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Association between dermatomyositis and malignancies
A literature review on patients' profile

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Συσχέτιση μεταξύ δερματομυοσίτιδας και κακοηθειών: Ανασκόπηση βιβλιογραφίας στο προφίλ των ασθενών

Περίληψη στο τέλος του άρθρου

Dermatomyositis is an idiopathic inflammatory myopathy with skin findings and can occur in both adults and children. The link between dermatomyositis and oncology is well established and the occurrence of cancer in patients suffering from dermatomyositis depends on different factors: subtypes of dermatomyositis they suffer from, time of cancer appearance before or after the dermatomyositis diagnosis, patients' age, patients' gender, obesity and cancer subtypes. The profile of the patients who suffer from both dermatomyositis and cancer concerns mainly males aged over 60 with elevated creatine kinase (CK), high level of C-reactive protein (CRP), cutaneous vasculitis, and rapid onset; up to four weeks. The median time between the diagnosis of dermatomyositis and cancer does not exceed the period of one whole year or a maximum five years. Patients with dermatomyositis and patients with both dermatomyositis and cancer show different clinical features and laboratory parameters or the same in different frequencies. Screening tests and the detection of specific autoantibodies seem useful tools in malignancy diagnosis for patients suffering from dermatomyositis without putting themselves in unneeded danger.

Key words

Age
Dermatomyositis
Gender
Malignancy
Obesity
Oncology

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1. WHAT WE KNOW SO FAR

Dermatomyositis (DM) is an idiopathic myopathy with skin findings and can occur in both adults and children. The association between dermatomyositis and malignancy is absolutely established[1] and the higher risk of cancer occurring at patients suffering from DM is well established as well.[2,3] The higher risk is determined, with approximately 15–30% of DM patients suffering from malignancies,[4] and varies according to different research studies; especially from 4.66-fold higher cancer risk,[5] to a 6–12 fold higher risk.[6] The relation between malignancy and DM is affected by numerous factors: subtypes of DM, median time between DM and cancer diagnosis, patients' age and gender, obesity and cancer subtypes as well. Therefore, the objective of this review is the determination of the relation between DM and cancer and how different factors, such as the DM or the cancer subtype, the patients' gender and age, as well the time before or after the diagnosis, affect the aforementioned correlation.

2. ASSOCIATION BETWEEN DERMATOMYOSITIS AND ONCOLOGY

Dermatomyositis is an idiopathic inflammatory myopathy, mainly characterized by myositis and skin findings and can occur in both adults and children (juvenile DM). A link between DM and malignancy is well established, despite no histologic clues to malignancy-associated DM have been reported in skin biopsies.[1] Numerous case series and population-based studies have confirmed this association, although estimation of malignancy incidence among DM patients varies from 15% to 27%,[2,3] and have shown that patients with DM have a significantly higher risk of developing malignant tumors compared to the healthy population, with approximately 15–30% of DM patients suffering from associated malignancies;[4] about 4.66 fold higher,[5] whereas other studies have reported a 6–12 fold higher risk.[6] The relationship between DM and cancer has a long history, first being suspected in 1916 when the disease was noted to co-occur with a case of stomach cancer. This suspected

relation, however, was only confirmed in 1976 in a study assessing 258 cases of DM associated with various cancers.[7]

2.1. Frequency of cancer cases in dermatomyositis patients depending on different factors

2.1.1. Subtypes of dermatomyositis. It is unknown if the risk differs between the subtypes of dermatomyositis: both cutaneous DM subtype (SDM) and older age at DM diagnosis are significant independent risk factors for underlying malignancy within the first two years of DM onset.[8] Current evidence supports that risk and incidence of malignancy in the clinically amyopathic DM population is similar to that of the classic DM population.[9–11] However, in a recent single academic center DM cohort, malignancy risk in clinically amyopathic DM patients was considerably lower than most other reported cohorts; 1.7% within two years of DM diagnosis and 5.4% within 5 years.[8]

