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Idiopathic Inflammatory Myopathy-Associated Cancer: A Review of Risk Factors and Screening Recommendations

Eugene Krustev, MD

Abstract

Idiopathic inflammatory myopathies (IIMs) are a group of rare autoimmune diseases that are characterized by autoimmune myositis. However, systemic extramuscular manifestations are frequently observed. IIMs have been associated with cancer, and given the increased frequency of co-incident cancers in IIM, malignancy screening in newly diagnosed IIM patients is an important consideration. That being said, cancer risk varies across IIM subtypes, antibody specificities, and with clinicodemographic factors. As such, cancer screening should be tailored using a risk stratification approach. This review discusses the evidence regarding cancer risk in IIM, as well as recently-published guidelines for cancer screening in IIM.

Introduction

Idiopathic inflammatory myopathies (IIM) represent a heterogeneous group of autoimmune diseases characterized by the presence of autoimmune myositis. They can be divided into six subtypes: dermatomyositis (DM), polymyositis (PM), antisynthetase syndrome (ASyS), immune-mediated necrotizing myopathy (IMNM), overlap myositis syndromes (OM), and inclusion body myositis (IBM).[1] It is well recognized that IIM patients have an increased risk of concurrent malignancies, many of which are diagnosed in the three years before or after the onset of IIM symptoms.[2] The first documented description of IIM-associated cancer was published by Dr. Stertz in 1916.[3] Since then, a significant body of research has been dedicated to this association. Several factors influence cancer risk in IIM, including IIM disease subtype, antibody specificity, clinical manifestations, and demographic factors.

Given the numerous factors that influence cancer risk in IIM, risk assessment is based on expert opinion.[4] At present, we do not have the tools to assign highly specific risk scores to patients. Based on the presence of certain risk factors, patients can be stratified into three groups: those with the highest risk of malignancy

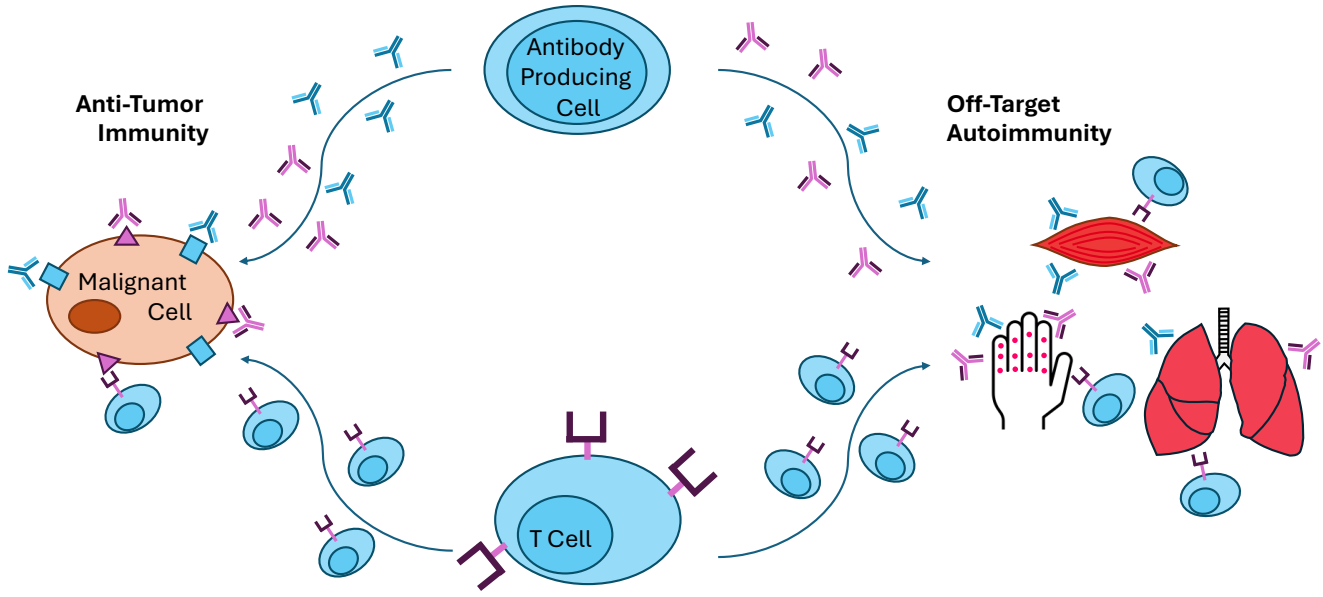

Figure 1. Anti-tumour and off-target immune responses in idiopathic inflammatory myopathy; *courtesy of Eugene Krustev, MD*

It has been postulated that in certain IIM subtypes, the initial immunologic trigger starts from an endogenous immune response directed toward cancer antigens. These antigens, which can be expressed either in a mutated form or over-expressed by malignant cells, induce an immune response. This immune response can then spread to off-target organs and result in the development of autoimmune myositis or other organ manifestations. The targeting of healthy cells can occur either from expression of the target antigen or other antigens with shared epitopes.

