PARANEOPLASTIC SYNDROMES: PAST, PRESENT AND DIVINING THE FUTURE

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DISCLOSURE

No financial or other relevant conflicts of interest

Off-label discussion of therapy
Overview-2015

- 1.3 million people from all 50 states and 140 countries came to Mayo Clinic for care.
- Staff physicians and scientists: 4,500
- Residents, fellows and others: 2,400
- Allied health staff (clinic and hospital): 57,100
- Total: 64,000
Patient care-
• Total clinic patients: 1,318,300
• Hospital admissions: 128,000
• Hospital days of patient care: 641,000

Research-
• Physicians and medical scientists: 575
• Allied health personnel: 3,392
Research activity-2015

- New human research studies approved by Institutional Review Board: 2,723
- Active human research studies: 11,028
- Research publications and review articles in peer-reviewed journals: 7,305
- Education and Research funding: $946M
- Government, foundations and industry: $440M
- Mayo Clinic funds and benefactor gifts: $506M
Education-

• Mayo trains doctors in 273 residency and fellowship programs, representing virtually all medical specialties.

• Enrollment: 1,696
2ND ANNUAL ALAN COOPER EPIDERM LECTURE

• Distinguished Mayo alumnus
• Exceptional physician, dermatologist and clinician
• Cherished colleague, mentor and friend
• Husband, father (and grandfather!) extraordinaire
• Golf partner, racounteur, humorist
• And... so much more!
PARANEOPlastic Syndromes

Introduction

• Among the most fascinating disease associations of the early era of clinical as well as 21st century medicine

• Presentations range from the obvious to obscure...some of the most challenging and elusive primary tumors and cutaneous pathologies

• Breadth of clinical presentations and associations present dilemmas in further investigating and uncovering the underlying tumor.
PARANEOPlastic SYNDROMES
Definitions

• Hormonal, neurological, hematological, and other clinical and biochemical disturbances associated with malignant neoplasms but not directly related to invasion by the primary tumor or its metastases.
PARANEOPlastic SYNDromes

Definitions

• *Hormonal, neurological, hematological*, and other clinical and biochemical disturbances associated with malignant neoplasms but not directly related to invasion by the primary tumor or its metastases.

• Neoplasia (paraneoplasia) ≠ malignancy. In selected cases, a non-malignant tumor growth is associated with the disorder.

• What’s missing here?
PARANEOPLASTIC SYNDROMES

Definition

- paraneoplastic syndrome (par“ah-ne“o-plas´tik) a collective term for disorders arising from metabolic effects of cancer on tissues remote from the tumor; such disorders may, for example, appear as primary endocrine, hematologic, or neuromuscular disorders. *Dorland’s*

- **NOTE! No mention of skin or cutaneous manifestations!**
PARANEoplastiC SYNDROMES
A Brief History

• Armand Trousseau, M.D. (1801-1867)
  Birth: Tours and career in Paris

• Trousseau(‘s) syndrome or sign

• 1865-- migratory thrombophlebitis ("phlegmasia alba dolens")

• Gastric and hepatobiliary malignancy (esp. mucin-secreting adenoCA) Uro-gynecologic, lymphoma, brain, etc

• Approximately 50% of cases are malignancy related. Hypercoaguable state-coag factors, platelets, vasculature

• Diagnosed his own (occult) gastric CA
  “I am lost, a phlegmasia that showed itself last night leaves no doubt about the nature of my affliction” 1-1-1867

Soubiran Presse Med 1967
PARANEOPLASTIC SYNDROMES
A Brief History

• Prof. Jan Waldenström (1906-1996) Born: Stockholm, career Malmö

• Macroglobulinemia, paraproteins, porphyrias and carcinoid syndrome

• Monoclonal vs polyclonal gammopathies

• Later career interested in Paraneoplasia as "biological signals in the diagnosis of cancer"
PARANEOPLASTIC SYNDROMES
A Brief History

“Experiences from a lifetime in clinical medicine and in biochemical research… to combine bench and bedside” JGW
PARANEOPLASTIC SYNDROMES
The Dermatologic Perspective!

