Characteristics of dermatomyositis patients with and without associated malignancy

Julia Lauinger¹, Kamran Ghoreschi², Sebastian Volc¹

(¹) Department of Dermatology, University of Tübingen, Tübingen, Germany
(²) Department of Dermatology, Venereology and Allergology, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Summary

Background: Dermatomyositis belongs to the rare idiopathic, inflammatory myositis group. A previously postulated link between some cases of dermatomyositis and malignancy has been established in recent years. Criteria suggestive of a malignancy association are still being explored.

Patients and Methods: We retrospectively analyzed data from 63 patients with dermatomyositis over a period of 15 years.

Results: The following criteria argue for cancer-associated dermatomyositis: older age (> 52 years [P = 0.001], > 65 years [P = 0.002], ≥ 75 years [P = 0.002]), shorter time between manifestation and diagnosis of dermatomyositis (malignancy group: 59 days vs. non-malignancy group: 137 days [P = 0.022]), typical skin involvement such as Gottron sign (P = 0.045), centrofacial erythema (P = 0.036) and typical erythema on the upper arms and forearms (P = 0.019), oropharyngeal involvement (P = 0.015) and increased ALT (P = 0.031). The following criteria argue for non-cancer-associated dermatomyositis: younger age (≤ 52 years [P = 0.001], 40–65 years [P = 0.045]) and pruritus (P = 0.026).

Conclusions: The aforementioned criteria have been documented in the literature, but reported findings are heterogeneous concerning the suitability of their markers for malignancy association. Small study populations, few prospective controlled studies, summarization of different forms of myositis and inconsistent use nomenclature contribute to biased results. Our study aims to make an important contribution toward the identification of risk factors in cancer-associated dermatomyositis.

Introduction

Dermatomyositis (DM) is a rare global autoimmune disease that can affect both skin and musculature. It belongs to the idiopathic inflammatory myositis group. Apart from the adult form that may be paraneoplastic in nature, there is also a juvenile DM [1]. Due to the rarity of the disease, only limited data are available beyond case reports and case series. Many criteria supporting an association with malignancy have been discussed in the literature, including skin-related and muscle-related symptoms, as well as laboratory parameters. In 1916, the first association of DM with malignancy was documented by Stertz, who described a DM patient with gastric cancer [2]. In addition, cancer-associated DM is listed as a subgroup in the classification of Bohan and Peter. To this day, several studies and case series regularly report on the frequent association of malignancies with DM. The association is considered an established fact [3–5]. In many cases, the malignancy is diagnosed within the first year of DM diagnosis. In principle, however, a malignancy may exist before or develop during the course of DM. 25–42 % of DM patients exhibit such an association with malignancy [6]. Strongly fluctuating percentages from 6–60 % have been reported [7]. Compared to the normal population, DM patients are at a 6–12-fold higher risk of developing a malignancy [6].

Accordingly, tumor search and follow-up play an important role. To this day, no standardized and binding guidelines exist for how and how often tumor screening should be performed [5, 8]. Common recommendations and the most frequently associated tumors [2, 9–14] and risk factors [2, 5, 6, 10, 15–19] are summarized in the Online Supplement.

Conflict of interest

None.
A notable observation from the literature search was the heterogeneous use of nomenclature for skin findings. For example, there is often a reference to either Gottron sign or Gottron papules; only in rare cases are these differentiated, as in Sontheimer [20] or in the classification of the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) [21]. Examples are presented in the Online Supplement [22, 23]. Didona et al. emphasize that the established classification criteria require revision and state that the skin-related symptoms play a key role in the diagnosis of DM [24].

The present work will provide both more data for the analysis of DM and a contribution to the important question of which risk factors argue for or against an association with malignancy.

