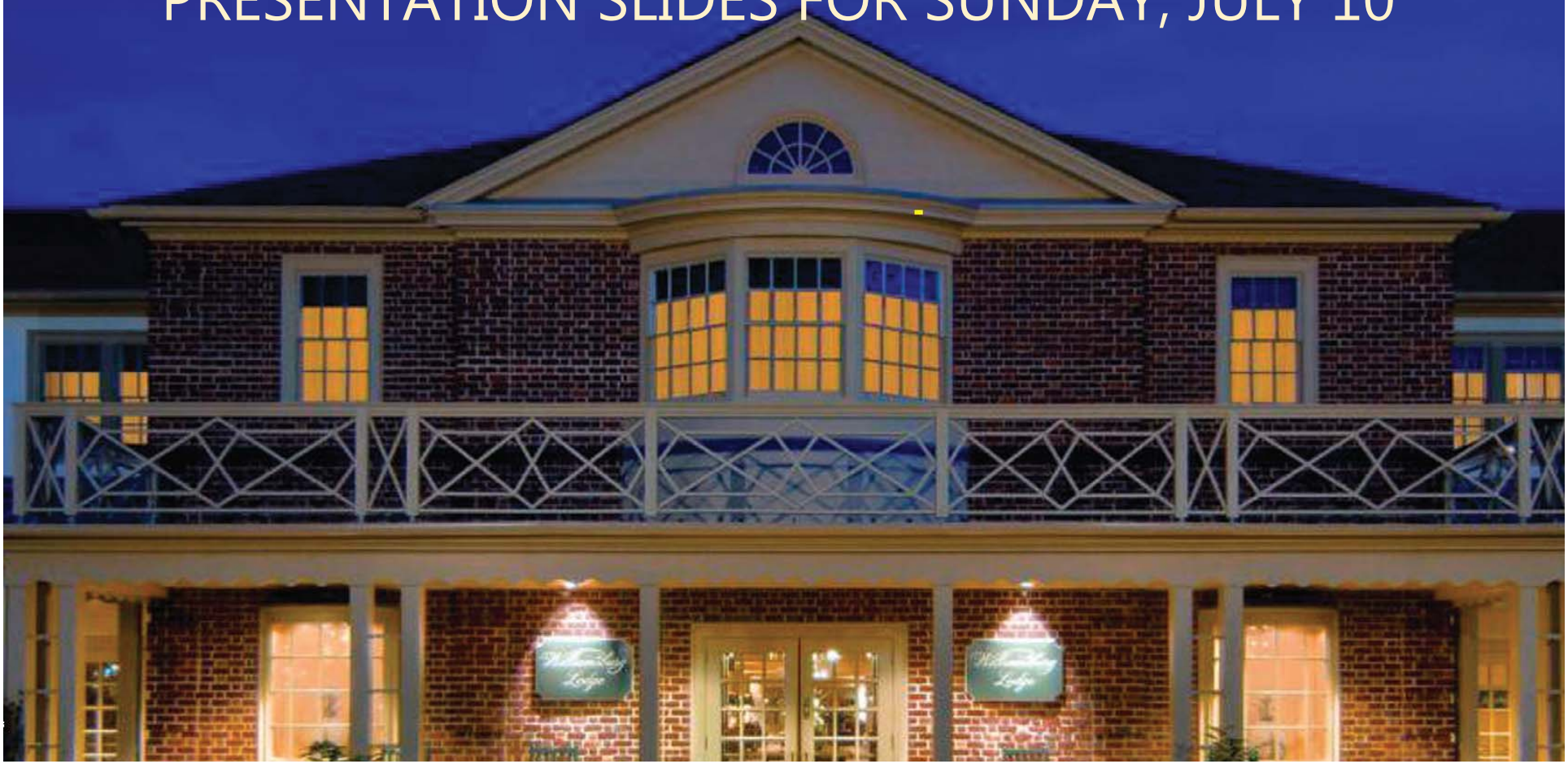
NORTH CAROLINA DERMATOLOGY ASSOCIATION

2016 Summer Meeting

PRESENTATION SLIDES FOR SUNDAY, JULY 10



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The Hidden Costs of Systemic Dermatologic Medications

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Disclosures

- No funding was received for this study
- The authors have no conflicts to disclose

Introduction

- Topical medications are a mainstay in the treatment of dermatologic diseases
- Systemic medications are often used to treat common, chronic, moderate-severe diseases:
  - Acne
  - Atopic dermatitis
  - Psoriasis
- Autoimmune and connective tissue disorders:
  - Dermatomyositis
  - Scleroderma
  - Lupus erythematosus

Introduction

- Changing environment of healthcare system
  - Complex interaction between insurance industry, drug companies, healthcare providers, and patients
  - Increases in the cost of laboratory testing and medications
  - Era with emphasis on innovation and cost-efficacy in clinical practice
  - Reduction of waste and duplicate test orders is essential to prudent clinical practice

Objectives

- The primary objectives of this study:
  - To develop treatment and monitoring paradigms for commonly used systemic medications
  - To determine the costs associated with long-term use of these medications

Methods

- 1 year treatment and monitoring paradigms:
  - Methotrexate
  - Cyclosporine
  - Mycophenolate mofetil
  - Azathioprine
  - Acitretin

