Malignancy in Idiopathic Inflammatory Myopathies

Anousheh Haghighi M.D.

Rheumatologist

Professor of Iran University of Medical Sciences

An association between inflammatory myopathy and cancer has been recognized since the report of two cases of PM and gastric cancer in 1916.

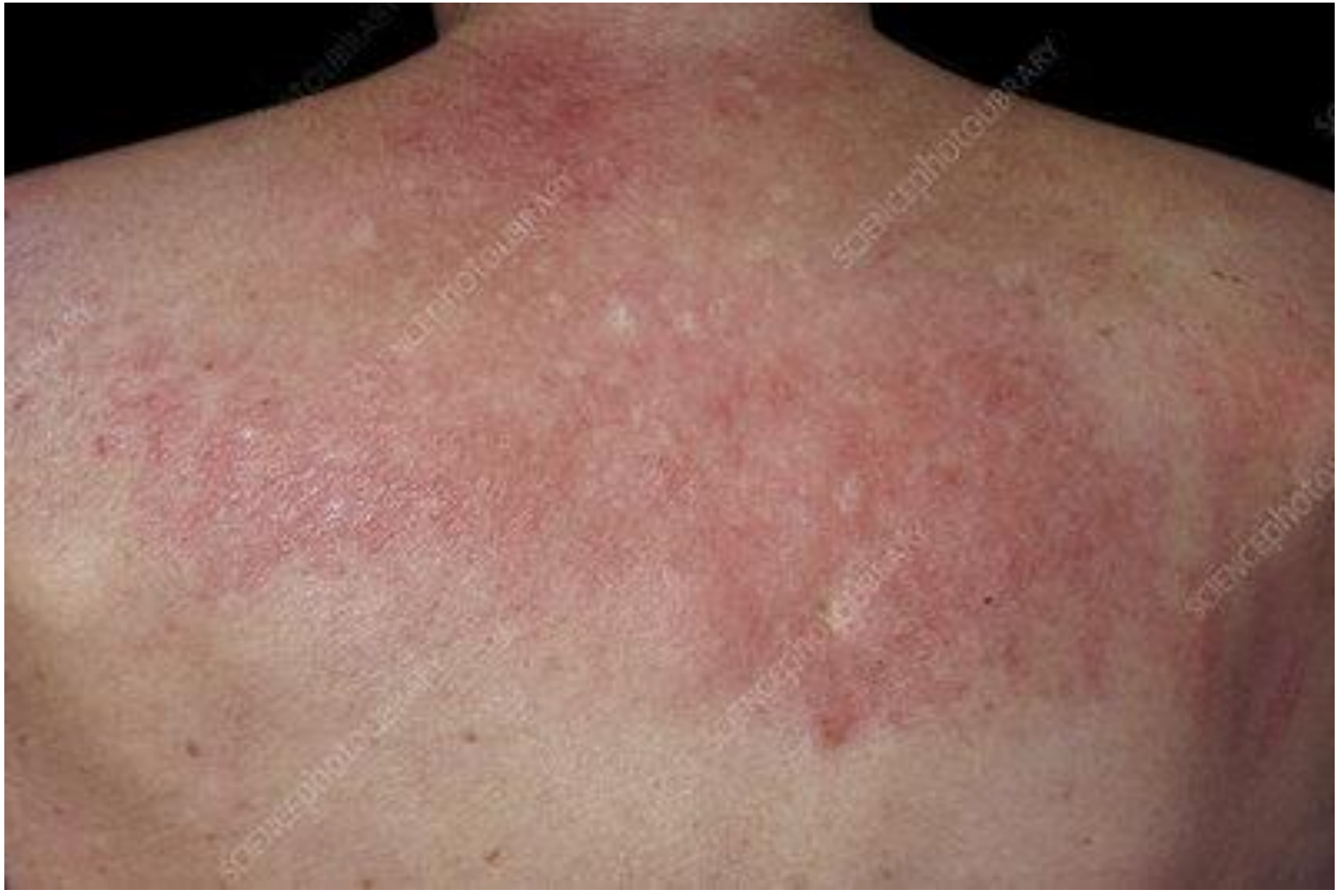
What are the evidence for an association between cancer and inflammatory myopathy?