- Pollitzer and Janowsky, 1890. Darier, 1893. Acanthosis Nigricans
- Pollitzer, Unna et al 1891. Florid Cutaneous Papillomatosis (Named in 1978, Schwartz and Burgess)
- Gougerot and Rupp 1922 (Bazex, 1965) Acrokeratosis Paraneoplastica (Bazex syndrome)
- Becker, Rothman et al 1942. Necrolytic Migratory Erythema
- Sweet, 1964. Acute Febrile Neutrophilic Dermatosis
PARANEOPLASTIC SYNDROMES
Dermatologic Pioneers

• Helen(e) Ollendorf Curth (1899-1982) Born: Breslau. Died: NYC

• Benign and malignant forms of acanthosis nigricans and other cutaneous signs of cancer

• Many other genetic and epithelial syndromic disorders described and investigated (Buschke-Ollendorf syndrome)

• Defined the requirements for Paraneoplastic Syndromes (Koch’s postulates for disease causality)

Burgdorf, Scholz JAAD 51: 84, 2004
PARANEOPLASTIC SYNDROMES
Curth “Postulates”

• Malignancy and syndrome must appear at the same time, and their clinical courses should not significantly differ.

• Remote cutaneous manifestations should be specific to the tumor causing them.

• Paraneoplastic syndromes should be uncommon relative to the prevalence of the cancer.

• The paraneoplastic syndromes and the cancer should be demonstrably associated.

• A genetic association exists between the malignancy and a specific cutaneous disease.

PARANEOPlastic SYNDROMES
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PARANEOPLASTIC SYNDROMES
The Literature

• Pubmed search: 08-16-2016

• Cumulative Citations:
  “Paraneoplastic” 11849
  “Paraneoplastic syndrome” 1910
  “Paraneoplastic” skin 1506
  “Paraneoplastic” neurologic 715
  “Paraneoplastic” brain 1479
  “Paraneoplastic” endocrine 1673
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  “Paraneoplastic” blood 2660
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Neurological paraneoplastic disorders are a group of rare degenerative diseases linked to the body's immune system response to cancer. Symptoms include increasing difficulty with walking, balance, and speech, severe dizziness, loss of small motor skills, mental changes, and other neurological problems. The symptoms, which can vary from patient to patient, may precede the discovery of cancer by months or even years and patients may initially be misdiagnosed as suffering from a stroke, alcoholism, Parkinson's, and other diseases.

If you or a loved one has been diagnosed with a paraneoplastic disorder, you have found the right place. This web site pulls together resources and information from a variety of sources to help you better understand what paraneoplastic disorders are, the treatment options available, and what lies ahead. Additionally, you may wish to join our Email discussion group for people affected by neurological paraneoplastic disorders.

DISCLAIMER: The information on this website is not intended as a substitute for professional medical help or advice. The information has not been written or prepared by a medical doctor, although medical references were consulted in its preparation. This site is intended to be used only as an aid in understanding current medical knowledge. A physician should always be consulted for any health problem or medical condition.
PARANEOPLASTIC SYNDROMES
Classification Schemes

• By organ system: Cutaneous/mucosal, neurologic, hematologic, endocrine, etc.

• By mechanism or mediating factors

• Clinically—Cutaneous/mucosal
  • Papulo-squamous lesions
  • Erythematous lesions
  • Vascular lesions
  • Bullous lesions
  • Miscellaneous lesions
PARNEOPLASTIC SYNDROMES
The Clinical Challenges

- **Detecting** the subtle, early manifestations developing in skin and oral cavity
- **Recognizing** the potential link between the new skin signs/symptoms and underlying tumor or neoplasia
- **Selecting** diagnostic tools to identify the tumor/neoplasia
- **Managing** the cutaneous manifestations
- **Eliminating** the primary neoplastic cause
PARANEOPLASTIC SYNDROMES
Skin ...and Much, Much More!