2.1.2. Time before or after the diagnosis. The greatest risk of malignancy exists in the first year after the diagnosis of dermatomyositis, which suggests that DM can develop as a paraneoplastic process.[12] Evidence reported that 64% of patients developed DM in the same year as the malignancy was discovered,[13] whilst an additional recent study involving two large United States (US) cohorts totaling 400 DM patients found that 72% of all malignancy diagnoses occurred in the five years preceding or following DM symptom onset.[9] It is well established that malignancy was most often detected within one year before or after DM diagnosis,[5,8,14] and DM patients maintain an increased risk of malignancy compared to the general population for at least five years following DM diagnosis.[3,15,16]

2.1.3. Patients' age. Importantly, the risk of malignancy primarily relates to patients with adult-onset DM subtypes and not juvenile-onset DM subtypes.[17] Increased malignancy risk among DM patients was associated with age >44–45 years.[1,16] Additionally, individuals with a DM diagnosis at age >40 years and positive TIF-γ antibodies showed an elevated risk; in particular 75% of cancer. Indeed, a feature observed in adults with DM is an increased incidence of lung cancer and the frequency of lung cancer in patients with DM is higher in the elderly than in younger patients.[21]

2.1.4. Patients' gender. Relating to gender, the stratified analysis showed higher malignancy risk in males compared to females,[16,18] despite that female DM patients with anti-TIF-γ antibodies have been found to have an increased risk of ovarian cancer.[19,22,31] Male patients with elderly onset DM (EODM) symptoms were found to be prone to lung cancer.[24]

2.1.5. Obesity. In the subset of patients with body mass index (BMI) data, underweight and overweight categories, as defined by BMI, were not significantly associated with higher odds of malignancy. However, obesity class I had 34% higher odds of malignancy, and class II or III of obesity conferred 42% higher odds of malignancy compared to normal weight, after adjustment. Consequently, patients with DM who had obesity had significantly higher odds of a subsequent cancer diagnosis compared to those DM patients without obesity. Compared to patients with DM who did not have an international classification of diseases (ICD) code for obesity, patients with DM and an obesity ICD code after DM diagnosis had an even stronger association with the development of subsequent cancer, independent of age at first DM diagnosis, year of birth, and sex.[25]

2.1.6. Cancer subtypes. It is well established an increased risk for breast, lung, colorectal, cervical, bladder, pancreatic, esophageal, nasopharyngeal, and renal cancer for DM patients.[18] The type of cancer that often occurs in patients with DM reflects characteristics such as origin, age, and gender. Tumors of breast, lung, and colorectal cancer are diagnosed as the three most common in patients in Western civilization, and nasopharyngeal cancer is one of the most common cancers in Southern Asia. However, every type of cancer can cause paraneoplastic syndrome as DM. It has been proved that polymyositis and DM are strongly associated with certain types of malignant lymphomas, especially Hodgkin lymphoma.[26] A significantly increased risk of cancer of the lymphatic and hematopoietic system, lung, ovary, colon, bladder, breast, cervix, pancreas and esophagus is reported, whereas no increased risk of stomach and prostate cancer is also observed.[9,27] Ovarian cancer appears to be most closely connected with DM, although the relationship of other cancers of the reproductive organ with DM is relatively weak.[12] Ultimately, not only is the cancer risk confirmed, but it is also presented statistically with the most frequently reported malignancies being the following: breast cancer (24.5%), hematologic malignancies (17.0%), colorectal cancers (9.4%), and prostate cancer (9.4%).[28]

2.1.7. Decreased malignancy risk. The presence of interstitial lung diseases (ILD), Raynaud's phenomenon, and anti-extractable nuclear antigen antibodies (anti-ENA) was associated with decreased malignancy risk.[29,30]

2.2. General patients' profile associated with high malignancy risk

The cancer risk factors in patients with dermatomyositis or polymyositis are presented in table 1.[12,25]

Table 1. Cancer risk factors in patients with dermatomyositis (DM).