(high risk), those with a moderate but still notable risk (intermediate risk), and those with the lowest likelihood of malignancy (low risk).[4] Additionally, the types of cancers associated with IIM vary significantly based on factors such as sex, age, ethnicity, and geographic location. Therefore, when discussing malignancies linked to IIM, we will consider the full spectrum of potential cancer types, including both solid organ and hematologic cancers, as well as all possible cancer stages. These variables influence cancer risk in IIM, allowing for both risk stratification and a personalized approach to cancer screening in individuals with IIM.

Pathobiology of Idiopathic Inflammatory Myopathy-Associated Cancer

The frequent co-incidence of cancer within three years before or after IIM onset suggests a paraneoplastic phenomenon. Recent evidence suggests that in some patients IIM develops as a secondary effect of an endogenous anti-tumour immune response, in which off-target autoimmunity is directed toward muscles and other organs[5] **(Figure 1)**. In patients with IIM-associated cancer who test positive for anti-transcription intermediary factor 1-γ (anti-TIF1-γ), their tumours often exhibit upregulated expression of the TIF1-γ antigen and may harbour a mutated form of TIF1-γ.[6] This provides preliminary evidence that the antibodies found in patients with IIM-associated cancer may initially arise in response to mutated neoantigens or upregulated tumour antigens. It is likely that the development of IIM then requires a 'second hit', which then results in the development of IIM. This 'second hit' could be an underlying genetic defect that impairs immune system checkpoints or an environmental trigger that reactivates an aberrant immune response. In some patients, this anti-tumour response is effective in eliminating malignant cells, resulting in the presentation of IIM without cancer. On the other hand, in others, the anti-tumour response may fail to clear the cancer, leading to the co-occurrence of both cancer and IIM. This hypothesis helps explain why cancer is frequently associated with IIM, as well as why some patients present without an identifiable malignancy.[7] Future research is needed to help us better

understand how anti-tumour responses result in paraneoplastic autoimmune phenomena, including IIM.

Cancer Risk by Idiopathic Inflammatory Myopathy Subtype and Antibody Specificity

Dermatomyositis

DM is characterized by autoimmune myositis accompanied by characteristic skin rashes and is associated with several antibodies, including anti-Mi-2, anti-nuclear matrix protein 2 (anti-NXP2), anti-TIF1-ɣ, anti-melanoma differentiation-associated protein 5 (anti-MDA5), and anti-small ubiquitin-like modifier activating enzyme (anti-SAE). Among IIMs, DM confers the highest malignancy risk. A meta-analysis, which included 69 studies with 19,135 patients, demonstrated that DM patients had a significantly elevated cancer risk compared to those with non-DM IIM subtypes (relative risk [RR] 2.21; 95% confidence interval [CI] 1.78, 2.77).[2] The DM-associated antibody anti-TIF1-γ is associated with the greatest malignancy risk in IIM and is present in almost half of IIM-associated cancers.[8-10] While earlier studies suggested a strong association between anti-NXP2 and malignancy,[11] more recent evidence suggests that this association is weaker than previously thought.[2,12] The association between anti-Mi-2 and anti-SAE antibodies and malignancy is mixed, though at least one study has shown an association.[8] In contrast, anti-MDA5 does not appear to confer an increased risk of malignancy compared to other IIM subtypes[13] or the general population.[8] As such, DM patients, especially those who are anti-TIF1-γ positive, require the most rigorous screening for co-incident malignancies.

The most common cancers that are found in DM patients vary based on age, sex, ethnicity, and country of residence. In an American cohort, breast and ovarian cancers were the most commonly observed malignancies among DM patients, specifically in those who tested positive for anti-TIF1-γ antibodies.[8] A meta-analysis of 14 studies conducted across Asian countries identified nasopharyngeal and lung cancers as the most common malignancies in this population.[14] In a cohort of patients from Europe, ovarian, lung, pancreatic, stomach, and colorectal cancers, as well as lymphomas, were the most commonly seen malignancies in DM patients.[15] It is important to note, however, that while these malignancies are frequently reported in specific cohorts, many other cancer-types have been described in DM patients.