### Table 1 Inclusion and exclusion criteria of the study population.

| 254 patients with ICD 10 diagnosis codes: |
|-------------------------------------------|
| - M33.0 (juvenile dermatomyositis) |
| - M33.1 (other dermatomyositis) |
| - M33.9 (dermatopolymyositis, unspecified) |
| - M35.1 (other overlap syndromes) |
| - M36.0 (dermatopoly(myositis in neoplastic disease C00-D48) |

| 175 patients with the exclusion criteria: |
|----------------------------------------|
| - dermatomyositis as secondary diagnosis |
| - dermatomyositis as suspected diagnosis |
| - dermatomyositis as part of an overlap syndrome |

| 8 patients with the exclusion criterion: |
|----------------------------------------|
| - observation period shorter than 30 days |

| 8 patients with the exclusion criterion: |
|----------------------------------------|
| - juvenile dermatomyositis (age < 18 years) |

| 63 patients included |
|---------------------|

| 19 patients |
|------------|
| malignancy group |

| 44 patients |
|-------------|
| non-malignancy group |

### Patients and Methods

#### Study population

This work is a retrospective, monocentric data analysis of patients diagnosed with DM that were treated in the Department of Dermatology of the University of Tübingen between January 2000 and December 2015. The patients were identified by means of the electronic patient record. 63 of the originally 254 patients were selected (Table 1) and subdivided into two groups. Patients that had, previously had, or developed one or more malignancies were included in the malignancy group; the remaining patients were allocated to the non-malignancy group.
Data

Laboratory values obtained from 2003 onward could be retrieved from the laboratory EDP system. The classification of skin manifestations was based on the criteria defined by Sontheimer [20] with further additions from the literature and our own observations.

Statistics

The statistical evaluation was performed with IBM SPSS Statistics version 26. A P value of < 0.05 was considered statistically significant. For independent, qualitative criteria, significance was assessed by chi-squared test. For samples < 20 or case numbers < 5, Fisher’s exact test was used. To assess the significance of independent, quantitative criteria, we used the t-test for normally distributed samples and the U test for non-normally distributed samples.

Results

Patient collective

Of the 63 patients examined, 19 patients (30.2 %) were allocated to the malignancy group and 44 patients (69.8 %) were allocated to the non-malignancy group. The gender distribution in both groups was similar: 63.2 % of the patients in the malignancy group and 66.0 % of the patients in the non-malignancy group were female (Table 2).

The time from onset of symptoms (initial manifestation) to diagnosis differed significantly and could be determined in all patients of the malignancy group and in 81.8 % of the non-malignancy group. The median was 59 days in the malignancy group compared to 137 days in the non-malignancy group (U test, \( P = 0.022 \)) (Table 2).

The mean age at the time of diagnosis was higher in the malignancy group compared to the non-malignancy group: 68.8 ± 11.6 years versus 52.4 ± 15.2 years (t-test; \( P = 0.001 \)). In both groups, the mean age at diagnosis was lower for female patients compared to male patients (malignancy group: \( \overline{\text{♀}} \ 66.6 ± 12.9 \) years and \( \overline{\text{♂}} \ 72.6 ± 8.5 \) years vs. non-malignancy group: \( \overline{\text{♀}} \ 49.4 ± 15.9 \) years and \( \overline{\text{♂}} \ 58.2 ± 12.1 \) years).

For better comparability of the data, Table 2 also shows the distribution of our population according to the age limits used by various authors [6, 25, 26].

Malignancy group

Characteristics of the malignancy group can be found in Table 3. Overall, 24 malignancies were documented in

| Table 2 Demographics and selected age classifications. |
|------------------------------------------------------|
| **Patient collective**                               |
| **MG**      | **NMG**     | **P value** | **Test**   |
|-----------------------------------------------|
| Gender (♀/♂)  | 63.2 %/36.8 % | 66.0 %/34.1 % | ns | – |
| Age at ID, mean [Y] | 68.8 | 52.4 | 0.001 | t-test |
| Time between IM and ID, median [days] | 59 | 137 | 0.022 | U test |
| Age categories based on specifications of authors, % (n) |
| Fardet et al. [6] | ≤ 52 years | 5.3 % (1) | 50.0 % (22) | 0.001 | chi-squared test |
| | > 52 years | 94.7 % (18) | 50.0 % (22) | 0.001 | chi-squared test |
| Hill et al. [28] | < 45 years | 5.3 % (1) | 25.0 % (11) | ns | – |
| | ≥ 45 years | 94.7 % (18) | 75.0 % (33) | ns | – |
| Stockton et al. [25] | < 45 years | 5.3 % (1) | 25.0 % (11) | ns | – |
| | 45–74 years | 52.6 % (10) | 68.2 % (30) | ns | – |
| | ≥ 75 years | 42.1 % (8) | 6.8 % (3) | 0.002 | Fisher’s test |
| Modified from Tang and Thevarajah [26] | < 40 years | 5.3 % (1) | 18.2 % (8) | ns | – |
| | 40–65 years | 31.6 % (6) | 59.1 % (26) | 0.045 | chi-squared test |
| | > 65 years | 63.2 % (12) | 22.7 % (10) | 0.002 | chi-squared test |

