfoquinase sérica de 124U/L. Com base nos resultados da revisão da literatura, a análise geral mostrou que: os fatores de risco associados ao pneumomediastino espontâneo foram: história de pneumopatia intersticial, níveis normais ou baixos de enzimas musculares, uso prévio de glicocorticoide sistêmico; >50% dos pacientes tiveram enfisema subcutâneo; houve alta mortalidade como consequência da gravidade da doença pulmonar intersticial.

**CONCLUSÕES**: Nossa série de casos revelou que o pneumomediastino é uma complicação rara na dermatomiosite e que ocorre em pacientes com história de pneumopatia intersticial e pode ser acompanhada por enfisema subcutâneo e pneumotórax.

**PALAVRAS-CHAVE:** Dermatomiosite; miosite; pneumomediastino; pneumopatia.

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## **Annex 1.** Clinical features and mortality of studied patients.

**Table A.** Clinical, laboratory and progression features of all patients with dermatomyositis and pneumomediastinum.

| | | Present Study | Published cases (4-49) | Total |
|---|---|---|---|---|
| Number of patients | | 9 | 72 | 81 |
| Age (years) | | 21-48 | 9-74 | 9-72 |
| Sex | Male | 6 | 35 | 41 (50.6%) |
| | Female | 3 | 37 | 40 (49.4%) |
| Diagnosis: | DM | 7 | 45 | 52 (64.2%) |
| | CADM | 2 | 24 | 26 (32.1%) |
| | Juvenile DM | 0 | 3 | 3 (3.7%) |
| Cutaneous involvement | Heliotrope | 2/9 | 34/54 | 36/63 (57.1%) |
| | Gottron's sign or papules | 3/9 | 50/55 | 53/64 (82.8%) |
| | Malar rash | 0/9 | 24/57 | 24/66 (36.8%) |
| | Neckline "V-neck" sign | 0/9 | 2/47 | 2/56 (3.6%) |
| | Shawl sign | 1/9 | 3/49 | 4/58 (6.9%) |
| | Periungual alteration | 1/9 | 18/47 | 19/56 (33.9%) |
| | Calcinosis | 0/9 | 0/49 | 0/58 (0%) |
| | Cutaneous vasculitis | 1/9 | 0/67 | 1/78 (1.3%) |
| Muscular involvement | Muscle weakness | 2/9 | 24/72 | 26/81 (32.1%) |
| | Normal muscle enzymes or <2 times the upper limit of normal | 7/9 | 50/70 | 57/81 (72.2%) |
| Pulmonary involvement | Interstitial pneumopathy | 9/9 | 68/70 | 77/79 (97.5%) |
| | Pneumothorax | 1/9 | 16/72 | 17/81 (21.0%) |
| | Subcutaneous emphysema | 5/9 | 44/72 | 49/81 (60.5%) |
| Vasculopathy (Raynaud's phenomenon, digital ulcers, necrosis) | | 2/9 | 24/67 | 26/76 (34.2%) |
| Joint involvement | | 4/9 | 28/70 | 32/64 (50.0%) |
| Gastrointestinal tract involvement | | 1/9 | 01/41 | 2/50 (4.0%) |
| Anti-MDA 5 antibody | | 0/9 | 10/13 | 10/22 (45.5%) |
| Previous use of glucocorticoid | | 7/9 | 59/70 | 66/79 (83.5%) |

CADM: clinically amyopathic dermatomyositis; DM: dermatomyositis.

**Table B.** Comparison of factors associated with mortality.

| | Mortality group | Improvement group |
|---|---|---|
| Total | 21/72 (29.2%) | 51/72 (70.8%) |
| Severe interstitial pneumopathy | 18/21 (85.7%) | 3/51 (5.9%) |
| Subcutaneous emphysema | 15/21 (71.4%) | 27/51 (53.0%) |
| Pneumothorax | 6/21 (28.5%) | 10/51 (19.6%) |
| Vasculopathy | 7/21 (33.3%) | 14/51 (27.5%) |
| Muscle enzymes: normal or less than 2 times the upper limit of normal | 16/21 (76.2%) | 34/51 (66.7%) |