Clinically Amyopathic Dermatomyositis

Some DM patients can present with active skin disease but little to no muscle disease, a subtype referred to as clinically amyopathic dermatomyositis (CADM). A meta-analysis reported that patients with CADM had a decreased risk of malignancy compared to patients across other IIM subtypes (RR 0.44; 95% CI 0.20, 0.97).[2] However, previous studies have shown a cancer risk comparable to that of DM.[16] Given the rarity of CADM and variability in its definition across studies, future research is needed to further clarify the actual cancer risk for those with CADM.

Antisynthetase Syndrome

ASyS is characterized by a constellation of potential manifestations including autoimmune myositis, interstitial lung disease (ILD), inflammatory arthritis, hyperkeratotic skin changes and rashes, fever, and Raynaud's phenomenon. That being said, not all patients exhibit the full complement of manifestations, and partial presentations are common. The defining autoantibodies in ASyS are directed against various tRNA synthetases. Most studies evaluating cancer risk in ASyS have involved smaller cohorts, which limits comparisons to the general population. One study reported that cancer risk in ASyS was comparable to that of the general population,[8] while a meta-analysis reported a trend toward reduced malignancy risk compared to other IIM subtypes (RR 0.28; 95% CI 0.00, 6554.79).[2] Furthermore, several clinical signs that are associated with ASyS confer a reduced cancer risk, which will be discussed below. Collectively, these results suggest that ASyS is generally not associated with cancer.[2]

Immune-mediated Necrotizing Myopathy

IMNM is characterized by significant muscle fiber necrosis observed on biopsy, along with significant elevations in muscle enzymes and muscle weakness.[17] The autoantibodies most frequently associated with IMNM include anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) and anti-signal recognition particle (anti-SRP). Studies looking at cancer risk associated with IMNM, especially anti-HMGCR-positive disease, have produced mixed results. While some cohorts have shown elevated cancer rates,[18] others have reported malignancy rates

	Low Risk Features	Intermediate Risk Features	High Risk Features
Diagnosis	• ASyS • CTD-associated IIM • IBM* • Juvenile-onset IIM*	• CADM • PM • IMNM	• DM
Antibody Specificity	• Anti-SRP antibodies • ASyS-associated antibodies • Myositis associated antibodies	• Anti-SAE1 antibodies • Anti-HMGCR antibodies • Anti-Mi-2 antibodies • Anti-MDA5 antibodies	• Anti-TIF1-ɣ • Anti-NXP2
Clinicodemographic Factors	• Raynaud's phenomenon • Inflammatory Arthritis • ILD	• Male sex	• Age >40-45 years** • Persistent disease activity despite treatment • Dysphagia • Cutaneous necrosis

Figure 2. Idiopathic inflammatory myopathy-associated cancer risk factors; *courtesy of Eugene Krustev, MD*

Abbreviations: anti-HMGCR: anti-3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; **anti-MDA5:** anti-melanoma differentiation-associated protein 5; **anti-NXP2:** anti-nuclear matrix protein 2; **anti-SAE:** anti-small ubiquitin-like modifier 1-activating enzyme subunit 1; **anti-SRP:** anti-signal recognition particle; **anti-TIF1-ɣ:** anti-transcriptional intermediary factor 1-gamma; **ASyS:** antisynthetase syndrome; **CADM:** clinically amyopathic dermatomyositis; **CK:** creatine kinase; **CTD:** connective tissue disease; **DM:** dermatomyositis; **IBM:** inclusion body myositis; **ILD:** interstitial lung disease; **IMNM:** immune-mediated necrotizing myopathy; **LDH:** lactate dehydrogenase; **PM:** polymyositis.

Cancer risk stratification in IMM can be guided by a combination of clinical subtype, the antibodies that are present, and clinicodemographic factors. All other risk factors are included in the IMACS cancer risk stratification guidelines.

* Both IBM and juvenile-onset-DM were excluded from the IMACS cancer screening guidelines but are usually not associated with malignancy.

** The IMACS guidelines consider age > 40 years as a high-risk factor; however, previous studies have suggested > 45 years.