- Epidemiologic evidence from large population studies
- Temporal relationship between the diagnosis of cancer and myopathy
- The improvement or resolution of myopathy after treatment of the cancer
- Relapse or development of myopathy associated with relapse of the cancer

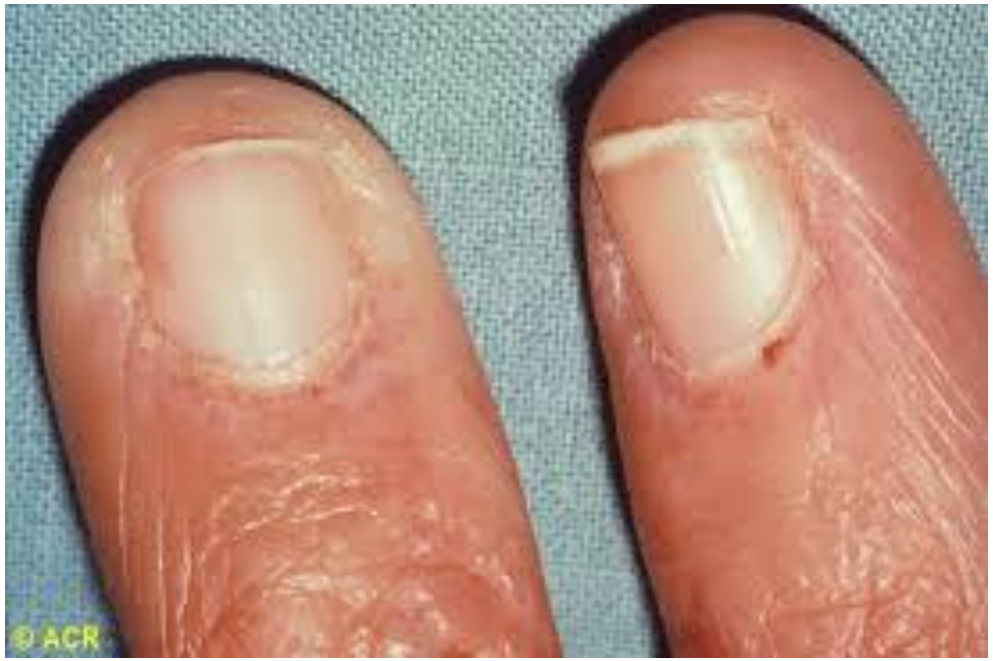
A 68 years old male came to the rheumatology clinic with 2 weeks history of erythema on the skin, and muscle weakness with severe dysphagia.

