Risk Factors and Cancer Screening in Myositis

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KEYWORDS

• Idiopathic inflammatory myopathies • Dermatomyositis • Cancer screening

KEY POINTS

- The idiopathic inflammatory myopathies, particularly dermatomyositis, are associated with an increased risk of cancer.
- Clinical risk factors for cancer-associated myositis include older age at disease onset, male gender, dysphagia, cutaneous necrosis, ulceration and vasculitis, rapid onset of myositis, and refractory myositis.
- Autoantibodies associated with greatest increase in the risk of cancer in myositis include anti–TIF1-gamma and antinuclear matrix protein-2.

INTRODUCTION

The idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous, systemic autoimmune rheumatic diseases that include adult polymyositis (PM), adult dermatomyositis (DM), necrotizing myopathy (NM), myositis associated with another autoimmune disease, cancer-associated myositis, juvenile myositis (mostly juvenile DM [JDM]), and inclusion body myositis (IBM). The IIMs are multisystemic diseases that can affect many organs, including skeletal muscle, skin, lungs, joints, and the esophagus. An association between IIM and cancer is well-established by epidemiologic evidence from numerous large population studies.[1–5] The association is strong for patients with DM and less for PM, uncertain for NM or IBM, and not

No financial conflicts of interest or any funding source relevant to this article.
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Rheum Dis Clin N Am 46 (2020) 565–576
https://doi.org/10.1016/j.rdc.2020.05.006
rheumatic.theclinics.com

present with JDM. The precise pathophysiologic links between cancer and myositis are not well-understood. In this review, we evaluate the risk stratification for cancer in myositis based on clinical and serologic features, including screening strategies.

DEFINITION AND TIMING OF CANCER-ASSOCIATED MYOSITIS

The association between inflammatory myopathy and cancer has led to the term cancer-associated myositis, generally referring to cancer that typically develops within 3 years of the diagnosis of myositis.[1–5] Although most cancers are diagnosed simultaneously with or during the first year after the diagnosis of myositis,[2,6] the cancer risk gradually decreases over 3 to 5 years and remains increased compared with the general population, particularly in DM.[6–10] Adenocarcinomas of the lung, ovaries, breast, cervix, bladder, pancreas, and upper and lower gastrointestinal tract, along with hematologic malignancies including Hodgkin lymphoma, are among the most commonly reported myositis-associated cancers.[2,5] However, the risk and distribution of malignancies may be influenced by genetic background and ethnicity. For example, southeast Asia has a higher frequency of nasopharyngeal, lung, and hematopoietic malignancies associated with DM.[6] Although the treatment of cancer may result in improvement or even resolution of myositis, a new myositis diagnosis or its recurrence has been reported with cancer relapse.[2,6]

Cancer Risk Based on Disease Subsets

Cancer risk is significantly higher in DM compared with PM, with reported standardized incidence ratios (SIRs) nearly double that of PM. In a meta-analysis of case control and cohort studies including 1078 myositis subjects (565 PM and 513 DM) with a comparable number of controls, the overall odds ratio (OR) for associated cancers with DM and PM was 4.4 and 2.1, respectively.[7] SIRs from large population-based studies in Denmark,[4] Australia,[3] Scotland,[2] and Taiwan[6] range from approximately 3.0 to 7.7 in DM and 1.3 to 2.1 in PM. In a Taiwan national health insurance database of 1012 DM and 643 PM patients from 1997 to 2007 with no prior malignancy history, there were 95 cancers (9.4%) in patients with DM and 33 cancers (4.4%) in patients with PM, resulting in SIRs of 5.11 (95% confidence interval [CI], 5.01–5.22) and 2.15 (95% CI, 2.08–2.22) in patients with DM and PM, respectively.[6] A recent meta-analysis of 5 studies with 4538 patients with DM or PM reported an overall relative risk (SIR) of cancer of 4.66 for patients with DM and 1.75 for patients with PM.[8] Clinically amyopathic DM has also been shown to have an association with cancer. In a systematic review of amyopathic dermatomyositis, 14% of 301 patients in the analysis had an associated malignancy.[11]

There is a paucity of studies assessing malignancy risk in IBM. In an Australian population-based cohort study, the SIR for IBM was 1.8,[3] whereas most epidemiologic studies report no increased risk of cancer in IBM.[12] Further, no association of cancer is reported in JDM, myositis associated with another autoimmune disease, the antisynthetase syndrome, or patients with anti- signal recognition particle (SRP)-positive NM.

