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Risk of cancers in polymyositis and dermatomyositis

ABSTRACT

Idiopathic inflammatory myopathy (IIM) is a rare autoimmune disease that women are more often diagnosed. The most common IIM are polymyositis (PM) and dermatomyositis (DM). More often than in other rheumatic diseases, various neoplasms develop in their course (CAM, cancer-associated myositis). The most common cancers included ovarian and reproductive organs cancer, breast, lung, gastrointestinal and hematopoietic cancer (mainly non-Hodgkin's lymphomas), melanoma, and nasopharyngeal cancer (the last one is widespread in Southeast Asia). It is worth emphasizing that a neoplastic disease may develop in IIM, and IIM may be a factor influencing the initiation of carcinogenic processes. The presented manuscript discusses the symptoms occurring in their course CAM and the risk factors for cancer development in detail. The importance of clinical observation of patients with PM/DM and the necessity of quick oncological diagnostics in the case of suspicion of such a process was discussed and emphasized (including the importance of screening tests).

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KEY WORDS: polymyositis; dermatomyositis; cancer risk; diagnosis

INTRODUCTION

Many systemic connective tissue diseases are characterised by risk of cancer development, but it is particularly high in the course of idiopathic inflammatory myopathies. They are classified as chronic multisystem autoimmune diseases with the presence of myositis which may be accompanied by dermal symptoms and/or interstitial lung disease (ILD) [1]. They involve primarily skeletal muscles, and their presence in adults is closely linked to risk of development of a neoplastic disease [2, 3]. They are among the few rheumatic diseases which, when they develop in adulthood, are linked to a significantly increased risk of carcinogenesis [4]. For this reason, for the purposes of clinical trials, as well as diagnostic needs used in everyday clinical practice, the definition of cancer-associated myositis (CAM) was adopted, which takes into account the development of a malignancy within 3 years of onset of an IIM [5]. Another definition proposed by András et al. suggests that any cancer diagnosed two years before or three years after diagnosis of an IIM can be considered a CAM [6]. Regardless of definition, it is believed that development of cancer in the course of an IIM is rarer after the first 3 years following diagnosis of myositis [7]. It is worth noting, however, that the longer the period of observation of a patient with an IIM, the higher the probability of carcinogenesis unrelated to myositis and characteristic of the given general population [8, 9]. This fact leads to some difficulty in determining the exact time frame for a cancer linked to the presence of myopathy versus one typical for the given age group. Hence, for Polish population, in addition to risk factors related to cancer development in the course of an IIM, it is necessary to take into account the cancers most commonly diagnosed in our country in men (prostate cancer) and women (breast cancer) [9].

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When discussing the course of IIMs, it is worth noting that the risk of aggressiveness of a neoplastic process depends on the presence or lack of risk factors related to activation/inhibition of carcinogenic processes (discussed below). If they are present, the risk of rapid cancer development is high and becomes the primary cause of death in adults with IIMs [10]. Results of clinical trials and population-based studies indicate that dermatomyositis (DM) is characterised by higher risk of cancer development compared to polymyositis (PM) [7]. This manuscript discusses the aetiopathogenesis, symptomatology and risk factors which can suggest the presence of cancers in the course of IIMs, both for Polish population and for population in other countries. Available diagnostic and therapeutic methods related to CAM are also explored.

CHARACTERISTIC FEATURES OF INFLAMMATORY MYOPATHIES

The most common inflammatory myopathies are polymyositis, which involves only striated muscles, and dermatomyositis, whose course includes, in addition to muscular symptoms, also dermal symptoms. Other, less frequent forms are inclusion-body myositis (IBM), antisynthetase syndrome, necrotizing autoimmune myositis (NAM) and, in children, juvenile dermatomyositis (JDM) [2, 11].

The incidence rate of inflammatory myopathies is 2.7/million/year; DM tends to occur more frequently than PM. Women develop IIMs three times more frequently than men. The average age of patients is 50–60 [3, 12]. The is also a correlation between the ratio of incidence of PM/DM and latitude — the closer to the equator, the more is DM prevalent over PM, which stems from increased exposure to ultraviolet radiation [13].