- Elecromyography reported evidence of myopathy

Shawl sign



Nail-fold Capillary Changes



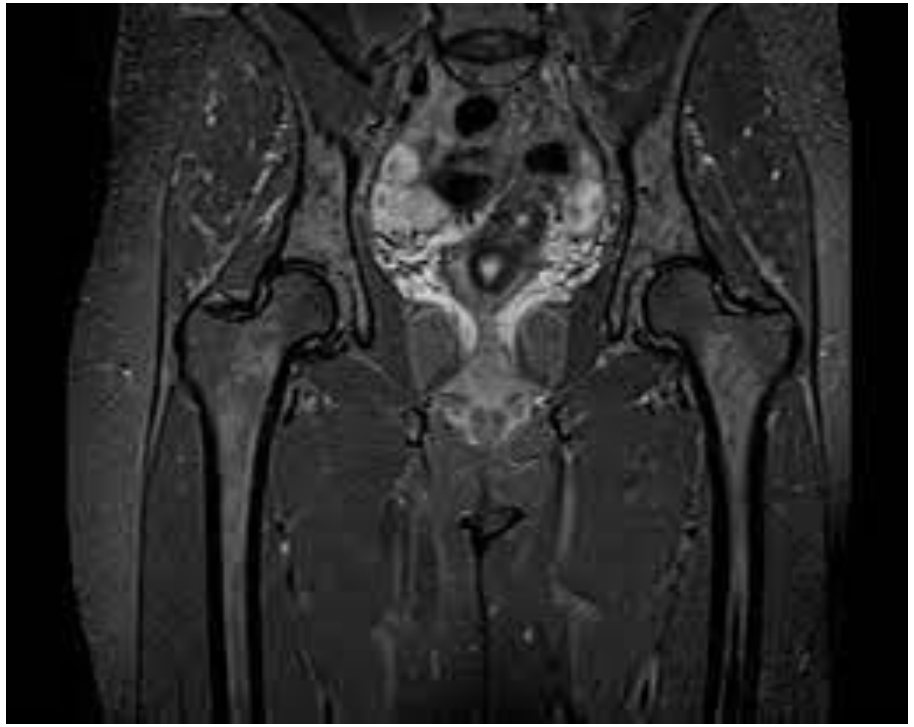
Helitrope Rash

Laboratory Results

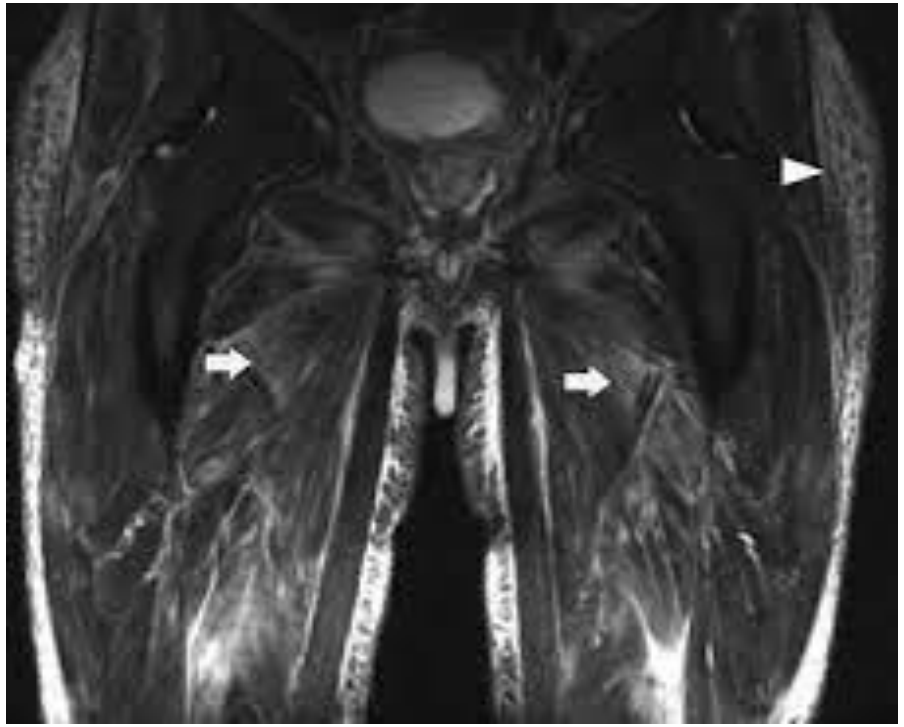
- CBC: Normal
- ESR: 98
- CPK: 1450 mg/dl
- LDH: 4500 mg/dl
- Cr: 1.6 mg/dl
- Anti-Mi-2, anti-SRP, and anti-MDA5, anti-RNP, anti-PM-Scl, anti-Ku were all negative

MRI Findings

Normal Thigh MRI



Patient's Thigh MRI



Based on the above findings, treatment as dermatomyositis with high dose steroid and azathioprine started.

After one month, response to treatment was poor.

- What else should be done?
- How likely is the possibility of malignancy in this patient?
- What kind of malignancy should be kept in mind?
- What are the risk factors of malignancy in this patient?

Why they are connected?!

Pathogenesis theory

Molecular mimicry

- It is suggest that the link between malignancy and inflammatory myopathy relates to the expression of common autoantigens between cancer tissue and muscle tissue in some patients with dermatomyositis (DM) or polymyositis (PM), and that the immune response directed at tumor cells may also target similar autoantigens in muscle tissue resulting in muscle damage.

Molecular mimicry

- According to this theory, antigens exposed by the tumor initiate an immune response directed against the neoplasm. If muscle injury occurs due to, for example, infection, trauma or toxin exposure (“second hit”), regenerating muscles start to express myositis-specific antigens, becoming a target for cross-over immune reaction, which leads to the outbreak of inflammatory myopathy

Incidence

Incidence

- According to the EuroMyositis registry, malignancies occurred at any time in 13% of patients with myositis, with most of them being diagnosed in close temporal association with the onset of myopathy.

Incidence

- The increased risk has subsequently been confirmed in population-based studies from a variety of countries. Standardized incidence ratios from population-based studies from Denmark, Australia and Taiwan range from approximately 3.0 to 6.0.

Types of malignancies

Types of malignancies

- The types of cancer associated with inflammatory myopathy appear to mirror the incidence of cancer in the general population.
- Significant discrepancies have been observed in the type of malignancies occurring in the patients of various races and ethnicities.
- Lung, breast and ovarian tumors are one of the most prevalent malignancies worldwide, which is also reflected in the myositis population.