*** There is a potential inverse relationship with muscle enzyme levels and cancer risk, meaning that patients with higher muscle enzyme elevations have a lower risk of cancer; however, this was not included in the cancer screening guidelines and requires further research to characterize this association.

comparable to those in the general population.[19] When cancers are detected in IMNM patients, they tend to occur in seronegative patients, those positive for anti-HMGCR antibodies, and in patients over 50 years of age.[16] One complicating factor is that anti-HMGCR-positive patients tend to be older, male, and have other co-morbidities,[20,21] all of which may contribute to increased cancer risk in this group. Given the mixed evidence on cancer risk in IMNM, recently-published guidelines on IIM cancer screening classify IMNM as having an intermediate cancer risk. Within this classification, anti-HMGCR-positive disease is considered to carry a greater risk, whereas anti-SRP-positive disease is associated with a lower risk.[2]

Overlap Syndromes

Several autoantibodies are commonly detected in patients with OM, including anti-ribonucleoprotein (anti-RNP), anti-polymyositis/scleroderma (anti-PM/Scl), and anti-Ku.[22] Clinically, OM is characterized by presentations that frequently overlap several connective tissue diseases, including IIM, systemic lupus erythematosus, and systemic sclerosis. Estimating cancer risk in OM has been difficult due to the heterogeneity of the manifestations and the lack of standardized classification criteria that can be used to study these patients. While rare cancers have been described in patients with anti-Ku positive OM, there is generally no strong or consistent association with malignancy.[23-25 REF] In patients with anti-PM/Scl positive OM, one study showed that cancer risk was comparable to that of the general population[26 REF]; however, another study reported cases of cancer in patients with anti-PM/Scl OM.[27 REF] Additionally, anti-RNP positivity is associated with mixed connective tissue disease (MCTD), which is considered a subset of OM. The

literature on cancer-risk in MCTD is primarily focused on patients with predominant features of systemic sclerosis. However, a few studies have focused on cancer in MCTD patients with IIM. Overall, there does not appear to be a strong association between cancer and MCTD.[28 REF] Several other autoantibodies have been associated with cancer in other connective tissue diseases, including anti-RNA polymerase III,[29 REF] anti-RNPC3,[30 REF] and anti-CENP-F,[31 REF] but future studies are needed to clarify their expression and cancer risk associations in IIM. In summary, evidence suggests that patients with OM tend to have a lower malignancy risk compared to the other IIM subtypes.[4]

Inclusion Body Myositis

Although IBM is classified as an inflammatory myopathy due to the frequent presence of inflammatory infiltrates on muscle biopsy, it typically is non-responsive to immunomodulating therapies. Furthermore, IBM tends to affect the distal upper limbs and proximal lower limbs, which makes it unique when compared to the other IIM subtypes.[32] Similar to anti-HMGCR-positive IMNM, IBM tends to occur later in life and is more prevalent in male patients,[33] which confounds cancer risk assessment in this population. Although cancers can be detected in IBM patients, their incidence is not different from age-adjusted controls. This suggests that older age, rather than the IBM diagnosis itself, is more likely contributing to cancer occurrence in these patients.[34] As such, IBM is generally not associated with co-incident malignancies; however, newer evidence would suggest that there may be an association with T cell large granular lymphocytic leukemia, which is an area of ongoing research.[35]

Polymyositis

The term PM is slowly falling out of favour as newer subtypes such as IBM, ASyS, and IMNM have been described. Many patients previously described as PM are now understood to fit better within these classifications.[36] The data on cancer risk in PM is confounded by the fact that historically the populations used to study cancer risk in PM likely contained patients from these other IIM subtypes. A metanalysis comparing PM to other IIM subtypes reported a significantly decreased risk of malignancy in PM, with an RR of 0.49 (95% CI 0.37, 0.65).[2] However, previous research has suggested an increased risk of malignancy in PM patients compared to the general population.[37] Given the mixed evidence regarding cancer risk in PM, the newly published guidelines classify PM as having an intermediate risk for malignancy.[4] As we continue to improve our classification criteria for IIM, future studies will be needed to determine the actual cancer risk amongst patients who truly meet the criteria for the PM subtype.