Proposed risk stratification based on myositis clinical subtype

Based on published evidence as well as the authors' experiences, we propose the following cancer risk stratification.

- *High risk*: DM
- *Intermediate risk*: clinically amyopathic DM, PM

- *Low risk*: Juvenile myositis (including JDM), IBM, antisynthetase syndrome, NM (anti-SRP antibody positive), myositis in overlap with another autoimmune disease

CLINICAL AND SEROLOGIC RISK FACTORS FOR CANCER ASSOCIATED MYOSITIS

Although various studies report a greater cancer risk in patients with myositis with particular clinical features and serum autoantibodies, there also seem to be protective clinical features for cancer-associated myositis.[13–20]

Clinical Risk Factors

- *Older age at disease onset:* patients with myositis with disease onset after age 50 have a higher risk factor for cancer-associated myositis. A meta-analysis of 20 studies with 380 patients and 1575 controls reported that older age increases the risk of cancer.[13] In a review of 198 patients with IIM, patients with DM with cancer were more frequently older than 45 years of age, whereas those without cancer were younger than age 45.[14] Another study of malignancy among 251 patients with myositis found cancer-associated DM significantly more common in older patients.[15] A Japanese study of 145 patients diagnosed with either DM/PM or clinically amyopathic DM noted that patients with malignancy were older than their counterparts without cancer (61.5 years vs 51.1 years; $P<.005$).[16]
- *Male gender:* Males are at greater risk for cancer-associated myositis, even though myositis is more common in females[13,20]—and a recent meta-analysis of 31 studies confirmed this observation. Further, in the aforementioned study of 198 patients with IIM, patients with DM with cancer were more frequently male.[14]
- *Dysphagia:* Dysphagia owing to weakness of the striated muscle of the upper one-third of the esophagus is associated with more severe disease and a worse prognosis, but is also an independent risk factor for cancer (OR, 2.41; 95% CI, 1.50–3.86).[13] This risk has been confirmed in other studies.[15,16]
- *Cutaneous necrosis, ulceration and vasculitis:* Cutaneous ulcerations as well as necrosis of the skin and subcutaneous tissue are occasionally seen in severe DM, as well as amyopathic DM. Although it is generally associated with refractory disease and a poor prognosis, skin ulceration and more specifically skin necrosis has been associated with cancer associated DM (OR, 5.5; 95% CI, 3.5–8.7).[13] The association between cutaneous manifestations and cancer has been suggested in a few other studies as well.[20–22] Furthermore, leukocytoclastic vasculitis (histopathologically characterized by neutrophilic infiltration and fibrinoid necrosis within and around blood vessel walls) was significantly associated with cancer in a small retrospective review of 23 patients with DM.[17]
- *Rapid onset of myositis:* In a retrospective study of 33 patients with DM and 7 patients with PM, the rapid onset of myositis (defined by a diagnosis made within 2 months of initial signs and/or symptoms) was associated with malignancy ($P = .02$).[19]
- *Refractory myositis:* Severe and refractory disease, especially involving the skin, often suggests an occult malignancy.[15,20,21,23]
- *Laboratory features:* In addition to elevated inflammatory markers such as the erythrocyte sedimentation rate and C-reactive protein, higher total creatine kinase levels may also be associated with a higher cancer risk.[19,21,24]

Protective Factors

Features of IIM that may be associated with a lower risk of cancer include interstitial lung disease (ILD), inflammatory arthropathy, and Raynaud phenomenon,[6,13,16,19,20] but this risk reduction is only relative.

- *ILD:* In 147 patients with DM or PM from Taiwan, patients with ILD had a significantly lower frequency of malignancies compared with patients with IIM without ILD ($P<.001$).[6] In a more recent meta-analysis of 20 studies with 380 patients with DM and patients with PM and 1575 controls, ILD was protective against cancer (OR, 0.32; 95% CI, 0.20–0.51).[13]
- *Inflammatory arthropathy:* This meta-analysis also showed that arthritis was associated with a lower cancer risk in myositis (OR, 0.38; 95% CI, 0.24–0.61),[13] a conclusion supported by another independent study.[15]
- *Raynaud phenomenon:* In a study of 309 patients with myositis, Raynaud phenomenon was less frequent in the cancer-associated myositis group (11% vs 26%; $P<.05$).[20] In another retrospective study of 33 consecutive adult patients with DM and 7 patients with PM, the absence of Raynaud phenomenon was associated with cancer ($P<.01$).[16]

Proposed risk stratification based on myositis clinical factors

Based on the evidence presented elsewhere in this article, we propose the following risk stratification.