Types of malignancies

- An increased risk of ovarian, lung, breast, pancreatic, prostate, cervix, colorectal and gastric cancers is reported in various studies.
- Hematologic malignancies (non-Hodgkin's lymphoma) are more frequent in PM than DM.
- Nasopharyngeal carcinoma was the most common type of malignancy in Asian patients with DM.

Temporal relationship

Temporal relationship

- Cancer can be diagnosed before, simultaneously with, or after the diagnosis of inflammatory myopathy. The peak incidence of a cancer diagnosis occurs simultaneously with and during the first year after the diagnosis of the muscle disease, and falls off gradually over the subsequent five years of follow-up, although there may still be some increased risk beyond five years

Risk Factors

Risk Factors

- Older age at disease onset
- Dysphagia
- Severe Cutaneous involvement (necrosis,vasculitis)
- Resistance to treatment
- Evidence of capillary damage on muscle biopsy
- Prior history of malignancy with the risk of relapse
- Absence of myositis-specific and myositis-associated antibodies

Age & Sex

- One of the factors strongly associated with the risk of malignancy is older age at the onset of myositis.
- The data remain less conclusive about the risk of cancer associated with the patient's gender, but most of the authors conclude that the male gender increases the risk of cancer in idiopathic inflammatory myopathies.

Muscle involvement

- Cancers were found to occur more frequently in patients with **prominent** skeletal muscle weakness as well as in patients with the involvement of the **distal** skeletal muscles of the limbs, skeletal **respiratory** muscles and esophageal muscles (**Dysphagia**).
- **Rapid onset** of myopathy should also encourage greater oncological vigilance.

Cutaneous Involvement

- Malignancy was reported to be associated with severe cutaneous lesions. The presence of several specific skin pathologies such as cutaneous **ulceration**, skin **necrosis** and leukocytoclastic **vasculitis** seem to indicate high malignancy risk.

Biochemical and Serological Tests

- Lower concentrations of creatine kinase and lactate dehydrogenase
- Highly elevated markers of inflammation such as C-reactive protein and erythrocyte sedimentation rate, unusual for isolated IIM

Biochemical and Serological Tests

- Positive risk– Cancer-associated myositis (CAM) in adults has been associated in several studies with antibodies to transcription intermediary factor (**TIF**)-1gamma (anti-p155, anti-p155/140) and with antibodies to nuclear matrix protein (**NXP)-2** (anti-MJ or anti-p140)
- Negative risk– Conversely, the presence of myositis-specific (anti-synthetase antibodies, anti-Mi-2, anti-SRP, and anti-MDA5) and myositis-associated antibodies (anti-RNP, anti-PM-Scl, anti-Ku) appears to be associated with a decreased risk of malignancy but an increased risk of interstitial lung disease in DM

Protective Factors

Patients with **interstitial lung disease** appear to have a lower frequency of malignancies.

Other symptoms from the spectrum of an antisynthetase syndrome such as **arthritis/arthralgia, fever and the Raynaud phenomenon** also seem to diminish the risk of tumors.

Cardiac involvement has been also considered a cancer-protective factor.

Fardet et al. demonstrated in the retrospective analysis the negative association of **lymphopenia** and probability of malignancy.

Approach to Screening

Review > Rheum Dis Clin North Am. 2020 Aug;46(3):565-576. doi: 10.1016/j.rdc.2020.05.006. Epub 2020 Jun 7.

Risk Factors and Cancer Screening in Myositis

Siamak Moghadam-Kia [1], Chester V Oddis [2], Dana P Ascherman [3], Rohit Aggarwal [4]

Affiliations + expand

PMID: 32631604 DOI: 10.1016/j.rdc.2020.05.006

- Moghadam-Kia et al published an interesting expert opinion on a proposed screening scheme.
- They divided patients into three groups based on risk factors