The symptoms of IIMs, despite some significant differences, are similar. They include: general fatigue, fever, weight loss, muscle pain and reduced muscle strength felt by the patient and confirmed by a physical examination. Symptoms typically occur in proximal muscles, but can also affect respiratory muscles or pharyngeal muscles [14]. Patients report that they tire quickly and have troubles performing basic tasks; in severe cases, due to advancement and rapid progression of the disease, patients may become unable to move on their own and experience increased dyspnoea and dysphagia [15]. Patients with DM additionally exhibit dermal symptoms. These usually take the form of Gottron's papules (small red or purple bumps on the dorsal surface of metacarpophalangeal joints and proximal and distal interphalangeal joints as well as wrists, elbows and knees), red and purple stains on the skin of the neck, chest and shoulders (the so-called „shawl sign") and discolouration of eyelids and the skin around the eyes (heliotropic erythema of the eyelids) [14].

Diagnosis of inflammatory myopathies, according to current diagnostic criteria, is based on the presence of clinical symptoms, increased levels of muscle enzymes (creatine kinase, lactate dehydrogenase, aldolase, alanine and aspartate aminotransferases), abnormalities in EMG record, presence of typical skin lesions (for DM) and histopathological examination of a muscle specimen [16]. Of importance is also the presence of characteristic anti-Jo1 antibodies, which are specific to inflammatory myopathies [3, 12, 17]. With respect to MAAs and MSAs, while they make it possible to identify individual groups of patients with IIMs, they occur only in approx. 40% of patients with myositis [18, 19]. For this reason, although they facilitate diagnosis, they are not necessary for it.

RISK OF CANCERS IN THE COURSE OF INFLAMMATORY MYOPATHIES

Both DM and PM entail an increased risk of malignancies, but DM is significantly more often associated with every type of cancer than PM, which is indicated by a large-scale study of Hungarian population (20.55% of patients with DM *vs.* 4.28% of patients with PM, n = 450) [6]. In turn, a study of Chinese population shows that cancers in the course of IIMs most frequently develop in the lungs, while adenocarcinoma is the most frequently diagnosed type of cancer in terms of histopathology [20].

It is worth noting that while an oncological disease may be diagnosed simultaneously with an idiopathic inflammatory myopathy, it is usually diagnosed either earlier or later. Over 80% of cancers are diagnosed within a year of occurrence of muscular symptoms, which means that this period should be deemed a period of increased risk of carcinogenesis, during which screening for cancer should be planned [6]. In these cases, secondary PM or DM is treated as a paraneoplastic syndrome which recedes once the neoplasm is removed completely [3].

Differentiation between a primary inflammatory disease and a paraneoplastic syndrome has significant clinical implications. For primary PM/DM, the activity of creatine kinase and lactate dehydrogenase is nearly always increased, and symptoms frequently appear before the age of 50. Skin lesions are typical for primary myopathies, and may or may not be accompanied by general symptoms. Response to standard treatment is good and usually leads to remission of the disease [21].

On the other hand, in the course of a paraneoplastic syndrome (secondary PM/DM), muscle enzyme levels are frequently elevated, but can also be normal, and symptoms typically appear later — between the age of 50 and 60. Skin lesions often take the form of necrosis or erythema which does not respond to standard treatment of myopathy. Skin lesions are nearly always accompanied by general symptoms. Response to standard IIM therapy is poor, but there is sudden and rapid improvement once the causative factor is removed, e.g. following a surgical tumour resection [3, 13].

AETIOPATHOGENESIS OF CAM

The pathogenesis of cancers in the course of IIMs is not fully understood. Furthermore, depending on the type of tumour, carcinogenesis proceeds differently and is related to different predictive factors. However, disorders stemming from abnormal cell-mediated and humoral immunity are the most important mechanism. They are likely related to secretory activity of neoplastic cells, including overproduction of a number of antibodies. Some of them (e.g. anti-Jo1) are associated with a low risk of carcinogenesis, while others with higher. It has been proven that cancer is more frequently diagnosed in case of detection of antibodies against melanoma differentiation-associated protein 5 (anti-MDA5) and antibodies against nuclear matrix protein 2 (anti-NXP2) as well as antibodies against transcriptional intermediary factor 1-gamma (anti-TIF1-γ) [13, 22]. During carcinogenesis, autoantigens specific to myositis — histidyl-tRNA synthetases (especially HRS/Jo1) — are expressed in muscular cells which undergo regeneration, but also in lung cancer cells, breast cancer cells and hepatocellular carcinoma cells, which suggests possible mutual cross-reactivity [13]. In addition, the overproduction by cancer cells of various growth factors, such as the vascular endothelial growth factor (VEGF) or the epidermal growth factor (EGF), as well as various hormones and pro-inflammatory cytokines (e.g. interleukin 6) may stimulate carcinogenesis [4]. It is worth noting that antinuclear antibodies are also more frequently present in cancer patients due to abnormal stimulation of the immune system [4, 12, 13, 22].