\( Abbr. \): ID, initial diagnosis; IM, initial manifestation; Y, years of life; MG, malignancy group; n, number; NMG, non-malignancy group; ns, not significant; \( \overline{\text{♂}} \), male; \( \overline{\text{♀}} \), female. Highlighted in italic = significant \( P \) values.
these 19 patients. In 16 of these 24 malignancies, DM was assessed as paraneoplasia (66.7 %), and in eight malignancies (33.3 %), the link between malignancy and DM was unclear. In five patients (26.3 %), two malignancies had been documented simultaneously or successively. The most frequent malignancies were breast cancer (50.0 %) and prostate cancer (42.9 %), followed by ovarian cancer (33.3 %), lung cancer (15.8 %) and melanoma (15.8 %). Colorectal cancer occurred in 10.5 %, while nasopharyngeal cancer, meningioma and CUP syndrome occurred in 5.3 % each. The median time between malignancy development and initial diagnosis of DM was 152 days. 79.2 % of the malignancies developed within a period of five years around the initial diagnosis of DM (within two years before the diagnosis of DM and within the first three years after the diagnosis; see dotted line in Figure 1). 41.7 % (n = 10) of the malignancies were diagnosed at the time of initial diagnosis of DM and another 29.2 % (n = 7) in the subsequent two years.

**Clinical features**

**Skin involvement:** in both groups, data on skin manifestations could be acquired for all patients. For a comprehensive list of the findings, see Table 4. The following skin findings...
Table 4 Distribution of clinical skin symptoms in dermatomyositis according to Sontheimer [20].

|                  | MG frequency (n = 19) | NMG frequency (n = 44) | P value  | Test          |
|------------------|-----------------------|------------------------|----------|---------------|
| Major skin criteria |                       |                        |          |               |
| Gottron papules  | 52.6 % (10)           | 72.7 % (32)            | ns       | –             |
| Heliotropic erythema | 94.7 % (18)         | 86.4 % (38)            | ns       | –             |
| Gottron sign     | 68.4 % (13)           | 40.9 % (18)            | 0.045    | chi-squared test |
| Pruritus         | 5.3 % (1)             | 31.8 % (14)            | 0.026    | Fisher’s test |
| TE on scalp/ anterior hairline | 36.8 % (7)    | 29.5 % (13)            | ns       | –             |
| Holster sign     | 15.8 % (3)            | 34.1 % (15)            | ns       | –             |
| Centrofacial TE  | 84.2 % (16)           | 56.8 % (25)            | 0.036    | chi-squared test |
| V sign           | 78.9 % (15)           | 54.5 % (24)            | 0.067    | chi-squared test |
| TE on upper arms/forearms | 68.4 % (13)   | 36.4 % (16)            | 0.019    | chi-squared test |
| Shawl sign       | 26.3 % (5)            | 18.2 % (8)             | ns       | –             |
| Palmar TE        | 0.0 % (0)             | 18.2 % (8)             | ns       | –             |
| Periungual TE    | 47.4 % (9)            | 43.2 % (19)            | ns       | –             |
| Calcinosis cutis | 0.0 % (0)             | 9.1 % (4)              | ns       | –             |
| Poikilodermatitis| 5.3 % (1)             | 9.1 % (4)              | ns       | –             |
| Ulcerations      | 21.1 % (4)            | 6.8 % (3)              | ns       | –             |
| Telangiectasias  | 26.3 % (5)            | 13.6 % (6)             | ns       | –             |
| Mechanic’s hands | 0.0 % (0)             | 9.1 % (4)              | ns       | –             |
| TE in auricular area | 10.5 % (2)        | 91 % (4)               | ns       | –             |
| TE on upper abdomen/trunk/abdomen | 15.8 % (3)        | 13.6 % (6)             | ns       | –             |
| Other criteria   |                       |                        |          |               |
| Oral area spared of erythema | 10.5 % (2)       | 9.1 % (4)              | ns       | –             |
| Alopecia         | 0.0 % (0)             | 11.4 % (5)             | ns       | –             |
| Photosensitivity (in history) | 0.0 % (0)       | 9.1 % (4)              | ns       | –             |
| Raynaud sign     | 5.3 % (1)             | 18.2 % (8)             | ns       | –             |
| Heliotropic erythema and/or centrofacial TE | 94.7 % (18) | 97.7 % (43)            | ns       | –             |