High- Risk Group

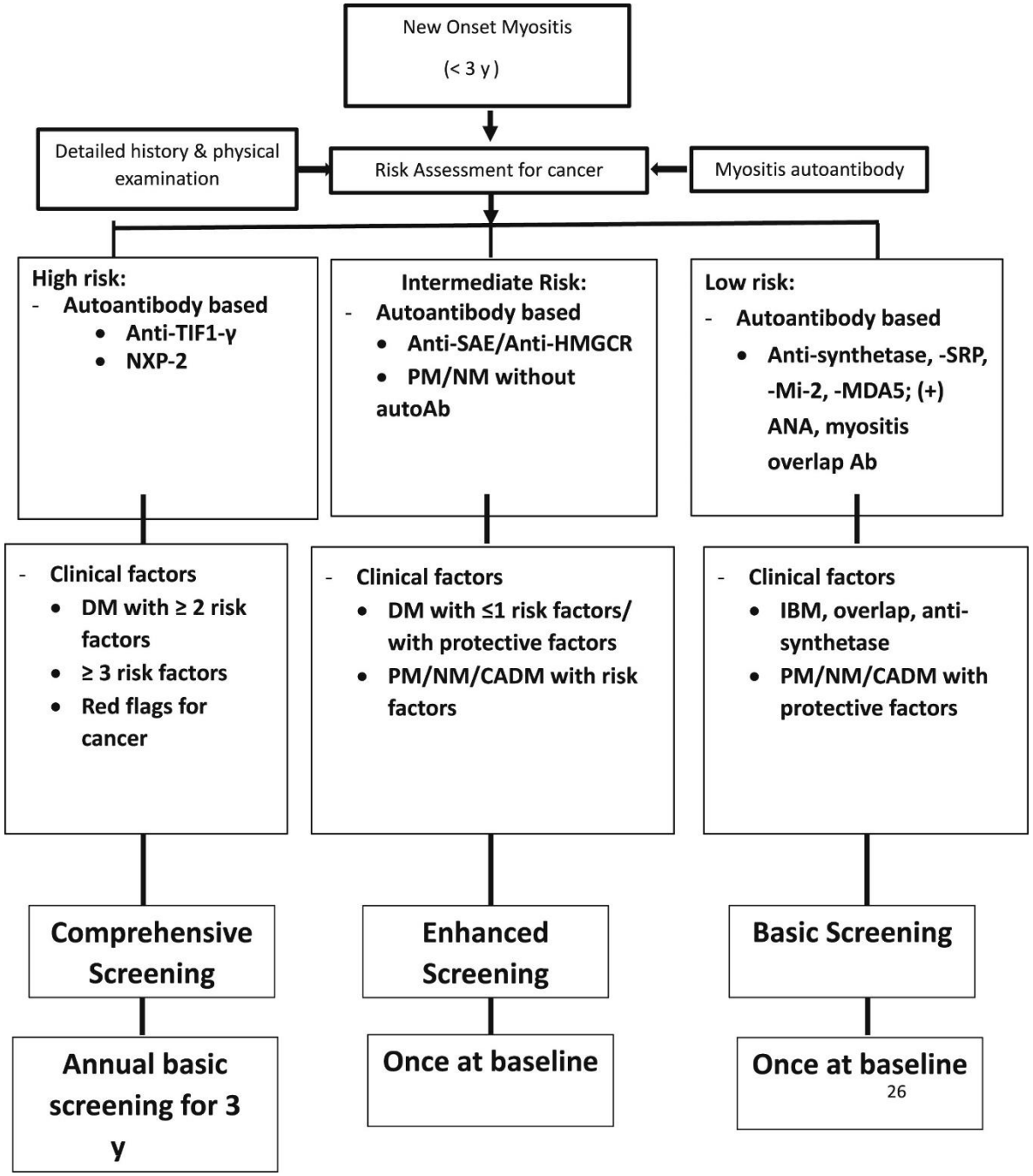
- Patients with dermatomyositis with at least two clinical risk factors (such as older age, male gender, dysphagia, cutaneous necrosis or ulcerations, vasculitis, rapid onset of IIM, refractory course of IIM, high inflammatory markers) and no protective factors (ILD, inflammatory arthropathy, Raynaud phenomenon), as well as patients with anti-TIF1-γ and anti-NXP-2 antibodies were considered high-risk groups.