• Muco-Cutaneous (Dermatologic) ≈ Neurologic
  Hematologic > Endocrine> Musculoskeletal,
  Renal, GI, Lung, Cardiac, etc.

• Pathologic targeting of one or more organ
  systems

• Understanding mechanisms of paraneoplastic
  response.

• The challenge: to not only understand the
disease, but also provide accurate diagnosis
and effective treatment
PARANEOPLASTIC SYNDROMES
Papulosquamous Conditions

- Acanthosis nigricans
- Acquired ichthyosis
- Acrokeratosis neoplastica
  Bazex syndrome
- Florid cutaneous papillomatosis
- Palmoplanta keratoderma
- Pityriasis rotunda
- Sign of Leser-Trélat
- Tripe palms
  Acanthosis palmaris
- Extramammary Paget

Nguyen et al Paraneoplastic Diseases eMedicine 9-18-2012 (updated)
PARANEOPLASTIC SYNDROMES

• Skin…that which is before you and your eye can see! (Goethe anglicized)

• The power of careful, critical and astute observation

• Apply your talents and curiosity to drive you, your practice and your career in dermatology!

• Patience and reflective follow-up often provides you wisdom when the present (vis à vis the future) leaves you with unanswered questions
PARANEOPLASTIC SYNDROMES
An Index Case Study

• 54 y/o M. Sudden, 3 mo. onset of multiple seborrheic keratoses
• Exam: acanthosis nigricans and mult. acrochordons
• Irregular dark brown (10x17mm) lesion left lower back..bx: SSM
• GI tract-endoscopy and contrast studies…benign polyps, no malignancy
• Immunochemistry exam of skin specimens and several urine collections
• WLE melanoma…clinical exam 5 mo later. Marked improvement of AN and improved seb kers and skin tags

NEJM 1987; 317: 1582-87
PARANEOPLASTIC SYNDROMES
AN, SK and Skin Tag Index Case

• Detected marked increase in urinary excretion of transforming growth factor-α (TGFα) by Western blot that decreased dramatically within 2 wks and remained undetectable at 5 mo following removal of the melanoma of the back.

Chance (and opportunity) favors the prepared mind!
PARANEOPLASTIC SYNDROMES
What’s New?

• New (re-discovered) associations, particularly granulomatous- and pigmentation- associated conditions

• New approaches and diagnostic algorithms to identify underlying neoplasia/tumor

• New mechanisms being characterized to understand disease causes and possibly harnessing pathobiology of disease for therapy.
PARANEOPLASTIC SYNDROMES
Disease Mechanisms

• **Trophic** -- Growth factors, cytokines or small molecules

• **Toxic** -- Cell destructive mediators, uncontrolled necrosis or apoptosis

• **Immunologic** -- Humoral or cell-mediated, innate or adaptive immunity

*Bhat and Steinman* Neuron 64:123, 2009
PARANEOPlastic SYNDROMES
Neurological Associations

• From 1960’s onwards, immune mediated peripheral and brain disorders associated with tumors as well as autoimmune neural diseases

• Classics: Myasthenia gravis (thymoma) and Lambert-Eaton Myasthenic Syndrome (LEMS) (SCLC >50%)

• Targeting cerebral cortex, diencephalon, basal ganglia, cerebellum, brainstem, spinal cord, peripheral nerve and ganglia, neuromuscular junction and muscle
PARANEOPlastic Syndromes
Neurological Associations

• Dr Edward Lambert-neurophysiologist and EMG pioneer at Mayo Clinic.