Abbr.: MG; malignancy group; NMG, non-malignancy group; n, number; ns, not significant; TE, typical erythema

Highlighted in italic = significant P values.

Figure 1 Correlation between malignancy diagnosis and initial dermatomyositis diagnosis. x-axis: time in months, timepoint 0 months corresponds to the time when the initial diagnoses of dermatomyositis and malignancy coincided. y-axis: absolute frequency of malignancies dotted line: Time window in which a malignancy is considered paraneoplastic according to Andras et al. [2, 10] —, before initial diagnosis of dermatomyositis.

Muscle involvement: in both groups, data on muscle involvement could be acquired for all patients. A detailed summary of muscle involvement can be found in the Online Supplement. We observed a significant difference for the

were statistically significant: Gottron sign (malignancy group: 68.4 % vs. non-malignancy group: 40.9 %; chi-squared test, P = 0.045; odds ratio [OR] = 3.130, 95 % confidence interval [CI]: 1.002–9.774), pruritus (malignancy group: 5.3 % vs. non-malignancy group: 31.8 %; Fisher’s test, P = 0.026; OR = 0.119, 95 % CI: 0.014–0.983), typical centrofacial erythemas (malignancy group: 84.2 % vs. non-malignancy group: 56.8 %; chi-squared test, P = 0.036; OR = 4.053, 95 % CI: 1.030–15.946), and typical erythemas on upper arms/forearms (malignancy group: 68.4 % vs. non-malignancy group: 36.4 %; chi-squared test, P = 0.019; OR = 3.792, 95 % CI: 1.206–11.926). The non-significant distribution of all other skin changes can be found in the Online Supplement.
involvement of the oropharyngeal musculature that occurred more frequently in the malignancy group (malignancy group: 70.6 % vs. non-malignancy group: 35.1 %; chi-squared test, \( P = 0.015 \); OR = 4.431, 95 % CI: 1.279–15.350). This was apparent as dysphonia (malignancy group: 75.0 % vs. non-malignancy group: 76.9 %) and/or dysphagia (malignancy group: 58.3 % vs. non-malignancy group: 38.5 %) (Table 5).

**Laboratory:** all laboratory values are summarized in Table 6. A significant difference was only observed for the frequency distribution of the increase of alanine transaminase (ALT; malignancy group: 88.2 % vs. non-malignancy group: 58.1 %; chi-squared test, \( P = 0.031 \). The odds ratio was 5.417 (95 % CI: 1.052–27.891). Details about the most important laboratory data, as well as myositis-specific antibodies (MSA) and myositis-associated antibodies (MAA) not documented in Table 6 are listed in the Online Supplement.