RISK FACTORS FOR CANCER DEVELOPMENT IN THE COURSE OF INFLAMMATORY MYOPATHIES

The pathogenesis of development of malignancies in PM/DM is not well understood, but it is believed that altered cell-mediated and humoral immunity is the main causative factor [13]. Risk factors for CAM development were considered in this manuscript on the basis of available clinical trials, epidemiological surveys, observational studies and case studies (Fig. 1).

EPIDEMIOLOGICAL FACTORS

Analyses of available studies indicate that age and sex are important in determination of risk [13]. It was found that male sex

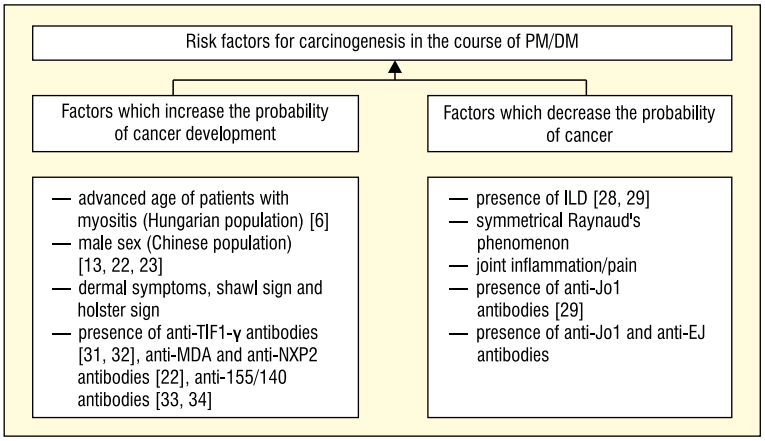

Figure 1. Risk factors for carcinogenesis in the course of polymyositis and dermatomyositis

Table 1. Frequency of occurrence of cancers in Poland and in Europe

Frequency of occurrence of cancers in Polish population and in European population expressed as percentage of new cases in 2020*			
	Cancer type	**Percentage of new cases****	
	Region	Europe	Poland
Sex			
Male (all ages)	Prostate cancer	20.2	19.3
	Lung cancer	13.5	17.5
	Colorectal cancer	12	11.5
	Bladder cancer	6.7	6.6
	Kidney cancer	3.7	Stomach cancer 4.2
			Other, such as kidney cancer, laryngeal cancer, pancreatic cancer, melanoma and brain tumour
Female (all ages)	Breast cancer	25.8	22.8
	Colorectal cancer	11.6	9.0 (including colon cancer 6.3% and rectal cancer 2.7%)
	Lung cancer	7.9	9.5%
	Cancer of the uterine body	6.3	Endometrial cancer 7.7%
	Melanoma	3.6	Ovarian cancer 4.6%
			Other, such as thyroid cancer, cervical cancer, kidney cancer, melanoma and stomach cancer

*based on the data from registry of the International Agency for Research on Cancer [8] and from the Polish National Cancer Registry [9]
**% of all cancer cases

and advanced age at the onset of PM/DM are significantly correlated with increased risk of cancer [22, 23].

DEMOGRAPHIC FACTORS

Cancer development in the course of PM/DM depends not only on the age or sex of the patient, but also on the region where the patient lives. For European population, the most commonly diagnosed types of cancer are breast cancer, lung cancer and colorectal cancer, while for Asian population (residents of southern China and Southeastern Asia), the most typical type of cancer is nasopharyngeal carcinoma. In this last case, carcinogenesis is related primarily to high exposure to Epstein-Barr virus infection in the region [4].

In Europe (primarily in northern and western regions), the most common type of cancer in 2020 was breast cancer (12.1% of all newly diagnosed cases of cancer), followed by colorectal cancer (11.8%), lung cancer (10.9%), prostate cancer (10.6%) and bladder cancer (4.6%) [8]. The frequency of occurrence of cancers depending on sex is shown in Table 1. The most frequent cause of death in the course of cancer in Europe, in turn, is lung cancer (20.5% of deaths), followed by colorectal cancer (8.1%) and breast cancer (7.1%) [24]. Data from the Polish National Cancer Registry showed that the most common oncological disease in women was breast cancer (22.8%), followed by lung cancer (9.5%) and colorectal cancer (9.0%), while in men it was prostate cancer (19.3%), followed by lung cancer (17.5%) and colorectal cancer (11.5%). An aggregated analysis revealed that lung cancer is the main cause of death due to cancer both in women and in men [9].