Age over 60 years
Male gender
Dysphagia
Skin necrosis
Cutaneous vasculitis
Rapid onset (<4 weeks)
Elevated creatine kinase (CK) (normal range: 22–198 U/L)
Increase in erythrocyte sedimentation rate (ESR)
High level of C-reactive protein (CRP) (normal range: 0.3–1.0 mg/dL)
Higher anti-TIFγ antibodies
Co-occurrence of diabetes with the above risks

2.3. Confirming research

Out of 63 patients examined, 19 (30.2%) were allocated to the malignancy group and 44 (69.8%) (were allocated) to the non-malignancy group. The gender distribution was similar in both groups: in the malignancy group 63.2% of the patients were female and 36.8% of them were male, while in the non-malignancy group, 66.0% of the patients were female and 34.0% of them were male. 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. In both groups, the mean age at diagnosis was lower for female patients compared to male patients (malignancy group: ♀ 66.6±12.9 years and ♂ 72.6±8.5 years versus non-malignancy group: ♀ 49.4±15.9 years and ♂ 58.2±12.1 years).

Overall, 24 malignancies were documented, of whom 16 (66.7%) were associated with paraneoplasia, and for the rest of them (8/24, 33.3%) the link between malignancy and DM was unclear. The most frequent cancer types by which DM patients suffer are presented in table 2. The median time between malignancy development and the initial diagnosis of DM was 152 days.

The symptoms of dermatomyositis appeared with different frequencies between the malignancy group and the non-malignancy group. These differences pertain to both clinical features and laboratory parameters and are presented in tables 3 and 4, respectively.[28]

Table 2. Most frequent cancer subtypes by which dermatomyositis (DM) patients suffered during Lauinger's et al research.

Cancer subtypes	Rate (%)
Breast cancer	50.0
Prostate cancer	42.9
Ovarian cancer	33.3
Melanoma	33.3
Lung cancer	15.8
Colorectal cancer	10.5
Nasopharyngeal cancer	5.3
Meningioma	5.3
CUP syndrome	5.3

CUP: Cancer of unknown primary site

Table 3. Differences in clinical features between malignancy and non-malignancy group.

Dermatomyositis clinical features and frequency	Malignancy group (%)	Non-malignancy group (%)
Heliotropic erythema	94.7	86.4
Heliotropic erythema and or centrofacial TE	94.7	97.7
Gottron papules	52.6	72.7
Gottron sign	68.4	40.9
Pruritus	5.3	31.8
Typical centrofacial erythemas	84.2	56.8
Typical erythemas on upper arms/forearms	68.4	36.4
Muscle weakness	82.4	81.1
Muscle pain	23.5	21.6
Muscle atrophy	5.9	2.7
Dysphonia	75.0	76.9
Dysphagia	58.3	38.5

TE: Trichoepithelioma

Table 4. Differences in laboratory parameters between malignancy and non-malignancy group.

Dermatomyositis laboratory parameters and frequency	Malignancy group (%)	Non-malignancy group (%)
CK increase	83.3	64.5
LDH increase	82.4	67.7
CRP increase	35.7	43.5

CK: Creatine kinase, LDH: Lactate dehydrogenase, CRP: C-reactive protein

2.4. Hepatocellular carcinoma

Lymphocyte antigen 6 (LY6E), interferon induced transmembrane protein 1 (IFITM1), growth arrest and DNA damage inducible alpha (GADD45A), metallothionein 1M (MT1M), and secreted phosphoprotein 1 (SPP1) are potential predictive targets for new-onset hepatocellular carcinoma

in patients with DM and the upregulation of SPP1 expression may activate the PI3K/ART signaling pathway through the mediation of integrins to promote the development and progression of hepatocellular carcinoma (HCC). DM signature genes *LY6E*, *IFITM1*, *GADD45A*, *MT1M*, and *SPP1* are risk factors for HCC, and they show good diagnostic efficacy, and are diagnostic targets for HCC.[32]