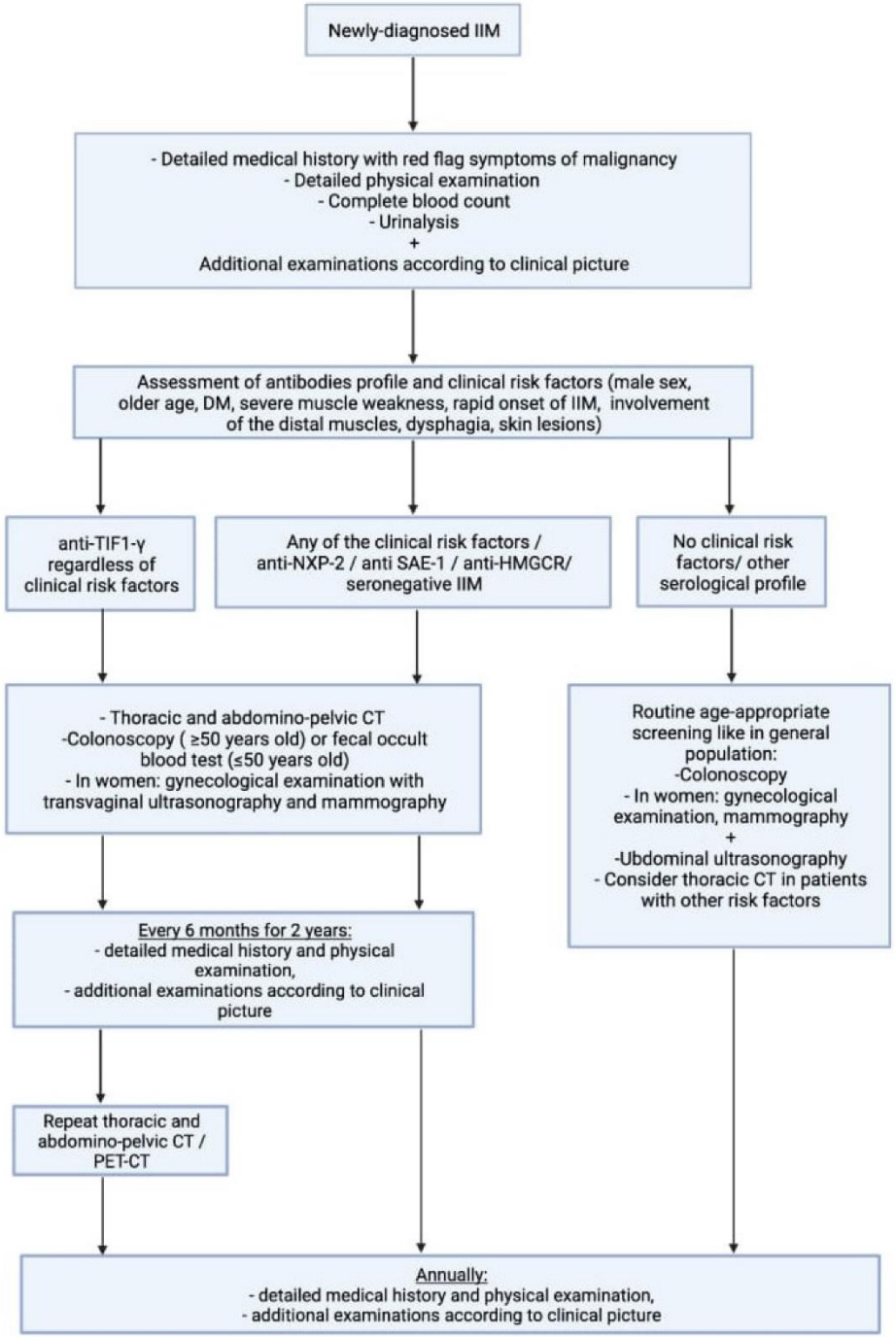
Moderate- Risk Group

- Seronegative patients
- Individuals with **anti-SAE** (Antibodies to small ubiquitin-like modifier activating enzyme) and **anti-HMGCR** antibodies
- Patients with one or two clinical risk factors in the presence of any of the protective factors.

Low- Risk Group

- The remaining patients were classified as probably having a low risk of malignant disease


New Onset Myositis
(< 3 y)
Detailed history & physical examination
Risk Assessment for cancer
Myositis autoantibody
High risk:
- Autoantibody based
• Anti-TIF1-γ
• NXP-2
Intermediate Risk:
- Autoantibody based
• Anti-SAE/Anti-HMGCR
• PM/NM without autoAb
Low risk:
- Autoantibody based
• Anti-synthetase, -SRP, -Mi-2, -MDA5; (+) ANA, myositis overlap Ab
- Clinical factors
• DM with ≥ 2 risk factors
• ≥ 3 risk factors
• Red flags for cancer
- Clinical factors
• DM with ≤1 risk factors/ with protective factors
• PM/NM/CADM with risk factors
- Clinical factors
• IBM, overlap, anti-synthetase
• PM/NM/CADM with protective factors
Comprehensive Screening
Enhanced Screening
Basic Screening
Annual basic screening for 3 y
Once at baseline
Once at baseline