• Syndrome recognized and reported at the Mayo Clinic by Drs. Lambert, Eaton and Rooke in 1956

• By 1972, the association with autoimmunity and malignancy established

• 1990’s research demonstrated the link with antibodies against P/Q-type voltage-gated calcium channels (pre-synaptic membrane)
PARANEOPLASTIC SYNDROMES
Neurological “Associations”

• Dr Ed Lambert, “father of EMG” (1915-2003)

• Dr Vanda Lennon, Professor of Neurology and Immunology, Mayo Clinic. Australian native, Sydney University Medical School, PhD-University of Melbourne and pioneering neuro-immunologist

• Described and characterized many autoimmune and paraneoplastic neurological syndromes and laboratory screening panels.

• Partners in marriage and research for many years
PARANEOPLASTIC SYNDROMES
Neurological Associations

• Neuroimmunology section-Mayo Clinic

• Significant advances in better diagnostic and screening tests, biomarkers and therapeutic advances for Neurologic PNS

• Advancing understanding of mechanisms targeting brain, peripheral nerve and muscle

• Model to understand mechanisms and targeting of skin in paraneoplasia
PARANEOPLASTIC SYNDROMES
Mayo-Arizona State University

The Biodesign Institute
PARANEOPLASTIC SYNDROMES
Mayo-Arizona State University
Welcome to the Center for Personalized Diagnostics

The mission of the Virginia G. Piper Center for Personalized Diagnostics is to drive the discovery and development of biomarkers for the early detection of diseases. With better disease detection and earlier treatment, we strive to have a profound impact on decreasing mortality caused by various diseases including cancer and autoimmune diseases. Towards this end, our center and its 10 research faculty are driven by innovation and technology development, creating new tools that foster biomarker discovery. In particular, we have developed and continue to improve the NAPPA protein arrays and to couple the NAPPA technology with other technologies to better understand disease. Besides creating tools and technology for use within the center, we also make these tools available to facilitate research projects in the wider research community. Through the plasmid repository, sequencing services and our most recent effort with the NAPPA protein array core, we have provided the tools to accelerate research in hundreds of laboratories around the world.
## Paraneoplastic Syndromes

### Mayo-Arizona State University

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<th>NAPPA</th>
<th>NAPPA Technology Overview</th>
<th>Epitope Mapping</th>
<th>High Density Arrays</th>
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*Welcome to the Mayo-Arizona State University Paraneoplastic Syndromes project. The mission is to research diseases related to cancer and develop tools that can be used in conjunction with other treatments to facilitate research on paraneoplastic syndromes.*
### PARANEOPlastic SYNDromes

**Mayo-Arizona State University**

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Immunosignature system for diagnosis of cancer

Phillip Stafford, Zbigniew Cichacz, Neal W. Woodbury, and Stephen Albert Johnston

Center for Innovations in Medicine, The Biodesign Institute, Arizona State University, Tempe, AZ 85287-5901

Edited by Philippa Marrack, Howard Hughes Medical Institute, National Jewish Health, Denver, CO, and approved June 23, 2014 (received for review June 19, 2014)
PARANEOPlastic SYNDROMES
Mayo-ASU Biodesign

PARANEOPLASTIC SYNDROMES
Mayo-ASU Biodesign

PARANEOPLASTIC SYNDROMES
Blistering Skin Disease

• Paraneoplastic pemphigus (PNP)-Paraneoplastic Autoimmune multi-organ syndrome (PAMS)

• Described by Anhalt et al, 1990. A more broad, encompassing term for non-acantholytic cases, PAMS (Grando et al, 2001)

• Disease spectrum ranging from acantholytic to BP-like, EM-like and lichenoid pathologies

• Strong association (>90%) with malignancy, esp. Castleman disease, lymphoma, CLL and thymoma
PARANEOPLASTIC SYNDROMES
PNP-PAMS

• Can be challenging both diagnostically and therapeutically.

• Range of treatment options, targeting malignancy along with immunosuppressive and/or immunodepletion

• Improved imaging strategies and diagnostic biomarkers
PARANEOPLASTIC SYNDROMES
PNP-PAMS
CT and 18F-FDG PET/CT (~90 and 10% cases, resp)

Both identified all solid tumors, but PET/CT facilitated staging and guided biopsies.

