Myositis and Cancer: What’s the Connection?

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• Review the epidemiology of cancer-associated myositis
• Consider recent data showing the association of specific autoantibodies with cancer
• Discuss cancer screening for patients with myositis
• Discuss a theory which could help explain the correlation between myositis and cancer
Introduction

• Association between cancer and myositis first described in 2 cases in 1916

• Observations suggesting that the association of cancer and myositis is not coincidental:
  – Improvement in rash and strength after cancer treatment
  – Recurrence of weakness with tumor relapse
  – Development of myositis around the time of cancer diagnosis
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<th>Study</th>
<th>DM (%)</th>
<th>PM (%)</th>
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<td>Bohan et al</td>
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<td>Callen</td>
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<td>Vesterager et al</td>
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<td>Mola et al</td>
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<td>Goh and Rajan</td>
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<td>Duncan et al</td>
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<td>Cox et al</td>
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<td>Maoz et al</td>
<td>45</td>
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Looking for an association between cancer and myositis: one good large study

• Hill, CL et al. 2001

Hill, CL et al. Lancet (357); 2001
Some Statistics…

– Standardized Incidence Ratio (SIR)
  • The ratio of the observed to the expected new cases of cancer
  • For example:
    – Expect 2 new cases of cancer
    – Observe 10 new cases of cancer
    – SIR = observed/expected = 10/2 = 5

    – Expect 2000 new cases of cancer
    – Observe 10,000 new cases of cancer
    – SIR = observed/expected = 10,000/2000 = 5
Cancer Increased in Dermatomyositis Patients

- 618 cases of DM
  - Mean age at diagnosis was ~ 55 years
- 198/618 (32%) had cancer
- SIR for all cancer types for DM: 3.0
  - SIR for men: 3.3
  - SIR for women: 2.8
- 115/198 (58%) of cancers developed AFTER the diagnosis of DM

Hill, CL et al. Lancet (357); 2001
Cancer Increased in Polymyositis Patients

- 914 cases of PM
  - Mean age at diagnosis was ~ 56 years
- 137/914 (15%) had cancer
- SIR for all cancer types for PM: 1.3
  - SIR for men: 1.4
  - SIR for women: 1.2
- 95/137 (69%) of cancers developed AFTER the diagnosis of PM

Hill, CL et al. Lancet (357); 2001
Cancers with Greatest Increased Risk

- **DM**
  - Ovarian (SIR 10.5)
  - Lung (SIR 5.9)
  - Pancreatic (SIR 3.8)
  - Non-Hodgkin Lymphoma (SIR 3.6)
  - Stomach (SIR 3.5)
  - Colorectal (SIR 2.5)
  - Breast (SIR 2.2)
  - Others

- **PM**
  - Non-Hodgkin lymphoma (SIR 3.7)
  - Lung (SIR 2.8)
  - Bladder (SIR 2.4)
  - Others

*Hill, CL et al. Lancet (357); 2001*
Temporal association of cancer and myositis

Hill, CL et al. Lancet (357); 2001
How Long is Cancer Risk Increased?

- Risk is highest within the first year of diagnosis.
- In those with polymyositis, the risk fell to expected rates 5 years after diagnosis.
- In those with dermatomyositis, the risk did not fall to expected rates.
  - Ovarian, pancreatic, lung remained high up to 5 years.
  - Pancreatic and colorectal cancer risks remained elevated past 5 years.

Hill, CL et al. Lancet (357); 2001
Another study demonstrating increased risk of cancer with myositis:

- Population based, retrospective study of 537 biopsy-proven myositis patients in Australia (1981-95)
  - DM: 36/85 had cancer (42%); SIR 6.2
  - PM: 58/321 had cancer (18%); SIR 2.0

*Buchbinder, R et al. Ann Intern Med 134; 2001*
Risk Factors Associated with Malignancy in Patients with Myositis

- DM (including amyopathic?) > PM > IBM
- Older age at onset
  - No increased risk in PM patients age 15-44
- Rapid onset of symptoms
- Capillary damage on muscle biopsy
- Cutaneous necrosis or vasculitis
- Poor response to treatment
- Protective: Presence of interstitial lung disease