Methods

- Expenses associated with treatment paradigms were determined from the third-payer perspective
- Expenses associated with physician visits and laboratory tests were determined using the mean U.S. reimbursement rates based on the 2016 Medicare physician reimbursement schedule and clinical laboratory fee schedule

Results

Methotrexate

- Dihidrofolate reductase inhibitor
- Immunomodulator used for the treatment of a wide range of inflammatory dermatologic conditions
- Once weekly dosing (IM, PO) with folic acid daily
- AEs: hepatotoxicity bone, marrow suppression, abortifacient

Results

- Monitoring schedule for methotrexate

Visit	**Studies**
Week 0	Urine pregnancy test, CBC, CMP
Week 2-3	CBC, CMP
Month 3	CBC, CMP
Month 6	CBC, CMP
Month 9	CBC, CMP
Month 12	CBC, CMP

Results

Cyclosporine

- Calcineurin inhibitor
- Used in psoriasis for acute flares or recalcitrant disease, atopic dermatitis, pyoderma gangrenosum
- Weight-based dosing, with maximum of 4-5 mg/kg/day recommended
- Best used on short term basis (< 6-12 months)
- AEs: Renal insufficiency, hypertension, electrolyte abnormalities

Results

- Monitoring schedule for cyclosporine

Visit	**Studies**
Week 0	Blood pressure, CBC, CMP, uric acid, K, Mg, lipid profile
Week 4	Blood pressure, CBC, CMP, uric acid, K, Mg, lipid profile
Week 8	Blood pressure, CBC, CMP, uric acid, K, Mg, lipid profile
Month 3 – 12 (each month)	Blood pressure, CBC, CMP, uric acid, K, Mg, lipid profile

Results

Mycophenolate mofetil

- Inhibitor of inosine monophosphate dehydrogenase, blocking DNA synthesis in T and B lymphocytes
- Used for autoimmune bullous diseases, atopic dermatitis, cutaneous lupus, pyoderma gangrenosum
- Dosing up to 3000 mg daily
- AEs: hepatotoxicity, hematologic abnormalities

Results

- Monitoring schedule for mycophenolate mofetil

Visit	**Studies**
Week 0	CBC, CMP
Week 2-3	CBC, CMP
Week 4	CBC, CMP
Month 3 – 12 (each month)	CBC, CMP

Results

Azathioprine

- Purine analogue that inhibits purine metabolism and cell division
- Used in psoriasis for acute flares or recalcitrant disease, atopic dermatitis, pyoderma gangrenosum
- Maximum of 2.5 mg/kg/day
- AEs: Renal insufficiency, pancytopenia, risk of malignancy, hypersensitivity reaction

Results

- Monitoring schedule for azathioprine

Visit	Studies
Week 0	CBC, CMP, hepatitis panel, HIV*, TST or IGRA*
Week 1	CBC, CMP
Week 3	CBC, CMP
Week 7	CBC, CMP
Month 6	CBC, CMP
Month 9	CBC, CMP
Month 12	CBC, CMP

*In high-risk groups

Results

Acitretin

- 2nd generation retinoid
- Used in psoriasis, disorders of keratinization
- Daily dosing 25-50 mg/day
- AEs: Teratogenicity, hyperlipidemia, hypertriglyceridemia, elevated liver function tests

Results

- Monitoring schedule for aceitretin

Visit	Studies
Week 0	CBC, CMP, lipid profile
Week 2-4	LFT, lipid profile
Week 6-8	LFT, lipid profile
Month 5	LFT, lipid profile
Month 8	LFT, lipid profile
Month 11	LFT, lipid profile

Results

Total calculated costs of 1-year treatment and monitoring paradigms

Drug	Cost of laboratory studies	Cost of office visits†	Cost of 1 year treatment
Methotrexate	$154.63	$421.74	$576.37
Cyclosporine	$727.48	$913.77	$1,641.25
Mycophenolate mofetil	$317.33	$913.77	$1,231.10
Azathioprine	$353.00	$492.03	$845.03
Acitretin	$170.36	$421.74	$592.10

†Based on R3: level 3 follow-up evaluation, CPT code 99213

Conclusion

- Treatment and monitoring paradigms were designed based on a combination of FDA and published consensus guidelines
- Cyclosporine was associated with the highest cost due to monitoring and return office visits, followed by mycophenolate mofetil
    - A large proportion of these costs were due to the high number of office visits required
- The lowest cost was observed with methotrexate and acitretin

Conclusion

- Additional work-up or follow-up studies in the event of abnormal laboratory values were not included in the analysis, and thus may underestimate the costs associated with real-life medication use
- There is a general lack of evidence-based guidelines for laboratory monitoring in many dermatologic systemic medications
- In this era of accountable care, an outcomes-based approach for laboratory medicine is necessary

Thank you!