Incidence of cancers in the course of myopathies depends on sex, age and presence of risk factors for cancer development. According to meta-analysis performed by Qiang et al., the standardized incidence ratio for cancers in the course of inflammation was 4.66 for DM and 1.75 for PM [5]. It is worth noting that any cancer, regardless of type, can cause a paraneoplastic syndrome, including onset of PM or DM [3, 13, 25]. At the same time, it is also worth noting that the 5-year survival rate of CAM patients is statistically significantly lower (15.4% for PM and 27.5% for DM) than survival rate of cancer-free PM/DM patients (100%) [6].

As the frequency of occurrence of individual cancer types in European and Asian

populations corresponds to the frequency of their occurrence in the course of PM/DM, it is worth paying particular attention to clinical symptoms typical for a given cancer type in the course of these myopathies.

CLINICAL FACTORS

Studies of the last decade show that the risk of onset of cancer is much higher in DM patients with comorbid skin ulceration. Another important risk factor for cancer development is severe course of the disease, with pharyngeal muscle involvement and dysphagia. On the other hand, patients with Raynaud's phenomenon and patients with interstitial lung disease detected at an early stage and lesions in CT show a lower risk of onset of cancer [22]. Additional factors which can increase the frequency of occurrence of cancers include advanced age of patients with myositis (Hungarian population) [6], male sex (Chinese population) [26], more frequent dermal symptoms (e.g. Gottron's papules or V-sign) [6] and asymmetrical Raynaud's phenomenon, while ILD [28, 29], symmetrical Raynaud's phenomenon [6, 29], joint inflammation/pain and the presence of anti-Jo1 antibodies [29] develop less frequently.

BIOCHEMICAL AND SEROLOGICAL FACTORS

Factors which increase this risk of cancer development are high levels of inflammatory markers (ESR, CRP) as well as high level of creatine kinase [22]. It is believed that the presence of antibodies against extractable nuclear antigens (ENAs), which include ANAs, is a protective factor and entails reduced risk of cancer development [17]. The large-scale meta-analysis performed by Oldroyd et al. shows that the presence of both MSAs and ANAs has no significant impact on development of IIM-associated cancer. Moreover, the authors of this meta-analysis clearly stressed that antibodies, such as anti-Jo1 or anti-EJ, are associated with significantly lower risk of cancer development [30].

The recently discovered antibodies against transcriptional intermediary factor 1-gamma (anti-TIF1-γ) are related to cancer development, and the correlation appears strong [31, 32]. Other DM-specific antibodies which may be significant for prediction of risk of cancer development include anti-MDA5 antibodies and anti-NXP2 antibodies [22]. Anti-NXP2 antibodies and anti-TIF1-γ antibodies frequently occur in DM-associated cancers. For this reason, some authors suggest that the lack of these antibodies reduces the risk of onset of cancers associated with idiopathic inflammatory myopathies [25].

Important role is also played by antibodies against 155-kDa protein, which occur in the course of DM with comorbid cancer in patients in whom no other MSAs/MAAs were detected. Anti-155 antibodies frequently occur together with another antibody against 140-kDa protein, forming a characteristic doublet (anti-155/140 antibody) [33, 34]. For these antibodies, a certain pattern was identified. It transpires that their presence is detected in patients with no diagnosed interstitial lung disease (ILD), while patients with anti-Jo1 antibodies develop ILD more frequently and cancer much less frequently [23]. This is confirmed by other studies which demonstrate that antibodies against 155/140 and the presence of ILD are mutually exclusive [33, 34]. This fact can be taken into account when planning diagnosis of IIM and screening for cancer. Moreover, it is believed that anti-155/140 antibodies (much like anti-Mi2 antibodies) occur almost exclusively in the course of DM [23].

Clinical experience shows that if an adult with an IIM has no typical antibodies (MSAs/MAAs), particular caution is required in screening for comorbid cancers [23]. It therefore seems correct to say that routine antibody testing is not a reliable method for detecting CAM.

DIAGNOSIS OF CAM

Determining reliable methods for predicting the risk of cancer in patients with inflammatory myopathies would greatly facilitate everyday clinical practice in a multitude of ways. Due to increased risk of cancer during the first few years following diagnosis of an IIM and lack of a specific diagnostic test which would indicate that risk with a high probability, oncological vigilance is necessary for all patients with IIMs. It is worth noting that the presence of ANAs should not be overestimated in the assessment of risk of cancer, and diagnosis should make use of other tumour markers typically determined in oncological diagnosis, such as: CEA, Ca 19-9, Ca 123.