Sparsa A et al. Arch Dermatol 138(7); 2002
Ponyi A et al. Ann Ny Acad Sci 1051; 2005
Increased mortality in cancer-associated myositis

Ponyi A. et al. Ann NY Acad Sci 1051; 2005

Myositis Autoantibodies and Cancer

- Chinoy et al (2007)
- 109 polymyositis – none with cancer
- 103 dermatomyositis – 15 with cancer
- 70 with myositis/CTD – 1 with cancer
  - Those with certain autoantibodies were “protected” from cancer
    - Jo-1, PM-Scl, U1-RNP, U3-RNP, Ku
  - Those with anti-155/140 had an increased risk of cancer
    - 8/16 cancer-associated myositis patients had 155/140 Ab

_Chinoy et al, Ann Rheum Dis (2007)_
Usefulness of tumor markers in predicting cancer

- Amoura et al. assessed values of CEA, CA-125, CA-19-9, CA-15-3 in 102 DM and PM patients
- All patients underwent H&P, CXR, Echo, CT, GI endoscopy, Gyn exam, mammogram
- Over 5 yrs of f/u, 10/102 developed a tumor
  - CA-125 and CA-19-9 at baseline was associated with an increased cancer risk (p=0.0001, OR 29.7, 95% CI 8.2-106.6)
  - Risk of cancer is high during the first year following increased CA-125/CA-19-9 levels

Amoura Z et al. Cancer Epidemiol Biomarkers Prev 14(5); 2005
Cancer Screening Recommendations

• A matter of debate
• Approach #1
  – Complete history and physical exam
  – Few routine blood and urine tests
  – Fecal occult blood
  – Chest x-ray
  – Additional tests in case of specific signs and symptoms
• Approach #2: Look really hard for cancer!
Aggressive Approach

- Routine laboratory evaluation (CBC, ESR, CMP, U/A), serum and urine immunofixation, tumor markers (CA-125 and CEA)
- Chest/abdomen/pelvis CT
- Women: Pap smear, pelvic exam, transvaginal U/S, mammogram
- Men: Digital rectal exam, PSA (over 50 years of age)
- Colonoscopy in older adults
- Screen yearly for up to 5 years
- Select patients (e.g., refractory to treatment): PET scan
Why do some patients have myositis and cancer?
Antibodies vs. Autoantibodies

Antigens vs. Autoantigens

Antibody – circulates in blood
(anti-hepatitis B)

Antigen – foreign body
(hepatitis B virus)

Autoantibody – circulates in blood
(anti-Jo1)

Autoantigen – found in patient tissues
(histidyl-tRNA synthetase)
Myositis autoantigen expression high in myositis muscle

Normal muscle

Polymyositis muscle

Jo-1 staining

Casciola-Rosen L et al. J Exp Med 201(4); 2005
Three observations about autoantigen levels

- An example: The Mi-2 autoantigen
  1. Expression increased 10-fold in DM muscle compared to control muscle
  2. Expression increased >10 fold in regenerating mouse muscle (unpublished observation)
  3. Expression increased 53-fold in breast tumors and 11-fold in lung tumors compared to normal breast and lung tissues

Growing tumors express high levels of myositis autoantigens

Immune response generated against cancer cells is redirected to regenerating muscle cells
Muscle-specific maintenance of immune response

Regenerating cells express Ag, high MHC class I

Immune response generated vs antigens expressed in regenerating cells, generating more damage
Possible Outcomes of Immune Response Against Tumor

Immune response against autoantigens in tumor

Muscle damaged, “myositis” autoantigens expressed, and immune response redirected to muscle

Genetic predisposition + Damage: virus toxins (statins) injury

Tumor eradicated

Tumor escapes and grows

Tumor eradicated – but myositis initiated

Tumor remains and myositis initiated
Summary

• Both DM and PM patients are at risk for developing cancer
• Cancer risk persists long after the diagnosis
• Appropriate cancer screening is controversial
• Perhaps autoantibody status can help guide screening strategies
• The cross-expression of similar antigens in tumors and regenerating muscle may help explain the relation of cancer to myositis