Newly diagnosed dermatomyositis in the elderly as predictor of malignancy

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ABSTRACT

Objective: Dermatomyositis (DM) symptoms may be a clue to the existence of a hidden cancer. Enhancing early detection is essential, but there are no studies evaluating short-term predictive factors in this disease. **Methods:** This is a single-center retrospective study, including patients diagnosed with DM meeting at least four of the five Bohan and Peter's criteria (1975), from 1991 to 2011. This study assessed malignancies occurring in up to 12 months after the diagnosis of DM. **Results:** Neoplasm was found in 12 out of 139 patients (skin, gastrointestinal tract, prostate, thyroid, breast, lungs, and genitourinary tract). Patients with neoplasm had a higher mean age than controls (56.8 ± 15.7 *vs.* 40.3 ± 13.1 years, respectively, P = 0.004, odds ratio 1.09; 95% confidence interval: 1.04–1.14). No statistical differences were observed regarding gender, ethnicity, frequency of constitutional symptoms, organ and systemic involvements, and/or laboratory alterations. **Conclusion:** In newly diagnosed DM, age at disease diagnosis was a predictive factor of malignancy.

Keywords: dermatomyositis, myositis, risk factors, neoplasms, aging.

INTRODUCTION

Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by clinical findings such as progressive, symmetric proximal muscle weakness in the four limbs, in addition to the presence of typical cutaneous changes, such as heliotrope rash and Gottron's papules.

The risk of developing neoplasias in idiopathic inflammatory myopathies is greater than that in the general population,[1–23] mainly in DM[1,4–7,12,15–17] and in the first years following the disease diagnosis.[1–6,8,10,13,21] The risk factors described in the literature are as follows: atypical cutaneous manifestations;[12,16–18,21] persistently high erythrocyte sedimentation rate (ESR);[12,17] refractoriness to treatment in the elderly;[20,21] rapid progression to muscle weakness;[12,16–22] presence of myositis-specific autoantibodies (anti-p155 or anti-p155/p140 antibodies);[23] cutaneous necrosis or periungual erythema;[12,16,17,21] dysphagia;[24] no lung impairment;[24] gender;[4,5,10,19,21] and advanced age on the occasion of disease diagnosis.[5,7,19,21,24]

However, those studies have analyzed predictive factors of malignancy in a general population of inflammatory myopathies[1–8,10,14–16,19,21] and/or independently of disease duration at the time of cancer diagnosis.[1–3,5,7,10,12–19,21,23]

This study assesses the prevalence and possible factors associated with neoplasias in a population constituted only by patients with DM diagnosed in the preceding year (newly diagnosed).

PATIENTS AND METHODS

This retrospective study assessed 139 patients diagnosed with DM, meeting at least four of the five criteria proposed by Bohan and Peter.[25,26] Those patients were on an outpatient clinic follow-up at our tertiary service from 1991 to 2011. Patients with amyopathic DM or diagnosed with possible or probable DM were not included. This study was approved by the local Ethics Committee [HC 0039/10].

Demographic, clinical, and laboratory data were obtained from a systematic review of the patients' medical records. The

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manifestations assessed were limited to up to one year after the diagnosis of DM. The following parameters were assessed: constitutional symptoms; cutaneous changes (heliotrope rash, Gottron's papules, ulcers, rash, calcinosis); joint involvement (arthralgia and/or arthritis); dysphagia; dysphonia; dyspnea; and muscle strength of the limbs (grade 0: no muscle contractility; grade I: signs of discrete contractility; grade II: range of motion that does not overcome gravity; grade III: normal range of motion that overcomes gravity; grade IV: full motion against gravity and certain degree of resistance; grade V: full motion against marked resistance and gravity).[27] The serum level of creatine kinase measured at the time of the initial diagnosis of DM by use of the automated kinetic method was also assessed. Complementary tests (electroneuromyography, muscle biopsy – brachial biceps or vastus lateralis muscles), when performed, were requested as routine in the first medical consultations. Electroneuromyography was considered positive in the presence of inflammatory proximal myopathy of the limbs with no neuropathy associated. The muscle biopsy was considered diagnostic when perifascicular atrophy with or without inflammatory infiltrate was evidenced.