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Multiple Cutaneous Leiomyomas and Reed's Syndrome

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7/10/16

Case Presentation

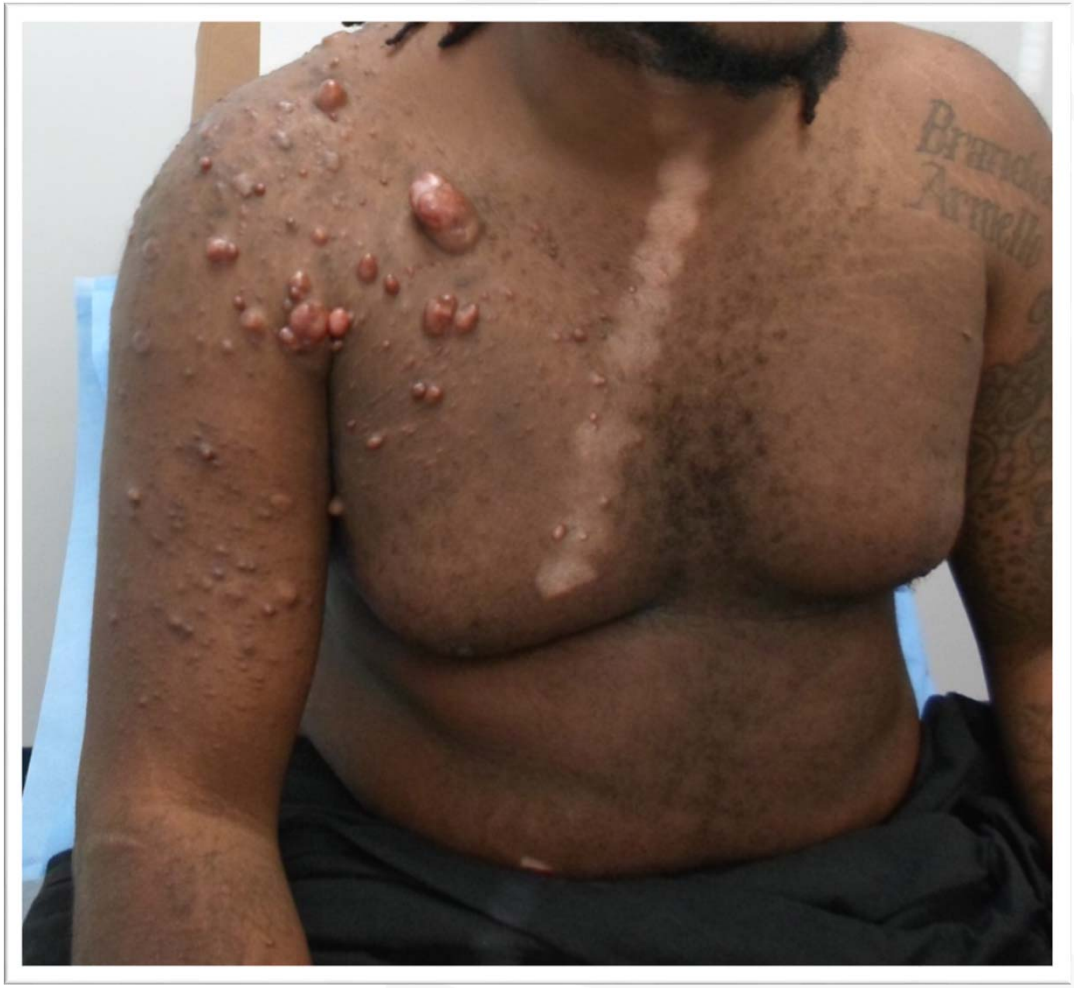
HPI: 25 year old male presents with a 5 year history of multiple lesions on his right shoulder and upper arm. They are painful when touched and occasionally pruritic. The lesions continue to grow and he continues to develop new lesions.