2.5. Screening tests

Malignancy screening tests are not entirely beneficial but carry with them the considerable potential for harm.[1] Research proved that only 7% quantified overdiagnosis and just 4% reported the rate of false positive results.[32] Despite abundant evidence demonstrating significant potential harm for most screening tests, both patients and clinicians have a tendency to overestimate the benefits of screening tests, implying a poor recognition of the potential risks.[1] In a study examining patients' understanding of malignancy screening, only 19.7% of respondents understood that screening test harms may outweigh the benefits.[33] On the clinician side, nearly all patients in one study reported that their clinicians addressed the benefits of cancer screening, but only approximately 25% reported that they received information about the risks.[34] Importantly, physicians need to be honest about both the potential benefits and harms of malignancy screening during such conversations, as well as about the unknowns concerning malignancy screening protocols and overall value in patients with DM.[1] Ordering malignancy screening tests in any DM patients require the clinician to responsibly learn about both risks and benefits of these tests and to engage the patient in decision-making. Instead of simply implementing malignancy screening protocols upon diagnosing a patient with DM, clinicians should discuss the risks and the benefits of malignancy screening with patients and make a shared decision concerning whether to pursue screening.[1] Additionally, it should be mentioned that the detection of some specific antibodies may be an important tool in the identification of patients with dermatomyositis at risk of developing malignancy.[5]

3. CONCLUSIONS

This research confirms the already established link between DM and malignancies and the impact of various factors on the aforementioned relation. However, provided that DM is an autoimmune disease and that the cause of the DM outbreak is unclear yet, the link connecting DM and oncology cannot be defined genetically, but mainly via statistical research. Consequently, further research needs to be done in order to identify both the genetic cause of DM and the genetic link between cancer and DM and the genetic impact of the other parameters (age gender, cancer or DM subtypes, obesity, the time before or after the diagnosis, etc.) in the connection DM-malignancy.

ΠΕΡΙΛΗΨΗ

Συσχέτιση μεταξύ δερματομυοσίτιδας και κακοηθειών: Ανασκόπηση βιβλιογραφίας στο προφίλ των ασθενών

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Η δερματομυοσίτιδα είναι μια ιδιοπαθής φλεγμονώδης μυοπάθεια με δερματικά ευρήματα και μπορεί να εμφανιστεί τόσο σε ενήλικες όσο και σε παιδιά. Η σχέση δερματομυοσίτιδας-ογκολογίας είναι καλά τεκμηριωμένη και η εμφάνιση καρκίνου σε ασθενείς που πάσχουν από δερματομυοσίτιδα εξαρτάται από διάφορους παράγοντες: υποτύπους δερματομυοσίτιδας από τους οποίους πάσχουν, χρονικό διάστημα εμφάνισης του καρκίνου πριν ή μετά από τη διάγνωση της δερματομυοσίτιδας, ηλικία ασθενών, φύλο ασθενών, παχυσαρκία, καθώς και υπότυποι καρκίνου. Το προφίλ των ασθενών που πάσχουν τόσο από δερματομυοσίτιδα όσο και από καρκίνο αφορά κυρίως σε άνδρες ηλικίας >60 ετών με αυξημένη CK, υψηλές τιμές C-αντιδρώσας πρωτεΐνης, δερματική αγγειίτιδα και ταχεία έναρξη (έως και 4 εβδομάδες). Ο διάμεσος χρόνος μεταξύ της διάγνωσης της δερματομυοσίτιδας και του καρκίνου δεν υπερβαίνει το διάστημα ενός ολόκληρου έτους ή το πολύ τα 5 έτη. Οι ασθενείς με δερματομυοσίτιδα και οι ασθενείς με δερματομυοσίτιδα και καρκίνο παρουσιάζουν διαφορετικά κλινικά χαρακτηριστικά (ευρήματα και εργαστηριακές παραμέτρους) ή τα ίδια σε διαφορετική συχνότητα. Οι προληπτικές εξετάσεις και η ανίχνευση συγκεκριμένων αυτοαντισωμάτων

καταδεικνύονται χρήσιμα εργαλεία για τη διάγνωση κακοήθειας σε ασθενείς που πάσχουν από δερματομυοσίτιδα, χωρίς να τίθενται σε περιττό κίνδυνο.

Λέξεις ευρετηρίου: Δερματομυοσίτιδα, Ηλικία, Κακοήθειες, Ογκολογία, Παχυσαρκία, Φύλο

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