Juvenile-onset Idiopathic Inflammatory Myopathy

Juvenile-onset IIM (previously referred to as juvenile dermatomyositis) is defined as IIM diagnosed in a patient <18 years of age. Numerous studies have looked at cancer risk in juvenile-onset IIM, with most concluding that paraneoplastic juvenile-onset IIM is rare.[38-40] A review of the literature did find several case reports of cancer-associated juvenile-onset IIM; however, the rarity of these cases suggests that additional cancer-focused investigations should only be pursued in patients with additional signs or symptoms suggestive of an underlying cancer.[41]

Clinicodemographic Factors That Affect Cancer Risk in IIM

Similar to the general population, advancing age confers a higher malignancy risk in IIM (weighted mean difference 11.19; 95% CI 9.29, 13.08).[2] A meta-analysis has reported that the mean age at IIM-onset among patients with cancer-associated myositis is 59 years, compared to 49 years in those without cancer.[2] Practically speaking, patients over the age of 45 tend to be at the highest risk for developing cancer.[42] Additionally, multiple studies have identified male sex as another factor associated with an increased risk of malignancy in IIM (weighted mean difference 1.53; 95% CI 1.34, 1.75).[2,43]

Several disease manifestations have been associated with an increased risk of malignancy in IIM, including dysphagia (relative risk 2.09; 95%CI 1.21, 3.60), cutaneous ulcerations (relative risk 2.73; 95%CI 1.33, 5.59), and severe treatment-resistant disease.[2,42] In contrast, both Raynaud's phenomenon (relative risk 0.61; 95%CI 0.39, 0.95) and ILD (relative risk 0.49; 95%CI 0.32, 0.76) have been associated with a decreased risk of malignancy, likely because these manifestations are frequently present in ASyS patients.[2] Interestingly, patients with more pronounced elevations in muscle enzymes (creatine kinase and lactate dehydrogenase) had a decreased risk of

malignancy compared to those with more subtle elevations or normal muscle enzymes.[2]

Cancer Screening Guidelines

The newly released cancer screening guidelines from the International Myositis Assessment and Clinical Studies Group (IMACS) represent a monumental achievement for guiding cancer screening in newly diagnosed IIM patients. The following section summarizes a risk-based approach to cancer screening in IIM, with reference to the guidelines; however, the complete guidelines can be accessed in the original publication.[4] It is important to note that these guidelines do not apply to patients with juvenile-onset IIM or IBM, as cancer risk in these groups is comparable to age-matched controls from the general population. Furthermore, the guidelines only apply to IIM patients who are either within three years of diagnosis or up to three years after diagnosis, as cancer incidence tends to decline to levels closer to the general population beyond this timeframe.

Numerous regional cancer screening protocols apply to the general population and are influenced by factors such as country of residence, demographic factors, and family history. Cancer screening protocols that apply to the general population are based on multiple factors and are constantly evolving. Regardless of an individual's IIM cancer risk, all patients should continue to undergo routine cancer screening as recommended for their geographic location, age, sex, and family history.[4]

In addition to following routine cancer screening protocols, all patients should undergo a 'basic screening panel'. This includes a comprehensive history and physical examination to assess for possible signs of malignancy, complete blood count, liver function tests, erythrocyte sedimentation rate, c-reactive protein, serum protein electrophoresis, urinalysis, and a plain chest x-ray.[4]

Patients with IIM can be stratified into cancer risk categories based on their clinical and serological features. These cancer risk categories are not defined by precise numerical risk estimates, but are instead based on expert opinion and literature review for classifying manifestations based on how commonly they occur in IIM patients with co-incident malignancies. The following high-risk features each individually carry an increased risk of malignancy and include a diagnosis of DM, positivity for anti-TIF1-γ antibodies, positivity for anti-NXP2 antibodies, disease onset after age 40 years, persistently high disease activity despite immunosuppressive therapy, moderate to severe dysphagia, and the presence of cutaneous necrosis. Intermediate-risk factors comprise CADM, PM, IMNM, male sex, as well as positivity for anti-SAE1, anti-HMGCR, anti-Mi-2, and anti-MDA5 antibodies. Low-risk features include ASyS, positivity for ASyS antibodies, CTD-associated IIM, Raynaud's phenomenon, inflammatory arthritis, and ILD. Although the association of individual features with cancer risk has been studied, it is difficult to assign a precise level of risk based on the presence of any single characteristic. Furthermore, determining how to assign cancer risk in patients with multiple features, often including a mix of high and low-risk features, is an area of future study. Nonetheless, according to IMACS guidelines, cancer screening can be guided by attributing risk based on the number of high or intermediate risk features present in a given patient.

As per the IMACS guidelines, patients with either one 'high risk' feature or two 'intermediate risk' features are classified as having a moderate cancer risk. These individuals should undergo an enhanced screening panel that includes a CT scan of the neck, thorax, abdomen, and pelvis; cervical cancer screening; mammography; prostate-specific antigen blood testing; CA-125 blood testing; pelvic or transvaginal ultrasonography for ovarian cancer; and fecal occult blood testing.[4] It should be noted that some of these tests may already be part of routine, general-population-directed cancer screening. Clinicians should consider the timing of previously completed tests to avoid unnecessary duplication.