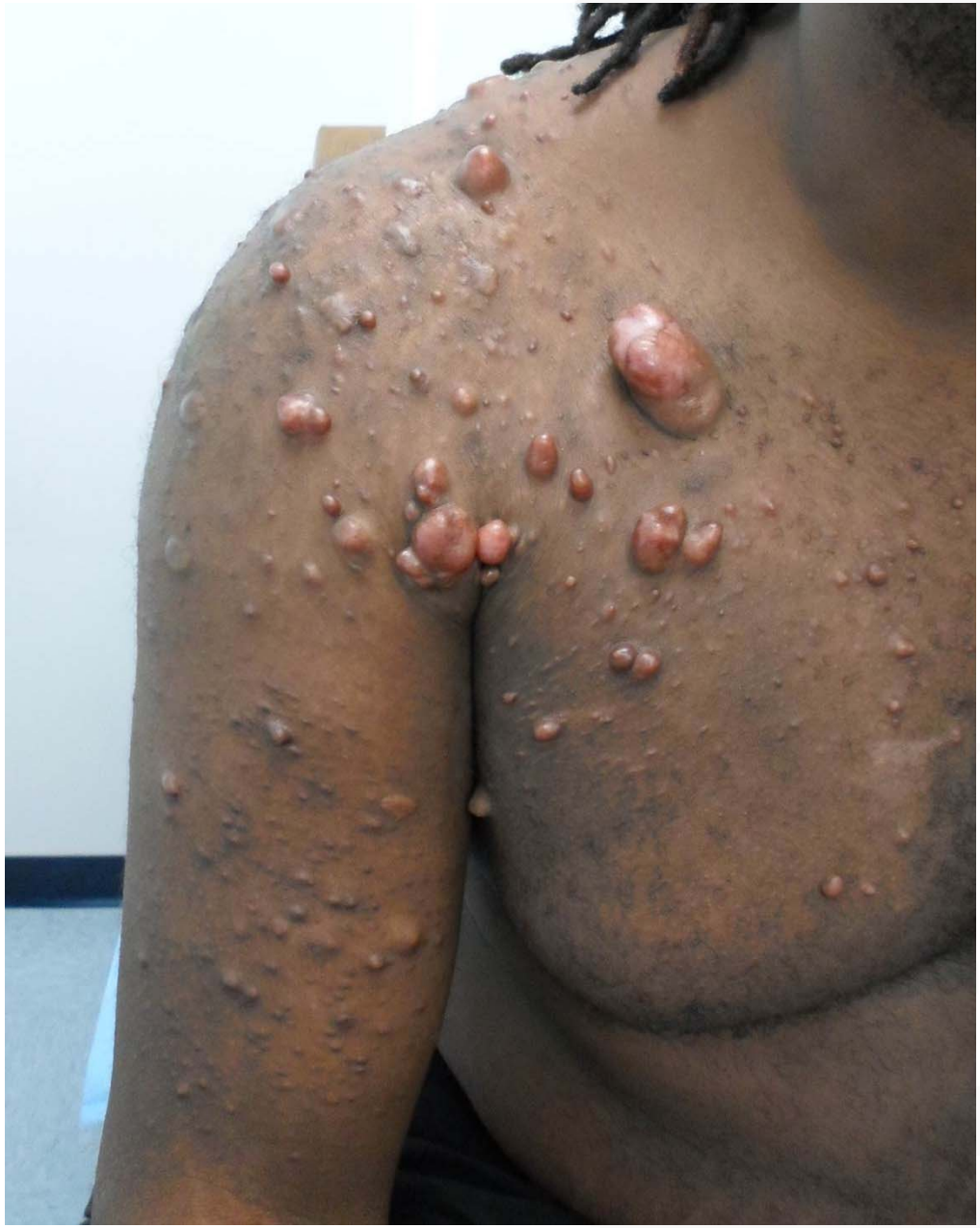
PMH: Otherwise healthy

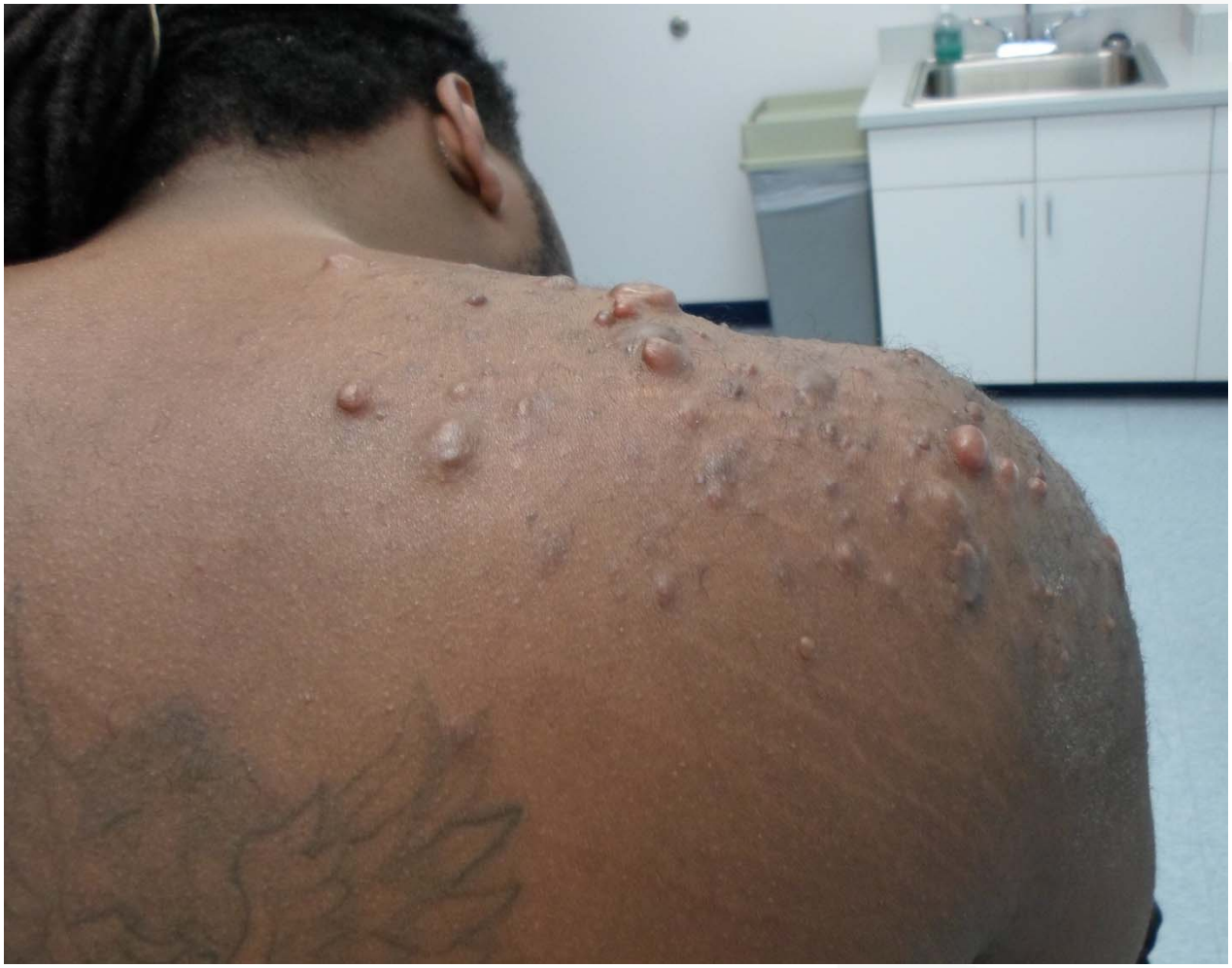
FH: No family members with similar findings.