Newly-diagnosed IIM
- Detailed medical history with red flag symptoms of malignancy
- Detailed physical examination
- Complete blood count
- Urinalysis
+
Additional examinations according to clinical picture
Assessment of antibodies profile and clinical risk factors (male sex, older age, DM, severe muscle weakness, rapid onset of IIM, involvement of the distal muscles, dysphagia, skin lesions)
anti-TIF1-γ regardless of clinical risk factors
Any of the clinical risk factors / anti-NXP-2 / anti SAE-1 / anti-HMGCR/ seronegative IIM
No clinical risk factors/ other serological profile
- Thoracic and abdomino-pelvic CT
-Colonoscopy (≥50 years old) or fecal occult blood test (≤50 years old)
- In women: gynecological examination with transvaginal ultrasonography and mammography
Routine age-appropriate screening like in general population:
-Colonoscopy
- In women: gynecological examination, mammography
+
-Ubdominal ultrasonography
- Consider thoracic CT in patients with other risk factors
Every 6 months for 2 years:
- detailed medical history and physical examination,
- additional examinations according to clinical picture
Repeat thoracic and abdomino-pelvic CT / PET-CT
Annually:
- detailed medical history and physical examination,
- additional examinations according to clinical picture

Post-treatment surveillance

- The value of repeat cancer screening in patients with established inflammatory myopathy is not well-established.
- Therefore, the diagnostic yield of continued surveillance for cancer after the initial screening is low, unless specific signs suggestive of an underlying malignancy appear, or a relapse of the inflammatory myopathy occurs after a period of remission.
- Patients should continue to have routine, age-appropriate screening (eg, mammogram, pelvic exam) as in the general population.

Impact of Malignancy on Disease Severity

- Myositis associated with cancer, responds more poorly to treatment than myositis in the absence of cancer, and survival rates are worse for patients with malignancy.
- Poor response to myositis treatment therefore should raise the possibility of an underlying malignancy.

- A **68 years** old male came to the rheumatology clinic with 2 weeks history of erythema on the skin, and muscle weakness with severe **dysphagia**.
- Anti-Mi-2, anti-SRP, and anti-MDA5, anti-RNP, anti-PM-Scl, anti-Ku were all **negative.**
- After one month, **response to treatment was poor**.

- What are the risk factors of malignancy in this patient?
- What else should be done?
- How likely is the possibility of malignancy in this patient?
- What kind of malignancy should be kept in mind?

Malignancy in other types of myositis

- Compared to DM, available data on malignancy in IBM is limited. Further studies are expected to reliably assess the risk of cancer in this subtype of IIM.
- Cancers were also frequently observed in patients with clinically amyopathic dermatomyositis.
- In patients with antisynthetase syndrome, risk of malignancy seems to be noticeably lower than in remaining types of myositis.

Take Home Massages

- Inflammatory myopathies are associated with malignancies in a significant minority of cases.
- The cancer rates reported with PM are consistently lower and questionable than that of DM.
- An increased risk of ovarian, lung, breast, pancreatic, prostate, cervix, colorectal and gastric cancers is reported in various studies.

Take Home Massages

- Cancer can be diagnosed before, simultaneously with, or after the diagnosis of inflammatory myopathy.
- Clinical factors associated with an increased risk of malignancy include older age at disease onset, dysphagia, evidence of capillary damage on muscle biopsy, cutaneous necrosis, cutaneous leukocytoclastic vasculitis.
- Patients with interstitial lung disease appear to have a lower frequency of malignancy. Arthritis/arthralgia, fever, the Raynaud phenomenon are known as protective factors too.
- Some serum autoantibodies confer a positive risk of malignancy (Anti-TIF, Anti- NXP-2), whereas others (Myositis specific Abs & Myositis associate Abs) are associated with a negative risk.

Take Home Massages

- All patients newly diagnosed with IIM should be evaluated for the possibility of an underlying malignancy.
- The value of repeat cancer screening is not well-established.
- Myositis associated with cancer, responds more poorly to treatment than myositis in the absence of cancer.

Thank You !