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Malignancy Risk and Myositis-Specific Autoantibodies in Dermatomyositis: A Comprehensive Review

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Abstract

Background. Dermatomyositis is a rare idiopathic inflammatory myopathy characterized by symmetrical proximal muscle weakness, cutaneous manifestations and systemic complications. DM has a notable association with cancer. Meta-analyses indicating an OR of 4.66 and a standardized incidence ratio (SIR) of over 4.5 independently of gender for developing malignancies. Especially within the first year of DM diagnosis. Myositis-specific autoantibodies (MSAs) have a distinct correlation with clinical phenotypes and the risk of developing a malignancy.

Aim. The aim of this review is to synthesize current knowledge on the risk of malignancy in adult DM patients positive for MSAs (anti-TIF1 γ , anti-NXP2, anti-SAE, anti-Mi-2, anti-MDA5) and to determinate how the presence of those antibodies affects the course of cancer.

Material and methods. Comprehensive literature research was conducted across PubMed, Scopus, Web of Science, and Google Scholar databases focusing primary on publications from the past 20 years (2006-2026). Search terms included dermatomyositis, malignancy, cancer risk and MSAs. Eligibility was restricted to systematic reviews, retrospective studies, cohort studies, and case reports, while conference abstracts and studies specifically concerning juvenile dermatomyositis were excluded. Data relied strictly on the original statistical findings of the primary literature.

Results. Anti-TIF1 γ antibody presents the strongest correlation with malignancy. With an OR of 9.37 in one study. The predominant cancer types are breast, lung, ovarian and gastrointestinal cancer. These solid tumours present at an advanced stage. The risk is increased by the presence of anti-TIF1 α antibody, age over 60 and male sex. Patients with anti-NXP2 antibodies have a 2.5 to 3.68-fold increased risk of cancer. The tumours also present at an advanced stage. Male sex and age over 60 are also a risk factor. Anti-Mi-2 and anti-SAE antibodies are highly population-dependent. Anti-Mi-2 elevates cancer risk in European cohorts (OR 2.09-2.5). The anti-MDA5 antibody presents a weak association with malignancy.

Conclusions. MSAs provide prognostic value for stratifying malignancy risk and optimizing screening timelines in adult dermatomyositis. Seropositivity for anti-TIF1 γ and anti-NXP2 requires an immediate and comprehensive cancer screening within the first year of DM onset. Systematic malignancy surveillance should be standardized for all newly diagnosed DM patients to facilitate early cancer detection and maximize treatment efficacy.

Keywords. Dermatomyositis, cancer risk, Dermatomyositis autoantibodies, anti-TIF1 γ , anti-NXP2, anti-SAE, anti-Mi-2, anti-MDA5, malignancy and myositis-specific autoantibodies

Introduction

Dermatomyositis is a rare idiopathic inflammatory myopathy. Occurring most frequently in adults aged 50-60. Primarily characterized by progressive proximal muscle weakness of the upper and lower extremities and cutaneous manifestations such as Gottron papules, heliotrope rash and the V sign. It also includes systemic manifestations - dysphagia, interstitial lung disease (ILD) and arrhythmias. Those clinical manifestations combined significantly deteriorate the quality of life and the physical fitness of patients. (2, 44). Furthermore, dermatomyositis has been strongly linked with malignancy. In 2017 a meta-analysis was performed to estimate the risk of malignancy in dermatomyositis. The results showed an OR of 4.66 and an SIR of 5.29 for males and 4.56 for females. The authors also highlighted that the risk is the highest within the first year after DM diagnosis. (43).

Patients with dermatomyositis are often positive for myositis-specific antibodies (anti-Mi-2, anti-NXP2, anti-SAE, anti-TIF1, anti-MDA5, anti-SRP, antibodies against aminoacyl-tRNA synthetases). Those antibodies are linked to clinical phenotypes and may help to predict the disease course and establish the most effective type of treatment. In the recent years many studies regarding the connection between an elevated risk of malignancy and the co-occurrence of certain myositis-specific antibodies have been conducted.

The primary purpose of this review is to synthesize the current knowledge regarding the incidence of malignancy among dermatomyositis patients positive for one of the following antibodies - anti-TIF1, anti-NXP2, anti-SAE, anti-Mi-2 and anti-MDA5. Additionally, we aim to find out if certain antibodies showcase a stronger correlation with specific cancer types.

2. Research materials and method

A comprehensive literature search was conducted using electronic databases to identify studies investigating the association between dermatomyositis and malignancy risk, with a primary focus on the predictive role of myositis-specific autoantibodies. The databases included PubMed, Scopus, Web of Science and Google Scholar. The following keywords were used for the search - Dermatomyositis, cancer risk, Dermatomyositis autoantibodies, anti-TIF1 γ , anti-NXP2, anti-SAE, anti-Mi-2, anti-MDA5, malignancy and myositis-specific autoantibodies. Boolean operators (AND, OR) were used to refine the search results. The primary focus remained on publications from the past 20 years (2006-2026). Articles dating prior to this period were mainly used to showcase the progress made by medicine in this area. Eligibility was restricted to systematic reviews, retrospective studies, cohort studies, and case reports, while conference abstracts and studies specifically concerning juvenile dermatomyositis were excluded. To maintain the integrity of the reported evidence, this review relies on the original statistical findings of the included primary research; consequently, no independent data synthesis or meta-analysis was performed.