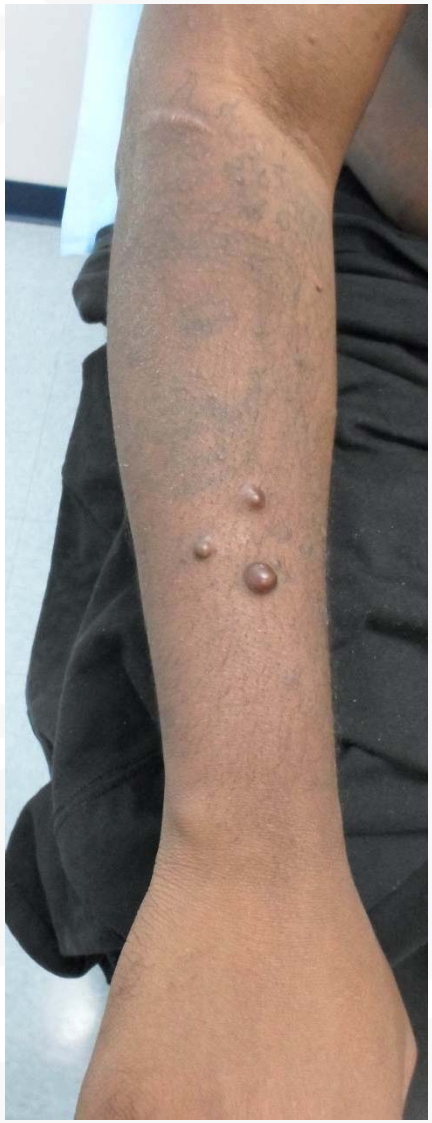
PE: Multiple 0.5 - 3 cm subcutaneous red to brown firm subcutaneous nodules in a clustered distribution over the right shoulder and upper arm