This study assessed neoplasias occurring in up to one year after the diagnosis of DM and confirmed by anatomopathological analysis. In our service, screening for neoplasia in all patients suspected of having initial DM is routine, with assessment of breasts, genitourinary and gastrointestinal tracts, lungs, hematologic system (particularly lymphoma), and skin.

The results were expressed as mean ± standard deviation (SD) or percentage. The Student *t* test was used for the statistical analysis of parametric data, and the Fisher exact test for categorical data. The 95% confidence interval (95% CI) was calculated by use of binomial distribution. The disease duration and adjusted age, odds ratio (OR), and 95% CI were calculated by using a non-conditional logistic model. Those calculations were performed by using the version 7.0 of the STATA software (STATA, College Station, TX, USA). Values of $P < 0.050$ were considered statistically significant.

RESULTS

In the period studied, 139 patients diagnosed with DM, meeting at least four of the five Bohan and Peter's criteria, were assessed, 12 of whom (8.6%) had a history of neoplasia in the first 12 months of disease.

Chart 1 lists the types of cancer found in the patients, which were in the following sites: breasts, genitourinary and gastrointestinal tracts, lungs, prostate, thyroid, and skin. Metastasis was identified in four (33.3%) patients at the time neoplasia was diagnosed. Of the 12 patients affected, 11 (91.7%) were females and 10 (83.3%) were white (Table 1).

Patients who had neoplasia (group A) were compared with those who did not (group B) (Table 1). The mean age at the time DM was diagnosed in group A was 56.8 ± 15.7 years (35–84 years), and, in group B, 40.3 ± 13.1 years (20–78 years) ($P = 0.004$). Even after analyzing age quartiles, statistical difference was observed between the groups (OR, 1.09; 95% CI: 1.04–1.14).

However, no differences were found in the groups regarding clinical laboratory manifestations and complementary tests (electroneuromyography and muscle biopsy) (Table 1).

Chart 1
Types of neoplasia seen in patients with newly diagnosed dermatomyositis

Spinocellular carcinoma in the lower limbs
Ulcerated well-differentiated keratinizing squamous cell carcinoma
Pulmonary spinocellular carcinoma, metastasis
Pulmonary epidermoid carcinoma, metastasis
Ovarian adenocarcinoma
Basal cell carcinoma of the face
Thyroid carcinoma
Colon adenocarcinoma, metastasis
Invasive epidermoid carcinoma of the uterus
Ductal carcinoma of the breast
Ovarian undifferentiated adenocarcinoma
Prostate adenocarcinoma, metastasis

Table 1
Demographic, clinical and laboratory data of patients with dermatomyositis with and without neoplasia

	Neoplasia (+) (n = 12)	Neoplasia (–) (n = 127)	P
Female gender (%)	11 (91.7)	100 (78.7)	0.459
White color (%)	10 (83.3)	123 (89.0)	1.000
Age at DM diagnosis			
Mean ± SD (years)	56.8 ± 15.7	40.3 ± 13.1	0.004
Variation (years)	35–84	20–78	0.022
Percentile (%)			
20–31 years	0	38 (29.9)	
32– 41 years	2 (16.7)	33 (26.0)	
42–51 years	4 (33.3)	29 (22.8)	
52–88 years	6 (50.0)	27 (21.3)	

(Continue...)