**Discussion**

We examined factors indicative for cancer-associated DM. The mean age at initial diagnosis was significantly higher in the malignancy group compared to the non-malignancy group (68.8 years vs. 52.4 years). Greater age (Table 3) is generally considered a risk factor for the development of cancer-associated DM [2, 6, 10, 25, 26]. Lu et al. showed in a meta-analysis that patients with malignancy develop DM at a later age than patients without malignancy [17]. However, only a few studies have examined a “pure” DM population to date. In a study by Fardet et al., DM patients with malignancy had a median age of 60 years, while DM patients without malignancy had a median age of 50 years [6]. We could confirm that the mean patient age constitutes a risk factor. In our study, we found statistically significant frequency differences with an odds ratio > 1 for patients older than 52, for patients older than 65, and for patients aged 75 and older. In this context, an odds ratio > 1 indicates an increased probability of developing cancer-associated DM. By contrast, an odds ratio < 1 for patients aged 52 or younger and for patients aged 40–65 indicates a higher probability of not developing cancer-associated DM. Similarly, in their DM study Fardet et al. showed, with statistical significance, that patients aged 52 or older have an increased probability of developing cancer-associated DM [6]. Marie et al. noted a significantly increased probability (in DM and polymyelitis patients) of developing a malignancy at an age \( \geq 65 \) [27]. In our study, we did not observe an increased probability of developing cancer-associated DM for the groups aged 45 and older and the group aged 15–44, as reported by Hill et al., and for the group aged 45–75, as described by Stockton et al. [25, 28].

We could show a statistically significant difference between both groups with respect to the median time between initial manifestation and initial diagnosis (malignancy group: 59 days vs. non-malignancy group: 137 days). This may suggest that patients with malignancy are diagnosed earlier than patients without malignancy. This was also observed by Fardet et al.: in patients with malignancy, the diagnosis was made earlier, after a median time of two months, whereas patients without malignancy were diagnosed only after a median time of five months. In addition, Fardet et al. state that the probability of developing cancer-associated DM is increased, if the time between initial manifestation and initial diagnosis is less than four months [6]. A potential cause may be that DM patients with malignancy may, individually, often exhibit acute and more severe skin-related symptoms and rather refractory muscle-related symptoms [8, 9, 15].

**Table 5** Distribution of clinical muscle symptoms in dermatomyositis.

|                      | MG frequency (n = 17) | NMG frequency (n = 37) |
|----------------------|-----------------------|------------------------|
| **Time of muscle involvement** |                       |                        |
| Initial              | 70.6 % (12)           | 64.9 % (24)            |
| Secondary            | 29.4 % (5)            | 29.7 % (11)            |
| Before skin manifestation | 0.0 % (0)           | 5.4 % (2)              |
| **Quality of muscle involvement** |                   |                        |
| Muscle pain          | 23.5 % (4)            | 21.6 % (8)             |
| Muscle atrophy       | 5.9 % (1)             | 2.7 % (1)              |
| Muscle weakness      | 82.4 % (14)           | 81.1 % (30)            |
| **Oropharyngeal involvement** |                   |                        |
| Dysphonia            | 75.0 % (9)            | 76.9 % (10)            |
| Dysphagia            | 58.3 % (7)            | 38.5 % (5)             |

Abbr.: MG; malignancy group; NMG, non-malignancy group; n, number; ns, not significant. Highlighted in italic = significant \( P \) values (test: chi-squared test).
Table 6  Laboratory parameters.