Our Patient

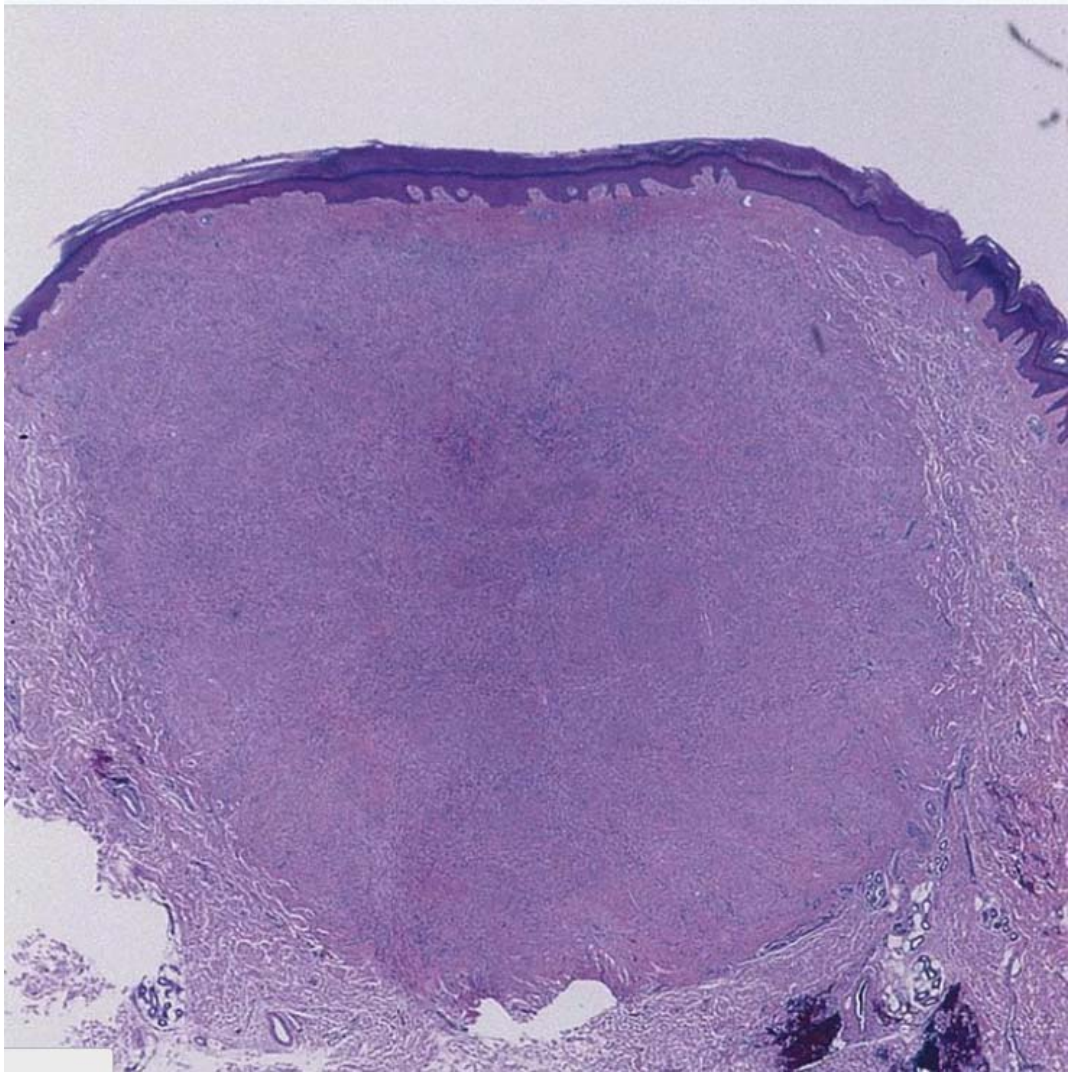






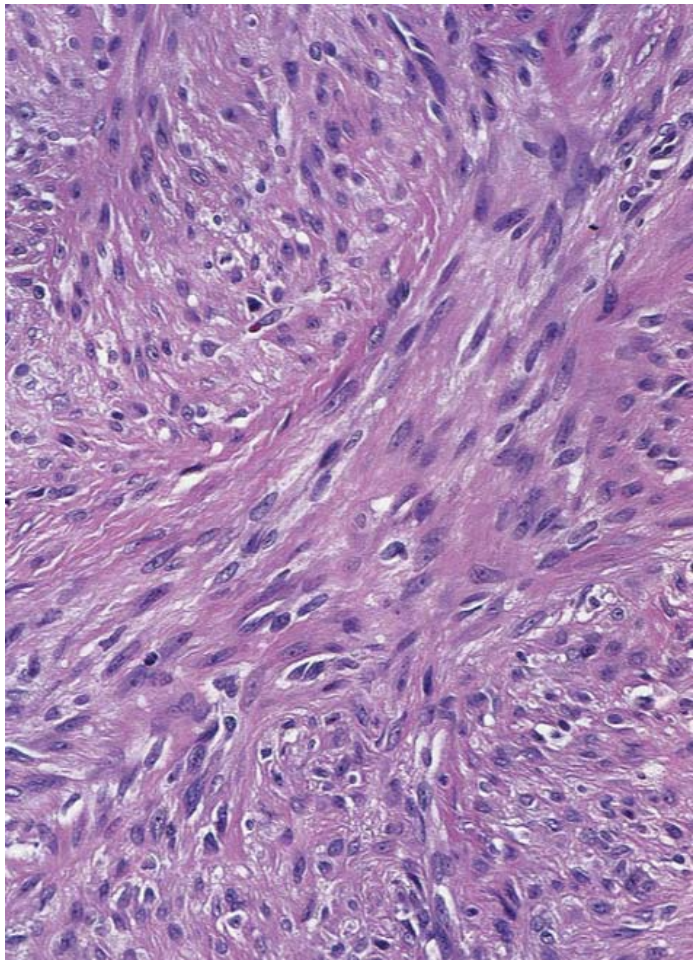


Pathology



Bolognia et al.

Pathology



Bolognia et al.

- **Myocytes:** Eosinophilic cytoplasm with blunted end and cigar- shaped nuclei
- **Stains:** Masson's trichrome stain, smooth muscle actin, desmin

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Background Information

Leiomyomas

- **Three types:**
  - **Piloleiomyomas** (arrector pili muscles)
  - Genital leiomyomas (dartoic, vulvar, or mammary smooth muscule)
  - Angioleiomyomas (dermal blood vessels)
- **Can be solitary or multiple**
- **Multiple can occur sporadically or can be associated with Reed's syndrome**

Background Information

- **Clinical Features Piloleiomyomas:**
  - Reddish-brown to skin-colored papules or nodules, normally 1-2 cm in size.
  - Multiple lesions are often clustered, linear, along Blashko's lines, or disseminated
  - Favor extremities and trunk (shoulder)
  - Associated with spontaneous or induced pain

Multiple Cutaneous and Uterine Leiomyomatosis Syndrome (Reed's Syndrome)

- Also known as Hereditary Leiomyomatosis and Renal Cancer Syndrome (HLRCC)
- AD, with variable penetrance
- Multiple germline mutations in the gene that encodes fumarate hydratase
- Mechanism unclear

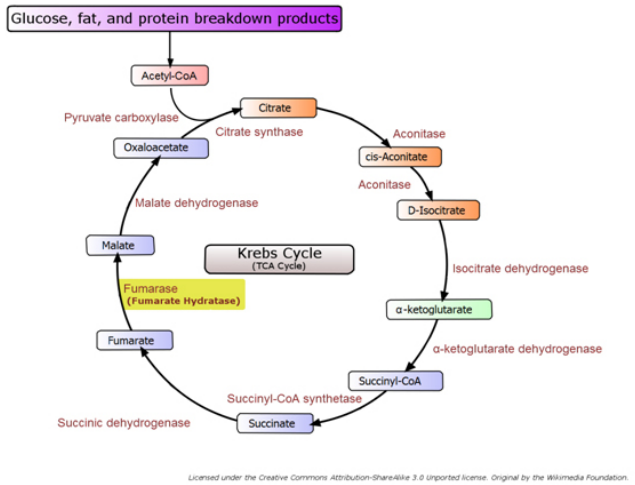

Figure 10 The Krebs Cycle

Reed's Syndrome

- **Cutaneous Leiomyomas:** Multiple painful grouped skin-colored to red-brown papules appear in the 2nd to 4th decade
- **Uterine Leiomyomas:** menorrhagia and pelvic pressure (>90% of affected women)
- **Renal Cell Cancer:** Early onset and aggressive type II papillary renal cell carcinoma (1-17% of affected patients).