(Continuation of Table 1)

	Neoplasia (+) (n = 12)	Neoplasia (–) (n = 127)	P
Clinical manifestations			
Constitutional symptoms (%)	5 (41.7)	60 (47.2)	0.770
Bedridden (%)	5 (41.7)	24 (18.9)	0.128
Cutaneous (%)			
Heliotrope rash	9 (75.0)	108 (85.0)	0.404
Gottron's papules	10 (83.3)	123 (96.9)	0.085
Ulcers	2 (16.7)	18 (14.2)	0.684
Rash	6 (50.0)	63 (49.6)	1.000
Calcinosis	0	9 (7.1)	1.000
Muscle (muscle strength)			
Upper limbs (%)			
Grade V	1 (8.3)	7 (5.5)	0.524
Grade IV	9 (75.0)	97 (76.4)	1.000
Grade III	2 (16.7)	21 (16.5)	1.000
Grade II	0	2 (1.6)	1.000
Lower limbs (%)			
Grade V	2 (16.7)	4 (3.1)	0.085
Grade IV	8 (66.7)	96 (75.6)	1.000
Grade III	2 (16.7)	24 (18.9)	1.000
Grade II	0	3 (2.4)	1.000
Articular (%)	8 (66.7)	50 (39.4)	0.123
Dysphagia (%)	8 (66.7)	49 (38.6)	0.071
Dysphonia (%)	4 (33.3)	20 (15.7)	0.221
Dyspnea (%)	4 (33.3)	39 (30.7)	1.000
Laboratory changes			
Creatine kinase			
Mean ± SD (U/L)	2758.7 ± 3945.4	3783.3 ± 5617.1	0.450
Percentile (%)			0.537
6–210 U/L	2 (18.2)	25 (26.0)	
211–823 U/L	5 (45.5)	22 (22.9)	
824–4880 U/L	2 (18.2)	25 (26.0)	
4881–22000 U/L	2 (18.2)	24 (25.0)	
Complementary tests			
Electroneuromyography* (n)	10/11	80/120	0.171
Muscle biopsy** (n)	9/9	80/83	1.000

DM: dermatomyositis; SD: standard deviation. *Presence of proximal inflammatory myopathy of the limbs; **Compatible with inflammatory myopathy.

DISCUSSION

This study found an 8.6% prevalence of neoplasia in individuals with newly-diagnosed DM, age being a risk factor associated with malignancy in that population.

Differently from the studies available in the literature,[1–8,10,14–16,20] we assessed the prevalence and possible predictive factors of cancer in a population comprising only DM. In addition, we restricted our sample to patients diagnosed with DM, whose disease duration did not exceed one year, unlike other studies.[1–3,5,7,10,12–19,21,23] That restriction is important because patients with a longer disease duration can have other parameters related to cancer development, such as the chronic use of immunosuppressive drugs.

András et al.[8] have reported that malignancy may precede myopathy by two years, while Maoz et al.[16] have described neoplasias in DM even after five years of disease. In general, the prevalence and incidence of neoplasias in the general population of DM ranges from 9.4%–28%.[3,4,13,15] Considering that cancer is more frequent in the first year of disease,[1–3,5,6,10] in this study, it was found in 8.6% of the patients, representing, thus, a prevalence within the expected range.

The sites of neoplasia usually found in DM are as follows: pulmonary,[2,3,5,16] ovarian,[2,3,5,16,28] nasopharyngeal,[16,29] pancreatic,[3] gastric,[3,16] colorectal,[3,16] uterine,[3,5] breast,[8,16] thyroidal,[16] and hematological, including lymphomas.[2,3,16] In this study they were in accordance with those reported in the literature and were as follows: pulmonary, ovarian, uterine, thyroidal, hematological, colorectal, cutaneous, and prostatic. In addition, one third of the patients already had metastasis at the time cancer was diagnosed.