Conventional tests used to diagnose cancers include: full physical examination, laboratory tests (complete blood count and comprehensive metabolic panel), faecal occult

blood test, chest and abdominal CT, tumour markers (carbohydrate antigen 125 [CA 125], cancer antigen 19-9 [CA 19-9], carcinoembryonic antigen [CEA], prostate-specific antigen [PSA]), gynaecological examination, ovarian ultrasound and mammography [35, 36]. It transpires that advanced tests for assessment of oncological risk, such as PET/CT with fluorodeoxyglucose (18 F-FDG), make it possible to detect cancer to a degree comparable to standard tests [35]. Nevertheless, it is worth noting that PET performed annually for 3 to 5 years in patients with suspected cancer may be the most cost-effective method for screening, given its effectiveness in revealing cancers.

Extended diagnosis for cancer is indicated especially in case of detection of typical antibodies linked to decreased risk of cancer development, such as anti-155/140, anti-TIF1 or anti-MJ/NXP2, which accompany cancer in the course of DM in adults more often than other antibodies [37].

Some authors emphasise the benefits of performing „blind" screening for proliferative diseases in patients with IIMs, even if there are no clinical symptoms. Examples of such an approach include studies by Leatham et al. and Sparsa et al., which made it possible to diagnose breast cancer, squamous cell carcinoma of the ovary, lung and the oesophagus, multiple myeloma and lymphoma in patients with no clinical symptoms [38, 39]. For both studies, the highest number of cancer cases was detected via CT of the chest, abdomen and pelvis (38% of analysed patients). However, in case of the study by Sparsa et al., cancers were detected more frequently in patients with symptoms suggesting a carcinogenic process than in patients with no such symptoms [39].

TREATMENT OF PRIMARY IIM AND PARANEOPLASTIC SYNDROME

If both DM and cancer are diagnosed, the patient should be treated simultaneously for inflammatory myopathy, as per current guidelines, and for cancer, like a patient without a myopathy. Complete surgical tumour resection may cause myopathy and skin lesions to recede. Treating DM alone and commencing oncological treatment only once skin lesions and muscular disorders recede is a mistake.

There is limited evidence for specific treatment strategies in the course of IIMs, which applies also to CAM [40]. Treatment of PM/DM involves mainly administration of glucocorticoids and drugs which modify the course of the disease (MTX, azathioprine, cyclosporine, cyclophosphamide and mycophenolate mofetil) and biological therapy (rituximab off label) [41]. Combination therapy involving administration of steroids together with immunosuppressive drugs is frequently used [3, 12, 13]. If both PM/DM and cancer are diagnosed, the patient should be treated simultaneously for IIM, as per current guidelines, and for cancer, like a patient without a myopathy. Due to increased risk of carcinogenesis, it is necessary to perform comprehensive oncological diagnosis before making use of immunosuppressive therapy, and employ adequate chemotherapy or surgical treatment if cancer is diagnosed.

CONCLUSIONS

The fact that idiopathic inflammatory myopathies are accompanied by cancers is indisputable and confirmed by multiple studies. For this reason, diagnosis should always take into account risk factors for cancer development, and in justified cases should be extended to include oncological examinations. Consequently, the importance of comprehensive diagnostic tests, be it biochemical tests, serological tests, imaging tests, determination of tumour markers or additional imaging tests, is emphasised. Atypical skin lesions and poor response to treatment in the course of an inflammatory myopathy should always lead one to consider a neoplastic syndrome. Data published so far emphasises the importance of commonly available biochemical and imaging tests, which for most patients are sufficient to ensure accurate diagnosis. Symptoms which suggest the existence of cancer include: intensified general symptoms (fever, weight loss), skin lesions with atypical locations, no response following inclusion of standard treatment for inflammatory myopathies (especially following administration of glucocorticoids). Factors predisposing to development of a carcinogenic process include primarily age over 50, male sex, skin ulceration in the course of DM, high levels of inflammatory markers and asymmetrical Raynaud's phenomenon. For this reason, early diagnosis remains vital, especially for patients with no typical biochemical and serological markers of myopathies and with pro-carcinogenic factors, as survivability increases with early detection of cancer and commencement of oncological treatment.

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