Reed's Syndrome

- **Screening:**
  - Complete H&P
  - Abdominal and pelvic CT or MRI
  - Pelvic Exam in women
  - Genetic testing for mutations in FH gene
- **Patients with confirmed Reed's Syndrome:**
  - Yearly H&P
  - Yearly pelvic exam in women
  - MRI/CT yearly from the age of 8 years (Schmidt, et al. and Menko, et al.)
  - H&P and US of first-degree family members

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Treatment Options

- **Surgical Excision**
- **Triamcinolone Injections (Liu, et. al.)**
  - » 1 patient with multiple piloleiomyomas
  - » Weekly injections of Kenalog 20mg/ml compared to 0.9% NaCl x 3 weeks
  - » No pain or enlargement of treated lesions at 1 year follow up

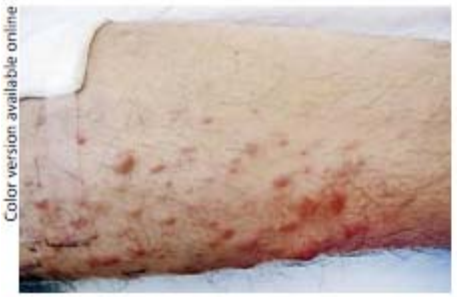


Fig. 1. Dusky red- or brownish red-coloured firm papules and nodules measuring 5–15 mm in diameter on the anterolateral side of the left lower limb.

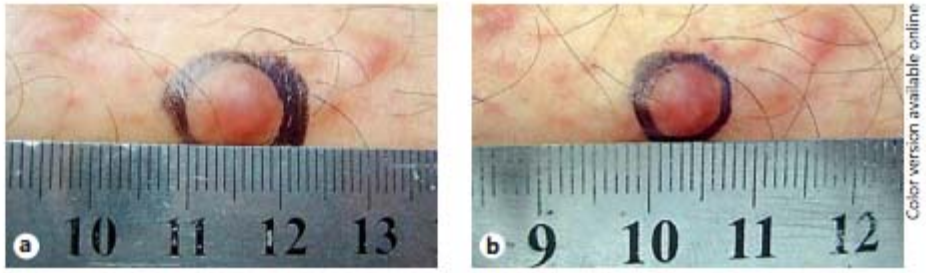
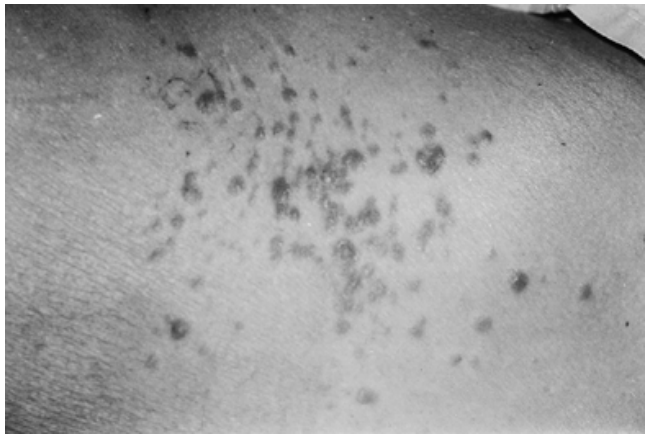


Fig. 3. Lesions before treatment (**a**) and 1 week after three treatment sessions (**b**).

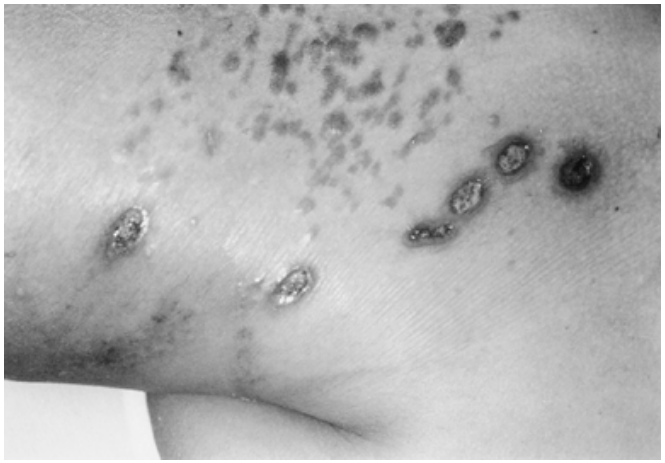
Treatment Options

- **Nifedipine (Biltz, et al.)**
  - 1 patient with disseminated lesions treated successfully for 3 years
- **Gabapentin (Alam, et al., Haugen, et al.)**
- **Botulinum Toxin (Sifaki, et al.)**
  - 1 patient with segmental piloleiomyomas
  - 200 units of BT-A total with 10-20 units per lesion and NaCl 0.9% used as placebo
  - Repeated every 3 months for 2 years with improvement in pain
- **CO2 Laser (Christenson, et al.)**
  - 1 patient with multiple piloleiomyomas
  - CO2 laser (10,600nm), 10W, 0.2cm spot size
  - No recurrence or pain at 9 month follow up

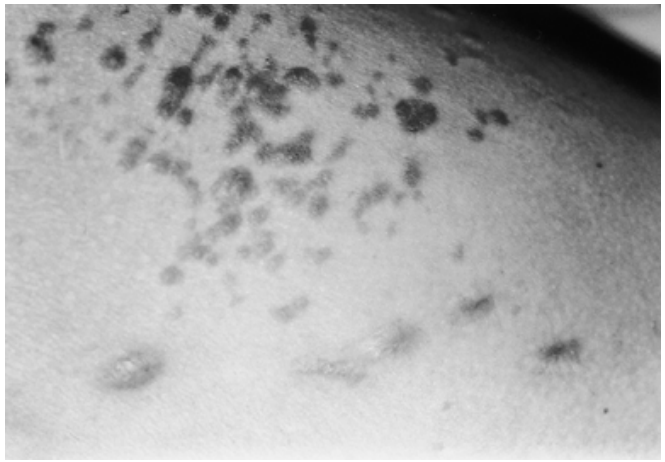
CO2 Laser (Christenson, et al.)