|        | MG       | NMG      | P value |
|--------|----------|----------|---------|
| CK     | CK level (median \([\text{U/l}]\), (N)\) | 1382.5 (18) | 396.0 (31) | ns |
|        | CK increase, % (N, n) | 83.3 % (18, 15) | 64.5 % (31, 20) | ns |
|        | CK increase > 1000 U/l, % (N, n) | 55.6 % (18, 10) | 35.5 % (31, 11) | ns |
| LDH    | LDH level (median \([\text{U/l}]\), (N)\) | 418.0 (17) | 334.5 (31) | ns |
|        | LDH increase, % (N, n) | 82.4 % (17, 14) | 67.7 % (31, 21) | ns |
| Leukocytes | Leukocyte level (median \([\*1000/\mu l]\), (N)\) | 6.16 (17) | 7.43 (30) | ns |
|        | Leukocytosis, % (N, n) | 17.6 % (17, 3) | 10.00 % (30, 3) | ns |
|        | Leukopenia, % (N, n) | 11.8 % (17, 2) | 10.00 % (30, 3) | ns |
| Lymphocytes | Lymphocyte level (median \([\*1000/\mu l]\), (N)\) | 0.89 (15) | 1.00 (22) | ns |
|        | Lymphopenia, % (N, n) | 66.7 % (15, 10) | 68.2 % (22, 15) | ns |
| Neutrophils | Neutrophil level (median \([\*1000/\mu l]\), (N)\) | 4.55 (15) | 5.15 (22) | ns |
|        | Neutrophilia, % (N, n) | 33.3 % (15, 5) | 27.3 % (22, 6) | ns |
|        | Neutropenia, % (N, n) | 0.0 % (15, 0) | 4.5 % (22, 1) | ns |
| NLR    | NLR level (median), (N) | 4.4 (15) | 5.5 (22) | ns |
|        | NLR ≥ 5.5, % (N, n) | 40.0 % (15, 6) | 50.0 % (22, 11) | ns |
| AST    | AST level (median \([\text{U/l}]\), (N)\) | 90.5 (16) | 55.5 (28) | ns |
|        | AST increase, % (N, n) | 81.3 % (16, 13) | 64.3 % (28, 18) | ns |
|        | AST increase > 200 U/l, % (N, n) | 31.3 % (16, 5) | 14.3 % (28, 4) | ns |
| ALT    | ALT level (median \([\text{U/l}]\), (N)\) | 80.0 (17) | 55.0 (31) | ns |
|        | ALT increase, % (N, n) | 88.2 % (17, 15) | 58.1 % (31, 18) | 0.037 |
|        | ALT increase > 200 U/l, % (N, n) | 5.9 % (17, 1) | 12.9 % (31, 4) | ns |
| CRP    | CRP level (median \([\text{mg/dl}]\), (N)\) | 0.4 (14) | 0.2 (23) | ns |
|        | CRP increase, % (N, n) | 35.7 % (14, 5) | 43.5 % (23, 10) | ns |
| ANA    | ANA positivity by enzyme immunoassay, % (N, n) | 20.0 % (15, 3) | 19.4 % (36, 7) | ns |
|        | ANA positivity by HEp-2 cells, % (N, n) | 55.6 % (9, 5) | 75.0 % (28, 21) | ns |
| MSA    | Anti-Mi-2, % (N, n) | 20.0 % (5, 1) | 27.3 % (11, 3) | ns |
| MAA    | Anti-Ro/anti-SSA, % (N, n) | 40.0 % (5, 2) | 9.5 % (21, 2) | ns |
|        | Anti-U1RNP, % (N, n) | 0.0 % (6, 0) | 12.5 % (16, 2) | ns |

Abbr.: ANA, antinuclear antibodies; ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; CRP, C-reactive protein; LDH, lactate dehydrogenase; MAA, myositis-associated autoantibodies; MG, malignancy group; MSA, myositis-specific autoantibodies; N, total number; n, number; NLR, neutrophil-lymphocyte ratio; NMG, non-malignancy group; ns, not significant.

Highlighted in italic = significant P values (test: chi-squared test).

The reported laboratory measurements were not available for all patients. Therefore, a format with N, n was chosen. N = Total number of patients in which this parameter was determined. n = This value was increased/decreased in a smaller number of patients (n) out of the total population (N).
This may result in earlier consultation of a physician and thus in faster diagnosis. In our population, we also observed such a case of vesiculobullous DM as a sign of paraneoplasia [29].

30.2 % of the patients in our collective showed an association with malignancy. This is consistent with data from the literature (25–42 %) [6]. Five of our patients had two tumor entities. This situation was also observed by András et al. and Stockton et al. [2, 25]. Hill et al. showed in their study that DM patients develop primarily ovarian cancer, lung cancer, gastric cancer, colon cancer, pancreatic cancer, and non-Hodgkin lymphoma, although other tumor entities have been described [28]. In our collective, the most frequent tumors were breast cancer and prostate cancer, followed by ovarian cancer, lung cancer and melanoma. In our study, each patient with verified malignancy was allocated to the malignancy group irrespective of the tumor entity, with the exception of non-melanocytic skin cancer. Accordingly, it was possible to register rare tumor entities. Cases rarely documented in the literature include melanoma [11, 12, 30, 31] and the rare combination of DM with CUP syndrome [14] and meningioma [13, 32].