AI tools were used strictly for linguistic editing and grammatical refinement to ensure clarity and adherence to academic writing standards. All analytical processes, data interpretation, and conclusions were conducted exclusively by the human authors without AI intervention in the research findings

3. Research results

3.1. anti-TIF1 gamma

The Intermediary Factor-1 Gamma Autoantibody was discovered in 2006. It is associated with more severe skin lesions, higher risk of gastric symptoms and at the same time with a lesser risk of interstitial lung disease, Raynaud syndrome and joint pain. (2,8,10) It is estimated that 8% to 41% of adult patients with dermatomyositis have this antibody. (3) The first correlation between this antibody and the occurrence of malignancy in Dermatomyositis patients was already noticed in 2006. (1) Since then, many studies have been conducted to assess how strong is this

correlation, what types of cancer occur in those patients and how can we use this knowledge to protect newly diagnosed patients. Results vary from study to study, but one thing is sure - that the Intermediary Factor-1 Gamma Autoantibody is strongly connected to malignancy in DM patients. One study found that regardless of the ethnicity and geographic area the presence of anti-TIF1 γ antibodies causes an increased prevalence of cancer compared to the anti-TIF1 γ -negative DM with OR of 9.37 (4). Another study showcased the same results - with an incidence of 68% in the anti-TIF1 γ -positive patients versus 14% in the anti-TIF1 γ -negative patients. (5) Studies also found that there is a higher prevalence of solid cancers than haematological malignancies. This is consistent with the fact that solid cancers are more common in DM (7,12). However, the risk of haematological cancers is still elevated in DM patients compared to the general population risk (12). In a Greek cohort study all malignancies in the anti-TIF1 γ -positive cases were solid tumours (6). It is also worth noting that some types of cancer are more common in this group of patients. Based on numerous studies the most frequent cancers among anti-TIF1 γ -positive patients were - breast cancer, lung cancer, ovarian cancer, gastric cancer and colon cancer. (9, 13, 10, 3, 6, 5, 16). It is worth noticing that the incidence of specific cancer types varies based on the population, for example in the Chinese population nasopharyngeal, gastric and oesophageal malignancies were the most common (14). It is a well-known fact that the risk of malignancy in DM is highest in the first year after diagnosis and it's still elevated beyond the fifth year (17). One study found that when it comes to anti-TIF1 γ -positive cases the period between DM onset and cancer diagnosis is significantly shorter. The median time was 1.4 years for the anti-TIF1 γ -positive cases compared to 5 years for the anti-TIF1 γ -negative cases (16). Another study confirmed this finding with a mean interval of 2.2 months between DM diagnosis and cancer diagnosis within the anti-TIF1 γ -positive group compared to 20 months in the negative group. Furthermore, it showed that at the moment of diagnosis cancers were more advanced in anti-TIF1 γ -positive DM patients than in anti-TIF1 γ -negative patients (5).

Other factors may influence the risk of cancer. Older age increased the likelihood of malignancy - especially for patients over the age of 60 as one study found (19). The simultaneous presence of anti-TIF1 γ antibody and anti-TIF1 α antibody increases the risk of malignancy (18). Another antibody found to be associated with anti-TIF1 γ antibody is Anti-CCAR1 autoantibody. They are specific for anti-TIF1 γ dermatomyositis, and their presence diminishes the danger of cancer to a level equal to that of the general population (20). Further research based on two anti-TIF1 γ -positive DM cohorts revealed that approximately one-third of patients are anti-SP4 positive and one-third are anti-CCAR1 positive. Both autoantibodies' subgroups are negatively associated with cancer in dermatomyositis (21).

3.2. anti-NXP2

Anti-nuclear matrix protein 2, also called anti-MORC3 or anti-MJ, is detected in 2-25% of patients with dermatomyositis, depending on the source (2). This antibody is associated with more prevalent weakness in the distal arms, distal legs, and neck. Anti-NXP-2 positive patients are at a greater risk of experiencing dysphagia, calcinosis, myalgia, and subcutaneous oedema than those without this antibody (22). Studies demonstrate that this antibody is linked to an increased risk of malignancy. One study indicates that anti-NXP-2 positive patients have a 3.68 times increased risk of malignancy compared to the general population of the same age and sex (22). This finding is consistent with the research conducted by Fiorentino et al.: among 37 people with anti-NXP-2 antibodies, 9 had cancer (OR 2.5, p=0.04). Furthermore, data from a Japanese study where 3 out of 7 patients suffering from anti-NXP-2- positive DM were diagnosed with cancer strengthens this theory.