High risk: Multiple risk factors (generally $\geq$2), but no protective factors.
Intermediate risk: One risk factor or 2 risk factors with protective factors.
Low risk: No risk factors and 1 or more protective factors.

Red flags for cancer include unexplained weight loss, loss of appetite, unexplained pain, lymphadenopathy, mass, nonhealing ulcers, excessive fatigue, night sweats, pruritus.

SEROLOGIC RISK FACTORS FOR CANCER-ASSOCIATED MYOSITIS

Myositis autoantibodies are highly specific biomarkers associated with unique clinical phenotypes having prognostic significance. Several “cancer-associated” autoantibodies may help in the risk stratification for cancer in patients with myositis and guide cancer screening strategies.[25–29]

Myositis Autoantibodies

- *Anti–TIF1-gamma*: This myositis autoantibody, also identified as anti-p155 or anti-p155/140, targets a 155-kDa protein and has been linked to cancer in several studies.[9,30–32] A recent review on the relationship between anti–TIF1-gamma and cancer-associated myositis encompassed 312 adult patients with DM[33]; in this analysis, the pooled sensitivity of anti–TIF1-gamma for diagnosing cancer-associated DM was 78% (95% CI, 45%–94%), with a specificity of 89% (95% CI, 82%–93%). The diagnostic OR for anti–TIF1-gamma was 27.26 (95% CI, 6.59–112.82), with a positive likelihood ratio of 6.79 (95% CI, 4.11–11.23) and a negative likelihood ratio of 0.25 (95% CI, 0.08–0.76). No association between cancer and anti–TIF1-gamma was seen in juvenile myositis (despite the high frequency of this autoantibody in JDM). Of note, this autoantibody is not typically found in PM or NM. In 263 DM cases with 3252 person-years of follow-up for a median of 11 years, all of the detected malignancy cases in the TIF1-gamma–positive cohort occurred between 3 years before and 2.5 years after DM onset.[10]

- *Antinuclear matrix protein (NXP)-2*: Anti–NXP-2 (previously termed anti-MJ) recognizes a 140-kDa protein and is one of the myositis autoantibodies seen in JDM as well as adult DM. Similar to TIF1-gamma, this autoantibody is associated with cancer only in adult patients with DM. In 213 patients with DM, a total of 17% and 38% had antibodies against NXP-2 and anti–TIF1-gamma by immunoprecipitation, respectively,[34] and cancer was associated with anti–NXP-2 or TIF1-gamma autoantibodies (OR, 3.78; 95% CI, 1.33–10.8) using multivariate analysis. Stratification by gender noted an NXP-2 cancer association only in males (OR, 5.78; 95% CI, 1.35–24.70). In a Japanese study of 507 patients, only 1.6% of patients had NXP-2 autoantibodies, but one-third developed malignancy, mostly within 1 year of diagnosis.[35]
- *Anti–3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)*: Anti-HMGCR is seen in patients with statin associated immune-mediated NM. In 207 Australian patients, there was a nonstatistically significant trend toward increased malignancy ($P = .15$) in anti–HMGCR-positive patients.[36] A recent study showed a higher (nonstatistically significant) prevalence of malignancy in patients with anti-HMGCR antibody,[27] whereas a French study demonstrated a higher incidence of cancer in anti–HMGCR-positive immune-mediated NM, but not with the anti-SRP antibody.[37] In a recent study in our center, there was no significant difference between the cancer frequency in the anti–HMGCR-positive NM group as compared with anti–HMGCR-NM ($P = .92$).[38]
- *Other myositis-associated autoantibodies*: In 627 patients with IIM, patients who were myositis-specific antibody-negative (SIR, 3.9; 95% CI, 1.9–7.1) or who possessed anti-SAE1 antibodies (SIR, 12.9; 95% CI, 3.2–32.9) were noted to have an increased risk of cancer compared with the general population.[30] Myositis-specific antibody negativity has been suggested to be associated with an increased risk of cancer in myositis in other studies as well.[34,39] Conversely, in another study of 231 patients with DM where 140 (61%) were antinuclear antigen (ANA) positive and 91 (39%) were ANA negative, there was a strong association between ANA positivity and a lower likelihood of malignancy (OR, 0.16; $P<.001$).[39] Similarly, having an antisynthetase antibody, especially anti–Jo-1, was associated with a lower risk of cancer-associated myositis.[24,30] As indicated elsewhere in this article, the risk of cancer has not been reported with anti–SRP-positive immune-mediated NM, compared with the general population.[40,41] There is no reported significant association of cancer with anti–Mi-2 or anti-MDA5 antibodies.