Patients exhibiting two or more high-risk features are considered candidates for intensive cancer screening strategies and should undergo both basic and enhanced screening at diagnosis, as well as yearly follow-up cancer screening with the basic panel.[2]

According to the IMACS guidelines positron emission tomography–computed tomography (PET-CT) should be considered in patients with a 'high risk' profile when both basic and enhanced screening panels fail to uncover an underlying malignancy.[4] They also suggest that clinicians consider PET-CT as a single screening procedure in patients with anti-TIF1-γ-positive DM with disease onset at >40 years of age and with ≥1 additional 'high risk' clinical feature, as these patients are at the highest cancer risk.[4] In these

very high-risk patients, PET-CT may eliminate the need for further tests while providing comparable diagnostic utility.[4]

The guidelines also recognize that certain regions have a high prevalence of nasopharyngeal carcinoma, and that in these regions nasopharyngeal endoscopy may be warranted.[4] Similarly, upper and lower gastrointestinal endoscopy may be justified in regions where gastrointestinal cancers are common. Additionally, for patients with high-risk symptoms, such as constitutional symptoms, a history of smoking, or a family history of malignancy, the authors recommend cancer screening regardless of their IIM-related risk profile.[4]

Since the publication of the IMACS cancer screening guidelines, several studies have looked at their performance in real-world settings. One retrospective study applied the guidelines to a cohort of 370 DM patients, of whom 18 patients (4.8%) were diagnosed with cancer. The authors found that the screening guidelines would have identified cancer in all of their cancer cases.[44] However, 338 patients (91.3%) would have been classified as high or moderate risk as per the guidelines, and therefore would have undergone extensive screening. The authors concluded that strict adherence to the guidelines may result in unnecessary testing for some patients. Another study conducted in an Australian cohort observed that many patients would have been considered 'under-screened' prior to the publication of the guidelines. Implementation of the guidelines would significantly increase the number of screening tests ordered. The authors also concluded that applying the screening guidelines could potentially increase costs compared to previous practices and may not be available in under-resourced areas.[45] An evaluation of the IMACS guidelines in a Hong Kong cohort demonstrated that the criteria performed well for identifying malignancies in the high-risk group; however, few cancers were detected in the intermediate-risk group.[45] Overall, the results of these studies show that while the IMACS criteria offer high sensitivity for cancer detection, they may also lead to over testing due to the breadth of these recommendations. Future prospective studies are needed to assess if the new screening guidelines improve the stage of cancer diagnosis and patient survival.

One possible solution to help avoid over-screening while applying the IMACS guidelines in clinical practice is a step stepwise approach. Both the basic screening and enhanced screening protocols are amenable to stepwise implementation where basic screening would be performed first, followed by further imaging that might be directed by relevant findings on basic screening. If a malignancy is identified early in the process, then further testing could be halted or redirected toward a more targeted approach, thus reducing the number of lower-yield tests. The exact order of testing will need to be decided based on individual patient risk factors, and future research is needed to assess if this is a feasible approach. Additionally, one downfall of taking a step wise approach is the potential risk of diagnostic delay. Therefore, clinicians should only consider this strategy when scheduled short term follow-up is feasible.

Emerging Diagnostics and Future Directions

The use of myositis-specific autoantibodies, especially anti-TIF-1-ɣ, are an essential part of risk stratification in IIM. Interestingly, the novel autoantibodies anti-CCAR1[46] and anti-SP4[47] have been shown to decrease cancer risk in DM patients. One proposed explanation is that patients with multiple antibody positivity may mount a more effective anti-tumour immune response, leading to the successful elimination of malignant cells.[48] Currently, testing for these antibodies is not widely available in clinical practice. Further research is needed for us to better understand how these antibodies might be integrated into risk stratification models, such as those outlined in the IMACS guidelines.

Conclusions

IIM represents a heterogenous group of diseases, each with distinct cancer risk profiles. Within each IIM subtype, cancer risk also varies depending on specific antibodies and clinicodemographic factors. The recently-published IMACS guidelines provide an effective framework for cancer screening in IIM; however, future research is needed to clarify these strategies for greater efficiency and precision in cancer screening. Future studies should focus on optimizing cancer screening approaches in IIM, as well as evaluating the clinical utility of novel biomarkers to provide a precise cancer risk assessment.

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