All the cancers were diagnosed at an advanced stage (23). Similarly to the anti-TIF1 γ -positive population, the frequency of cancer is more significant in patients over the age of 60 (19). Another factor increasing the frequency of malignancy within the anti-NXP-2 positive population is male sex (19, 23).

3.3 anti-SAE

Small Ubiquitin-Like Modifier Activating Enzyme Antibodies were discovered in 2007 (24). Their occurrence varies depending on ethnicity. In the Asian population the frequency is 1-3% and it is slightly more common in the European population 5-10% (25). Those antibodies are mostly associated with severe skin involvement, rash and

an amyopathic or mild muscle involvement. (26, 27, 28). The correlation between anti-SAE antibodies and malignancy varies depending on the study. A study from 2019 which included 42 anti-SAE positive patients found no association with cancer (29). Similarly, no malignancies were found in a Spanish cohort (30).

In contrast to that another research reported that the prevalence of malignancy was considerably higher in the anti-SAE-positive cases than in the anti-SAE-negative cases (3/6 vs 18/ 143, $p < 0.0369$). However, in this case the cohort was smaller and consisted only of 6 anti-SAE-positive patients (31). Nevertheless, another study on a larger cohort of 49 anti-SAE-positive patients revealed that the prevalence of cancer in this group was fivefold higher than that observed in the general population ($p < 0.001$). The incidence of malignancy was 16.3%. and it accounted for the majority of deaths among anti-SAE-positive patients (32). A similar incidence of cancer (15.4%) was reported in a multi cohort study in China with cancer being the preeminent cause of mortality (25). The most commonly observed malignancies were lung cancer, colorectal cancer, gastric cancer and ovarian cancer (25, 27, 28, 31, 32).

3.4 anti-Mi-2

Anti-Mi-2 antibodies target a nuclear DNA helicase that plays a role in transcription. While their prevalence among adult dermatomyositis patients ranges from 4% to 35% in literature, actual rates fluctuate depending on the patient's ethnicity, geographic location, and the specific testing method used (26). It is typically associated with a good response to steroid treatment, mild to moderate muscle involvement and typical cutaneous findings (33, 34). The correlation between anti-Mi-2 antibodies and malignancy alter depending on the study. Data from a large European cohort showed an increased risk of cancer (OR 2.5) among those patients (29). This finding aligns with a study among the French population, which reported an elevated risk of cancer among anti-Mi-2 positive DM patients with an SIR of 5.1 (35). This positive correlation is further supported by a recent study showing an association between the presence of anti-Mi-2 and an elevated risk of cancer (OR 2.09) (12).

Conversely, studies among Japanese, Brazilian, and Indian populations observed no correlation between the incidence of malignancy and the presence of anti-Mi-2 antibodies (34, 36, 37, 38).

3.5 anti-MDA5

Anti-MDA5 antibodies target the melanoma differentiation-associated protein which is an RNA-specific helicase involved in antiviral immune response. It is more common among clinically amyopathic dermatomyositis. The most common clinical features are ILD, rapidly progressive ILD, painful palmar papules, ulcerations and panniculitis (26, 39, 40).

Results from a recent retrospective cohort study found no positive association between cancer and the presence of the anti-MDA5 antibody (15). The same conclusions were made in a Japanese study (41). Another Japanese study highlighted the weak correlation between anti-MDA5 antibody and malignancy (34).

Nevertheless, some cases of patients diagnosed with anti-MDA5 positive dermatomyositis and cancer (thyroid cancer and metastatic small cell carcinoma) have been reported (42). Therefore, physician treating this group of patients should remain cautious of the potential risks.

4. Conclusions

Numerous research demonstrates the importance of using myositis-specific autoantibodies to stratify the risk of malignancy and establish screening timelines among dermatomyositis patients. Specifically, patients testing positive for anti-TIF1 γ and anti-NXP2 antibodies belong to a high-risk profile for rapidly progressive and advanced-stage solid tumours. Especially within the first year of DM diagnosis. Hence the need for prompt screening. The risk of malignancy is further amplified by advanced age (>60), male sex and specific antibodies pairing, such as the coexistence of anti-TIF1 γ antibody and anti-TIF1 α antibody. Nonetheless, the presence of anti-CCAR1 or anti-SP4 antibodies along with anti-TIF1 γ appear to have a protective effect and diminish the risk of cancer to that of the general population.

Data regarding the risk of malignancy among anti-SAE and anti-Mi-2 positive patients differ significantly depending on the population. There is a stronger correlation between anti-Mi-2 (+) patients and cancer within the European population. No such conclusions can be made about the anti-SAE positive DM patients. The MSAs with the weakest connection to cancer is the anti-MDA5 antibody.

All patients diagnosed with dermatomyositis should be screened for the presence of MSAs (anti-TIF1 γ , anti-NXP2, anti-SAE, anti-Mi-2 and anti-MDA5) and be screened for potential malignancies. Early detection of cancer would increase the chance for an effective treatment and improve long-term patient quality of life.

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