PROPOSED RISK STRATIFICATION BASED ON MYOSITIS AUTOANTIBODIES

Based on the studies discussed, the risk of cancer development in patients possessing specific autoantibodies can be stratified into high-, intermediate-, and low-risk groups.

- *High risk*: anti–TIF1-gamma, anti-NXP2
- *Intermediate risk*: Anti-SAE, anti-HMGCR, myositis autoantibody negative
- *Low risk*: Anti-synthetase, anti-SRP, anti–Mi-2, anti-MDA5 (melanoma differentiation antigen 5), ANA, antibodies associated with overlap myositis

SCREENING STRATEGIES

Basic or Age-Appropriate Screening

Over the years, myositis experts have recommended age- and sex-appropriate cancer screening, including basic laboratory testing at least at diagnosis as well as yearly

for 3 years from initial diagnosis. This basic screening should be considered in all patients with myositis regardless of their risk stratification. This analysis includes a complete history and physical examination, complete blood count, serum chemistry panel, and cancer screening as per the national guidelines (**Box 1**).

Enhanced Screening

Enhanced screening would include basic screening as well as computed tomography (CT) scanning of the chest, abdomen, and pelvis, which could be performed in patients with increased risk for developing cancer. In addition, tumor markers as well as gynecologic/pelvic examination and/or ultrasound examination in women and testicular ultrasound examination in men should be considered.

In a study of 40 consecutive adult patients with DM (33 cases) or PM (7 cases), the yield of malignancy searches was increased with thoracic CT scans.[19] As indicated elsewhere in this article, all high-risk female patients with cancer red flags need to undergo a gynecologic/pelvic examination and pelvic/transvaginal ultrasound examination to screen for occult ovarian cancer.[42,43] In addition, males less than 50 years of age should undergo testicular ultrasound examination given the high risk of testicular cancer in at-risk male patients.

However, the use of tumor markers in myositis-associated cancer screening is controversial. In a single blinded, case-control study of 14 women with DM and 10

Box 1
Cancer screening in myositis

Basic screening
- Comprehensive history and physical examination; family history
- Routine blood tests: Complete blood count, liver function tests, urinalysis
- Chest radiograph
- Age-appropriate screening
  - Colonoscopy: The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years.
  - Mammography: The USPSTF recommends biennial screening mammography for women aged 50 to 74 years.
  - Screening for cervical cancer: The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women aged 21 to 29 years. For women aged 30 to 65 years, the USPSTF recommends screening every 3 years with cervical cytology alone, every 5 years with hrHPV testing alone, or every 5 years with hrHPV testing in combination with cytology (cotesting).
  - Screening for prostate cancer: Per USPSTF, for men aged 55 to 69, the decision to undergo periodic prostate-specific antigen-based screening for prostate cancer should be an individual one.

Enhanced screening: Includes basic screening and consideration of one or more of the following evaluations.
- Computed tomography scanning of the chest/abdomen/pelvis
- Tumor markers
- Gynecologic/pelvic ultrasound examination in women, and testicular ultrasound examination in men (age <50 years)

Comprehensive screening: Includes basic or enhanced screening with consideration of the following evaluations.
- PET with computed tomography scanning of the chest/abdomen/pelvis

Abbreviations: hrHPV, high-risk human papillomavirus; USPSTF, US Preventive Service Task Force.