In our study, we could show that most malignancies (41.7 %) are discovered at the time of DM diagnosis and during the subsequent two years (29.2 %). These time windows, which are also a subject of debate, have in part been confirmed by other studies [2, 16, 28, 33]. The predominant discovery of malignancies around the time of DM diagnosis may, in part, be explained by the more comprehensive diagnostic workup performed, in particular due to the known association of DM with malignancies [34].

In our study, Gottron sign, typical centrofacial erythemas, and typical erythemas on upper arms and/or forearms were indicative for an increased probability of cancer-associated DM. In contrast, pruritus was a symptom indicative for non-cancer-associated DM.

In their univariate analysis, Fang et al. could significantly show that patients with malignancy have a higher probability of developing Gottron signs than patients of the non-malignancy group. This result was not reproducible in the multivariate analysis [18]. However, Fang et al. described only Gottron signs and did not differentiate them from Gottron papules. The comparison with the mentioned study is also limited by the selection of the study population that included both patients with polymyositis and patients with juvenile DM and overlap patients. In our study, we deliberately excluded these cases. In their study from 2019, András et al. could also significantly show that Gottron papules are more often found in the malignancy group than in their comparison group [10]. Whereas Gottron signs were distinguished from Gottron papules in the study of András et al. from 2008 [2], this was no longer the case in the 2019 study [10].

Similar difficulties with the nomenclature exist for heliotropic erythema and erythemas in the facial area. Based on the clinical documentation, we distinguished in our study between heliotropic erythema, referring to erythema around the periorbital region and the eyelids, and typical centrofacial erythema. The higher incidence of typical centrofacial erythema in malignancy patients was statistically significant (P = 0.036). We did not find any significant differences between the groups with respect to heliotropic erythema alone and in combination with typical centrofacial erythema. While Fang et al. could show a significant difference and an increased incidence of heliotropic erythema in patients with malignancy [18], the differences were not significant in the studies of Fardet et al. [6] and Chen et al. [35]. In our view, consensus on this issue is indispensable for a valid comparison of data from studies.

To our knowledge, there are still no statistically significant data in the literature on the frequency of erythemas on upper arms and/or forearms in relation to malignancy and non-malignancy groups of DM patients.

In our study, we observed a statistically significant, higher incidence of pruritus in the non-malignancy group. In many publications, pruritus plays a diagnostic role, although it is, in summary, unclear whether it argues for or against an association with malignancy. András et al. examined the symptoms of ulceration and pruritus and could show a significantly increased incidence in the examined malignancy group. However, the symptom of pruritus was examined together with ulcerations [2]. Ulcerations are not itchy, but painful. Given that they present per se an aggressive process and are often observed in oncology, it is feasible that the combination of the symptoms of pruritus and ulceration may have produced a biased result. Whereas Gallais et al. reported that pruritus is a statistically significant predictive factor for developing a malignancy [36], Kim et al. [37] could not find a significant difference between the groups.

One task of future examinations should be the documentation of clinical impressions that go beyond the criteria of Bohan and Peter [4] in order to find new parameters and factors that allow for a statement with respect to the probability of malignancy. A similarly important aspect, however, seems to be the adherence to a standardized nomenclature. This is a prerequisite for the comparison of clinical findings. It should also be noted that the CDASI is used in some clinical studies. Advantages of this score are its objectivity and reliability with respect to the clinical findings of DM patients and that it facilitates the interpretation and comparison of studies [21]. A major disadvantage is the considerable time requirement, which is why it is rarely used in clinical routine. In our analysis, the CDASI was not available for any of the patients.

The majority of DM patients experience muscle involvement during the disease course. It is one of the criteria of
Table 7 Risks, discussed in relation to dermatomyositis with malignancy, adapted from Zahr and Baer [15], and amended with Fardet et al. [6], Sigurgeirsson et al. [16], Andras et al. [2, 10], Lu et al. [17] and Nakashima [19] and with own data (Online-Supplement).