Value of IIF, rat bladder, ELISA and improved biomarker screening
PARANEOPLASTIC SYNDROMES
Disease Associations

- **Granulomatous paraneoplastic syndromes**
  - Multicentric reticulohistiocytosis
  - Granuloma annulare-like, interstitial granulomatous dermatitis, necrotizing-caseous granulomas
  - Miscellaneous histiocytic-granulomatous disorders
PARANEOPLASTIC SYNDROMES
Granulomatous PNS

- Multicentric reticulo-histiocytosis
- Progressive cutaneous and erosive joint and arthritis findings
- Malignancy associated, approx. one-third of cases
- Lymphoma, adenocarcinomas, SCC lung
- MTX, TNF alpha antagonists
PARANEOPlastic SYNdromes

Granulomatous PNS

- 71y/o male, weakness and 60# wgt loss.
- 2 year history of progressive erythematous papules, coalescing to plaques over trunk and extremities
- Hgb11gm/dl, monocytosis 42%
- Biopsy: interstitial granulomatous dermatitis
- Bone marrow: Myelodysplastic Syndrome Within 2 months, developed AML, pneumonia and died.

Balin et al, Arch Derm, 2011
PARANEOPLASTIC SYNDROMES
Granulomatous PNS
PARANEOPLASTIC SYNDROMES
Granulomatous PNS

- 62 y/o male, B-CLL 5 years
- Fludaribine treatment. Remission, developed hypogammaglobulinemia
- IVIg x several yrs
- Generalize, widespread non-infectious, caseating granulomas
- Infliximab therapy with clearance. Development of leukemia cutis that cleared w/ PUVA

Podjacek, Pittelkow. Med Derm Soc, Miami 3-2010
PARANEOPLASTIC SYNDROMES
Granulomatous PNS

Post-infliximab
PARANEOPlastic SYNDROMES
Melanocytic PNS-BDUMP

- Bilateral diffuse uveal melanocytosis (BDUMP)
- Uniformly malignancy related
- 64 y/o woman, uterine carcinoma and decreased vision over several mo.
- Plasmapheresis. Biologic analysis of plasma factors

Duong et al AJO 2006  Saito et al AJO 2005
PARANEOPLASTIC SYNDROMES
Melanocytic PNS-BDUMP

Miles et al. Retina, 2012
PARANEOPLASTIC SYNDROMES
Imaging Advances

• CT, MRI, PET, PET/CT, PET/MRI

• Indications and yields for dx of unknown primary malignancies

Podoloff et al JNCCN 7: Suppl 2, 2009
PARANEOPLASTIC SYNDROMES

- 84y/o male. 2 yr hx of pruritus and urticarial eruption
- Extensive previous evals at regional VA hospital.
- w/u neg except eosinophilia and eosinophilic dermatitis.
- ANA >12, +anti-dsDNA. Periph. blood eosinophilia. DIF and IIF neg. Bxs: Eosinophilic dermatitis and LCV (ankle)
PARANEOPLASTIC SYNDROMES

Prior PET scans for comparison: None.

INDICATION: Evaluation of paraneoplastic syndrome. Possible vasculitis.

FINDINGS: FDG PET scan images with fused CT images show mild increased FDG uptake within hilar nodes bilaterally with the nodes on the left being calcified. Calcified anteromedial node also has mild increased FDG uptake. Mild increased uptake is seen in the subclavian, external iliac and femoral vessels bilaterally. No increased FDG uptake however seen within the aorta. Diffuse increased FDG uptake throughout the enlarged prostate. This is more likely inflammatory but evaluation to exclude prostate carcinoma is recommended. There is prominent focal increased FDG uptake in the colon in the region of the hepatic flexure. This is likely normal physiologic uptake but a tumor mass cannot be completely excluded. Colonoscopy or CT colography may be helpful. The remainder of the images are normal.