healthy controls, CA 125 was found to have a sensitivity of 50% and specificity of 100% for the detection of ovarian cancer.[44] A more recent study assessing the diagnostic values of CA 125, carcinoembryonic antigen, CA 19-9, and CA 15-3 for the detection of solid cancer in DM/PM patients also concluded that CA125 and CA19-9 assessment could be useful markers of cancer risk in patients with DM and PM.[45] For example, elevated CA125 and CA 19-9 at screening were higher in patients who developed cancer within 1 year or in patients without ILD. Based on these studies, a physician can consider CA 125 and CA 19-9 for the screening of patients at higher risk for cancer associated myositis. However, these findings have not been confirmed in other studies, and in a 21-year retrospective study, tumor markers did not predict occult tumors.[20] Furthermore, transient elevation of CA 15-3 was reported as a marker of ILD rather than underlying cancer in a patient with amyopathic DM.[46]

Comprehensive Screening

Comprehensive screening including basic or enhanced screening as well as PET with CT scanning of the chest, abdomen, and pelvis can be considered in patients with a particularly high risk for cancer. This advanced imaging approach (which combines [18F] fluorodeoxyglucose [FDG] labeling/PET and CT scanning) represents one of the most sensitive techniques available for the detection of occult malignancy and are increasingly being used in patients with myositis.[47,48] In a large prospective study of 55 consecutive patients with a recent diagnosis of myositis, whole body FDG-PET/CT scanning was compared with conventional cancer screening for the detection of malignancy.[47] The performance of a single FDG-PET/CT scan for diagnosing occult cancer in patients with myositis was comparable with that of a large number of conventional cancer screening techniques, including a complete physical examination, laboratory testing (complete blood count and serum chemistry panel), thoracoabdominal CT scanning, tumor markers (CA125, CA 19-9, carcinoembryonic antigen and prostate-specific antigen), and gynecologic examination in women, including ultrasound examination and mammography. The authors concluded that it is reasonable to perform PET/CT scans for high-risk patients rather than subjecting them to a many tests and procedures. Moreover, a cost analysis study showed that the expense of a whole body PET/CT scan was greater than conventional panels for insurance companies, but lower for patients in terms of out-of-pocket expenses.[49] These findings were supported by a Japanese study, where PET/CT scanning was able to effectively detect underlying cancer in patients with myositis.[50] However, a retrospective cohort study from Canada evaluating 100 FDG PET/CT studies in 63 unique patients (31 DM, 1 PM, 25 overlap myositis, 1 IBM, 1 orbital myositis, and 4 unspecified myositis) failed to show any additional benefit of FDG PET/CT scanning.[51] Unfortunately, all of these studies assessed the usefulness of the whole body FDG PET/CT in consecutive patients with myositis, irrespective of their cancer risk. Further studies are therefore necessary to determine the role and specificity of FDG-PET/CT scanning in risk-stratified cancer screening among patients with IIM.

APPROACH TO SCREENING

Despite an increasing number of studies examining the usefulness of various screening strategies, existing data do not permit consensus, evidence-based recommendations for cancer screening in myositis. However, based on these limited data and personal observation, we recommend that all newly diagnosed patients with myositis (duration of <3 years) undergo stratification of cancer risk. Age- and sex-

appropriate screening, including history, physical examination, and basic laboratory testing, should be done on all patients with myositis regardless of their risk category. This comprehensive history and physical examination should include an assessment of clinical risk factors, protective factors, and any red flags for malignancy as discussed elsewhere in this article. Serum should also be assessed for myositis-specific autoantibodies in all newly diagnosed patients with IIM for the identification of high-risk patients. Patients can then be categorized into low-risk, intermediate-risk, and high-risk groups based on clinical characteristics and myositis autoantibody results (Fig. 1). Although not entirely evidence based, we further recommend that patients at low risk, intermediate risk, and high risk be considered for basic, enhanced, or comprehensive cancer screening, respectively. Finally, high-risk patients should likely undergo basic cancer screening annually for 3 years from diagnosis; Fig. 1 provides further details.