| Risk increase | MG | NMG |
|---------------|----|-----|
| Demography    |    |     |
| – different statements: male gender [6] or female gender [22] | ns | ns |
| – advanced age of patient at ID | Yes | No |
| – time between IM and ID of DM < 4 months [6] | Yes | No |
| Skin-related signs |    |     |
| – necrosis and ulceration, ulceration and pruritus [2] | nod | nod |
| – periungual erythema [6, 10] | ns | ns |
| – V sign [3] | ns | ns |
| – heliotropic erythema [6] | ns | ns |
| – Gottron papules/sign [3] | Yes | No |
| – leukocytoclastic vasculitis | nod | nod |
| – resistance to therapy | nod | nod |
| Muscle-related signs |    |     |
| – distal muscle weakness | ns | ns |
| – oropharyngeal involvement | Yes | No |
| – involvement of respiratory muscles | nod | nod |
| – refractory | nod | nod |
| Laboratory |    |     |
| – increased ESR and CRP | ns | ns |
| – low levels of complement C4 | nod | nod |
| – increased tumor markers | nod | nod |
| – myositis-specific autoantibodies: |    |     |
| – anti-NXP2 [24] | nod | nod |
| – anti-TIF1-y/anti-P155/140 [24] |    |     |
| Risk mitigation |    |     |
| Overlap characteristics |    |     |
| – ILD | nod | nod |
| – arthritis/arthralgias | nod | nod |
| – Raynaud phenomenon | ns | ns |
| – fever | nod | nod |
| – heart involvement | nod | nod |
| – ANA positivity | nod | nod |
| – Jo-1 antibodies | nod | nod |
| – lymphopenia | ns | ns |

Abbr.: ANA, antinuclear antibodies; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DM, dermatomyositis; ID, initial diagnosis; IM, initial manifestation; ILD, interstitial lung disease; nod, no information from own data; MG, malignancy group; NMG, non-malignancy group; ns, not significant.

Highlighted in *italic* = significant results.
Bohan and Peter [4]. The involvement of the oropharyngeal musculature in the malignancy group was statistically significant (Table 5). In the literature, this risk factor is often discussed from the aspect of dysphagia and/or dysphonia [2, 10, 17, 18, 35, 38]. However, only a few studies – for example, Fang et al. [18], Lu et al. in their meta-analysis [17], and So et al. [38] – could show a significant difference between the groups with increased probability in the malignancy group.

We observed a significant difference in frequency distribution for the increase of ALT (malignancy group: 88.2 % vs. non-malignancy group: 58.1 %; Table 6). Our data suggest an increased probability of cancer-associated DM in case of initial ALT increase without therapy association. This is in contrast to the results described by Lu et al. in their meta-analysis, according to which an ALT increase is more likely to occur in the group without malignancy [17]. This result was based on three studies [6, 39, 40]. From these three studies, only Prohic et al. obtained the statistically significant result that patients with malignancy have, on average, a higher ALT level, but also that both groups show an ALT increase [39]. Fardet et al. demonstrated that increased ALT levels were more indicative for cancer-associated DM, but that levels > 200 U/l were less common in the malignancy group [6]. Lee et al. note that non-malignancy patients have, on average, higher ALT levels than malignancy patients, and that the mean of malignancy patients is within the normal range [40]. The findings of these studies are very heterogeneous. One reason may be the different size of the studied populations, another reason may be the use of different values (mean vs. median). Only rarely is it mentioned in the literature whether an increase in ALT level occurred initially or during the course of the disease; indeed, this has only been stated by Lee et al. [40]. Hence, the message is that an ALT increase may be relevant, but available data are insufficient to support this.

The analysis of MSA and MAA was performed in individual cases with a standardized nomenclature, are required to allow a comparison of risk factors in relation to cancer-associated DM. The differences in nomenclature of skin findings that we have identified, some of which are highly discrepant (see Online Supplement) illustrate the key role of clinical physicians and highlight the requirement of standardized medical assessments, for example by CDASI. Although the association with malignancies is considered an established fact [8], no standardized guidelines for primary tumor assessment and follow-up in DM patients have been published. Future studies should, therefore, be designed in such a way that they allow for statements on this issue.

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**Correspondence to**

Sebastian Volc, MD
Department of Dermatology
University of Tübingen
Liebermeisterstraße 25
72076 Tübingen, Germany
E-mail: sebastian.volc@med.uni-tuebingen.de

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