In our study we observed that age at the time of disease diagnosis was a predictive factor of the development of malignancy in DM, in accordance with other studies in the literature.[5,7,10,20–22,24] In addition, similarly to Sigurgeirsson et al.[4] and Stockton et al.,[5] we showed that the neoplasias affected predominantly women, although other studies have reported a higher incidence among men.[10,19,21]

Other risk factors reported in the literature are as follows: cutaneous necrosis or periungual erythema,[12,16,17,21] persistently high ESR values,[12,17] refractoriness to treatment in elderly patients,[20,21] presence of myositis-specific autoantibodies, such as anti-p155 and anti-p155/140 antibodies,[23] no pulmonary involvement,[24] dysphagia,[24] and amyopathic DM.[30]

In this study neither cutaneous necrosis nor refractoriness to treatment was observed. Regarding pulmonary involvement and presence of dysphagia, the same distribution was found in patients with and without neoplasias. In amyopathic DM, the incidence of neoplasias is higher than in classic DM.[30] In the presence of neoplasia, it is difficult to differentiate whether the patients really have amyopathic DM or whether the manifestations are paraneoplastic; thus, we limited our analysis only to DM meeting at least four of the five Bohan and Peter's criteria.

Because this was a retrospective study, we had some limitations such as unavailability to some laboratory tests (ESR, C-reactive protein, aldolase) of some patients. In addition,

the possible autoantibodies related to the neoplasias were not assessed in this study.

Our study emphasizes the concept that patients with DM should be routinely screened for neoplasias, mainly those with newly diagnosed DM. Among other predictive factors of cancer, DM initiating at advanced age should be considered, when a more extensive assessment for cancer is recommended.

In conclusion, we showed that age was a factor associated with malignancy in newly-diagnosed DM.