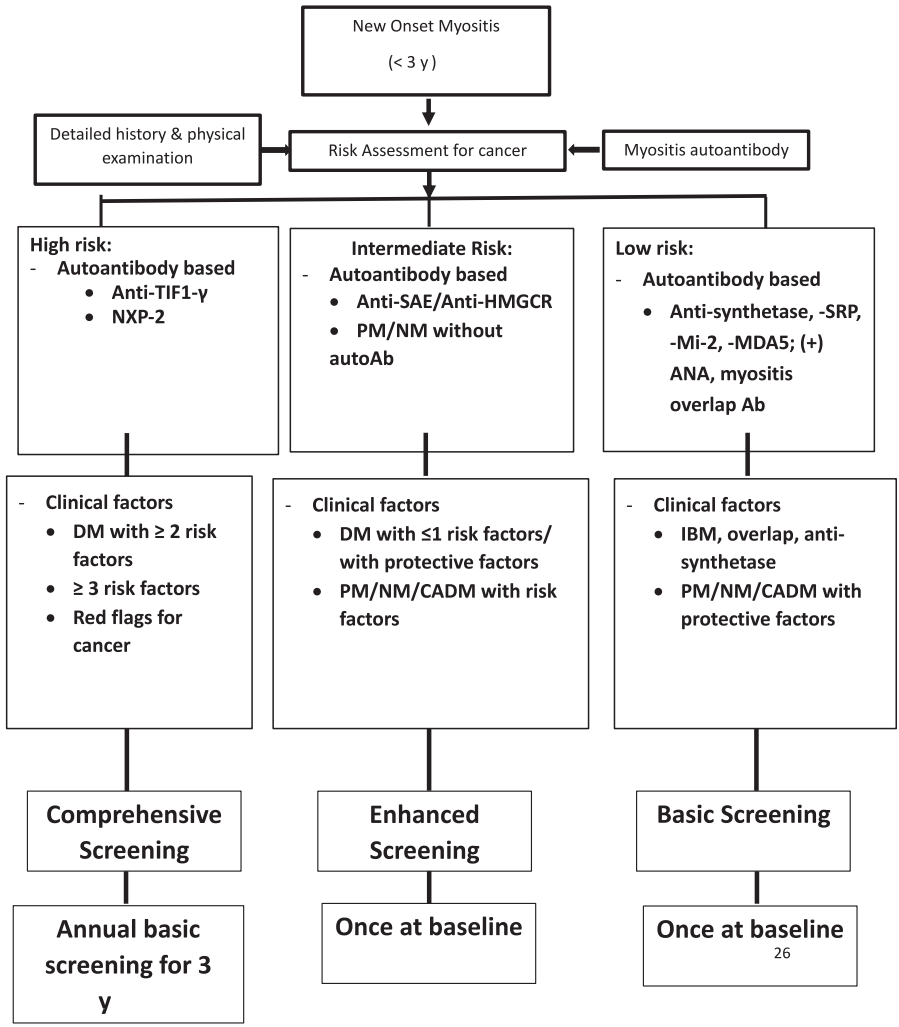

Fig. 1. Approach to cancer screening in myositis.

SUMMARY

Cancer screening is important in myositis, particularly at disease onset and within the first 3 years of disease. Risk stratification for cancer in patients with myositis can be completed based on a combination of clinical risk factors and protective factors, myositis clinical subtypes, and autoantibody profile. Despite a paucity of data- or consensus-driven recommendations, we have proposed a cancer screening strategy based on this paradigm of risk stratification. Large multicenter studies are needed to test our proposed recommendations as well as other strategies for early detection of cancer in myositis. High-risk patients should be monitored regularly and receive aggressive cancer screening to detect occult malignancy, although all patients should continue to obtain age- and gender-appropriate cancer screening as recommended for the general population.

CLINICS CARE POINTS

- Risk stratification for cancer in myositis can be completed based on a combination of myositis clinical subtypes, clinical risk factors, and autoantibodies.
- Cancer risk is significantly higher in DM as compared with other myositis clinical subtypes.
- Clinical risk factors for cancer in myositis include older age at disease onset, male sex, dysphagia, cutaneous ulceration, necrosis or vasculitis, rapid onset of myositis, refractory myositis and laboratory features including elevated inflammatory markers.
- The risk of cancer development in patients with myositis possessing anti–TIF1-gamma and anti-NXP2 is the highest among the myositis-associated and myositis-specific autoantibodies.
- Appropriate cancer screening strategies in IIMs are based on the risk level and include a comprehensive history and physical examination; routine blood tests; age-appropriate malignancy screening; CT scanning of the chest, abdomen, and pelvis; tumor markers; gynecologic/pelvic ultrasound examination in women; testicular ultrasound examination in men; and PET-CT scanning of the chest, abdomen, and pelvis.

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