Additional CT findings from the non-diagnostic, non-contrast CT: Extensive vascular calcifications including coronary. Tortuous aorta. Dilated thoracic aorta measuring 4.4 cm. Cholecystectomy.

IMPRESSION: No definite findings for malignancy. Diffuse FDG uptake in the prostate and focal tracer within the colon at the hepatic flexure can be seen with nonmalignant causes but malignancy cannot be completely excluded. FDG uptake within the subclavian, external iliac and femoral vessels is mild but suggests vascular inflammation.

• 14.77 mCi F-18 FDG
• Finger-stick blood glucose level at time of PET scan injection was 104 mg/dL.
• Electronically signed by:
Prior PET scans for comparison: None.

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FINDINGS: FDG PET scan images with fused CT images show mild increased FDG uptake within hilar nodes bilaterally with the nodes on the left being calcified. Calcified anteromediastinal node also has mild increased FDG uptake. Mild increased uptake is seen in the subclavian, external iliac and femoral vessels bilaterally. No increased FDG uptake however seen within the aorta. Diffuse increased FDG uptake throughout the enlarged prostate. This is more likely inflammatory but evaluation to exclude prostate carcinoma is recommended. There is prominent focal increased FDG uptake in the colon in the region of the hepatic flexure. This is likely normal physiologic uptake but a tumor mass cannot be completely excluded. Colonoscopy or CT colography may be helpful. The remainder of the images are normal.

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PARANEOPLASTIC SYNDROMES

DIAGNOSIS: Colon, right, hemicolecctomy: Tubulovillous adenoma with low grade dysplasia and focal high grade dysplasia, forming a mass (8.4 x 4.1 x 2.4 cm) in the ascending colon. All surgical resection margins are negative for tumor. Multiple (26) regional lymph nodes are negative for malignancy. The appendix is grossly unremarkable
PARANEOPLASTIC SYNDROMES
Imaging in Paraneoplasia (PNS)

- Despite many clinical indications in dermatology, no studies have been performed on the rates of detection for muco-cutaneous PNS.

- In neurologic PNS, presence of anti-neuronal antibodies and clinical suspicion of malignancy identified patients for PET/CT. Of 56 pts, PET/CT +ive in 22 (39%) and bx performed and positive in 10 pts (18%).

PARANEOPLASTIC SYNDROMES
Current PET Indications

• NCCN Task Force Report: Clinical Utility of PET in a Variety of Tumor Types

• National Oncologic PET registry (NOPR) (5-06)

• “Initial treatment strategy” and “Subsequent treatment strategy”

• ~41,000 scans (~34,000 pts)
  • 35% Initial staging
  • 36% restaging after treatment
  • 29% recurrence after treatment

Podoloff et al JNCCN 7:suppl. 2, 2009
PARANEOPLASTIC SYNDROMES
Current PET Indications

- Change in intended management in 38% of cases.
- Non-treatment to treatment -- 30%
- Treatment to non-treatment -- 8%
- “Imaging-adjusted impact” accounts for add. MRI or CT use

Podoloff et al JNCCN 7:suppl. 2, 2009
PARANEOPLASTIC SYNDROMES
Past, Present and Divining the Future

Closing Quotable Quotes

• “People like us, who believe in physics, know that the distinction between past, present, and future is only a stubbornly persistent illusion.” Albert Einstein

• “All life is an experiment. The more experiments (observations) you make, the better” Ralph Waldo Emerson
PARANEOPLASTIC SYNDROMES

Summary

• A wide-variety of muco-cutaneous PNS have been recognized over the past 150 years

• Dermatologic PNS represent a significant percent of all PNS, similar to neurologic PNS

• Skin biopsy and further imaging studies (PET, CT or PET/CT) should be part of the current work-up for suspected dermatologic PNS

• With newer, more sensitive imaging modalities and biomarkers earlier treatment may avert more advanced, complicated and worse prognosis cases of PNS
A man's friendships are one of the best measures of his worth.

Charles Darwin