REFERENCES

1. Buchbinder R, Forbes A, Hall S, Dennett X, Giles G. Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. Ann Intern Med 2001; 134(12):1087–95.
2. Chow WH, Gridley G, Mellemkjaer L, McLaughlin JK, Olsen JH, Fraumeni JF Jr. Cancer risk following polymyositis and dermatomyositis: a nationwide cohort study in Denmark. Cancer Causes Control 1995; 6(1):9–13.
3. Hill CL, Zhang Y, Sigurgeirsson B, Pukkala E, Mellemkjaer L, Airio A *et al*. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet 2001; 357(9250):96–100.
4. Sigurgeirsson B, Lindelöf B, Edhag O, Allander E. Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study. N Engl J Med 1992; 326(6):363–7.
5. Stockton D, Doherty VR, Brewster DH. Risk of cancer in patients with dermatomyositis or polymyositis, and follow-up implications: a Scottish population-based cohort study. Br J Cancer 2001; 85(1):41–5.
6. Zantos D, Zhang Y, Felson D. The overall and temporal association of cancer with polymyositis and dermatomyositis. J Rheumatol 1994; 21(10):1855–9.
7. Airio A, Pukkala E, Isomäki H. Elevated cancer incidence in patients with dermatomyositis: a population based study. J Rheumatol 1995; 22(7):1300–3.
8. András C, Ponyi A, Constantin T, Csiki Z, Szekanecz E, Szodoray P *et al*. Dermatomyositis and polymyositis associated with malignancy: a 21-year retrospective study. J Rheumatol 2008; 35(3):438–44.
9. Callen JP, Hyla JF, Bole GG Jr, Kay DR. The relationship of dermatomyositis and polymyositis to internal malignancy. Arch Dermatol 1980; 116(3):295–8.
10. Wakata N, Kurihara T, Saito E, Kinoshita M. Polymyositis and dermatomyositis associated with malignancy: a 30-year retrospective study. Int J Dermatol 2002; 41(11):729–34.
11. Barnes BE, Mawr B. Dermatomyositis and malignancy. A review of the literature. Ann Intern Med 1976; 84(1):68–76.
12. Basset-Seguin N, Roujeau JC, Gherardi R, Guillaume JC, Revuz J, Touraine R. Prognostic factors and predictive signs of malignancy in adult dermatomyositis. A study of 32 cases. Arch Dermatol 1990; 126(5):633–7.
13. Bonnetblanc JM, Bernard P, Fayol J. Dermatomyositis and malignancy. A multicenter cooperative study. Dermatologica 1990; 180(4):212–6.
14. Manchul LA, Jin A, Pritchard KI, Tenenbaum J, Boyd NF, Lee P *et al*. The frequency of malignant neoplasms in patients with polymyositis-dermatomyositis. A controlled study. Arch Intern Med 1985; 145(10):1835–9.
15. Chen YJ, Wu CY, Huang YL, Wang CB, Shen JL, Chang YT. Cancer risks of dermatomyositis and polymyositis: a nationwide cohort study in Taiwan. Arthritis Res Ther 2010; 12(2):R70.
16. Maoz CR, Langevitz P, Livneh A, Blumstein Z, Sadeh M, Bank I *et al*. High incidence of malignancies in patients with dermatomyositis and polymyositis: an 11-year analysis. Semin Arthritis Rheum 1998; 27(5):319–24.
17. Amerio P, Girardelli CR, Projetto G, Forleo P, Cerritelli L, Feliciani C *et al*. Usefulness of erythrocyte sedimentation rate as tumor marker in cancer associated myositis. Eur J Dermatol 2002; 12(2):165–9.
18. Gallais V, Crickx B, Belaich S. Prognostic factors and predictive signs of malignancy in adult dermatomyositis. Ann Dermatol Venereol 1996; 123(11):722–6.
19. Chen YJ, Wu CY, Shen JL. Predicting factors of malignancy in dermatomyositis and polymyositis: a case-control study. Br J Dermatol 2001; 144(4):825–31.
20. Shimizu J. Malignancy-associated myositis. Brain Nerve 2010; 62(4):427–32.
21. Antiochos BB, Brown LA, Li Z, Tosteson TD, Wortmann RL, Rigby WF. Malignancy is associated with dermatomyositis but not polymyositis in Northern New England, USA. J Rheumatol 2010; 36(12):2704–10.
22. Fardet L, Dupuy A, Gain M, Kettaneh A, Chérin P, Bachelez H *et al*. Factors associated with underlying malignancy in a retrospective cohort of 121 patients with dermatomyositis. Medicine (Baltimore) 2009; 88(2):91–7.
23. Trallero-Araguás E, Rodrigo-Pendás JÁ, Selva-O'Callaghan A, Martínez-Gómez X, Bosch X, Labrador-Horrillo M *et al*. Usefulness of anti-p155 autoantibody for diagnosing cancer-associated dermatomyositis: a systematic review and meta-analysis. Arthritis Rheum 2012; 64(2):523–32.
24. Sow MW, Koo BS, Kim YG, Lee CK, Yoo B. Idiopathic inflammatory myopathy associated with malignancy: a retrospective cohort of 151 Korean patients with dermatomyositis and polymyositis. J Rheumatol 2011; 38(11):2432–5.
25. Bohan A, Peter JB. Polymyositis and dermatomyositis. Pt I. N Engl J Med 1975; 292(7):344–7.
26. Bohan A, Peter JB. Polymyositis and dermatomyositis. Pt II. N Engl J Med. 1975; 292(8):403–7.

27. Medical Research Council. Aids to the investigation of peripheral nerve injuries. War Memorandun No 7, 2.ed. London: Her Majesty's Stationery Office, 1943.
28. Whitmore SE, Rosenshein NB, Provost TT. Ovarian cancer in patients with dermatomyositis. Medicine (Baltimore) 1994; 73(3):153–60.
29. Hu WJ, Chen DL, Min HQ. Study of 45 cases of nasopharyngeal carcinoma with dermatomyositis. Am J Clin Oncol 1996; 19(1):35–8.
30. Whitmore SE, Watson R, Rosenshein NB, Provost TT. Dermatomyositis sine myositis: association with malignancy. J Rheumatol 1996; 23(1):101–5.