Prior to Treatment



2 weeks postoperatively



6 months postoperatively

Table 1. Summary of Treatment Methods and Outcomes for Symptomatic Cutaneous Leiomyomas (Christenson, et al.)

Treatment	Outcome
Nifedipine 30–90 mg/day	Initial benefit, then ineffective [1]
	No benefit [5]
Phenoxybenzamine 20–60 mg/day alone or in combination with nifedipine	Relief of pain [5,6]
Nitroglycerin alone or in combination with analgesics	Relief of pain [7]
	No benefit [5,13]
9% hyoscine hydrobromide	Delayed time to onset of pain
Liquid nitrogen	Delayed time to onset of pain
Methotrexate 50 mg IV weekly	No benefit [13]
Analgesics	Limited benefit [13]
Excision	Recurrence in 50%[11]
	Recurrence in 100%[6,13,16]

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One Case of MIDAS Syndrome

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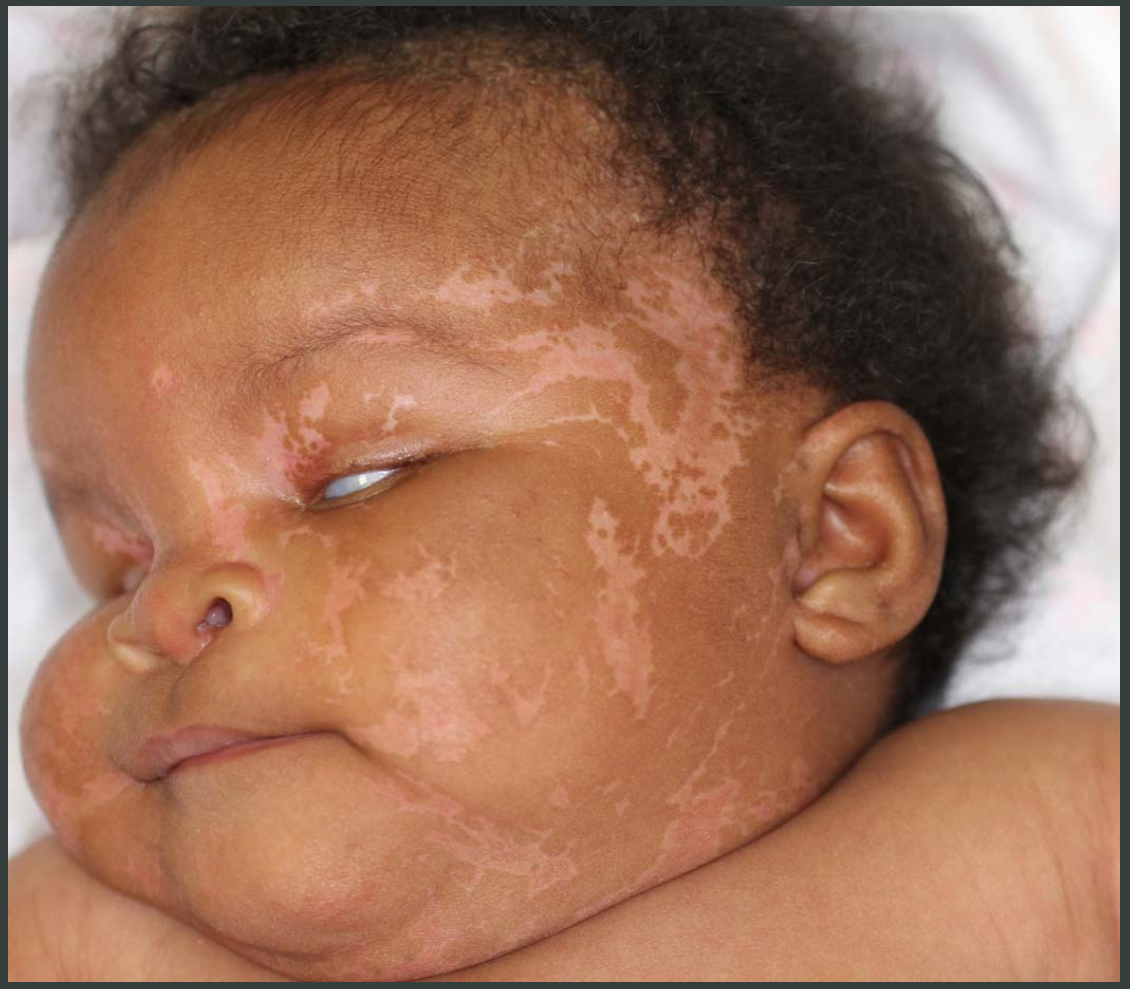
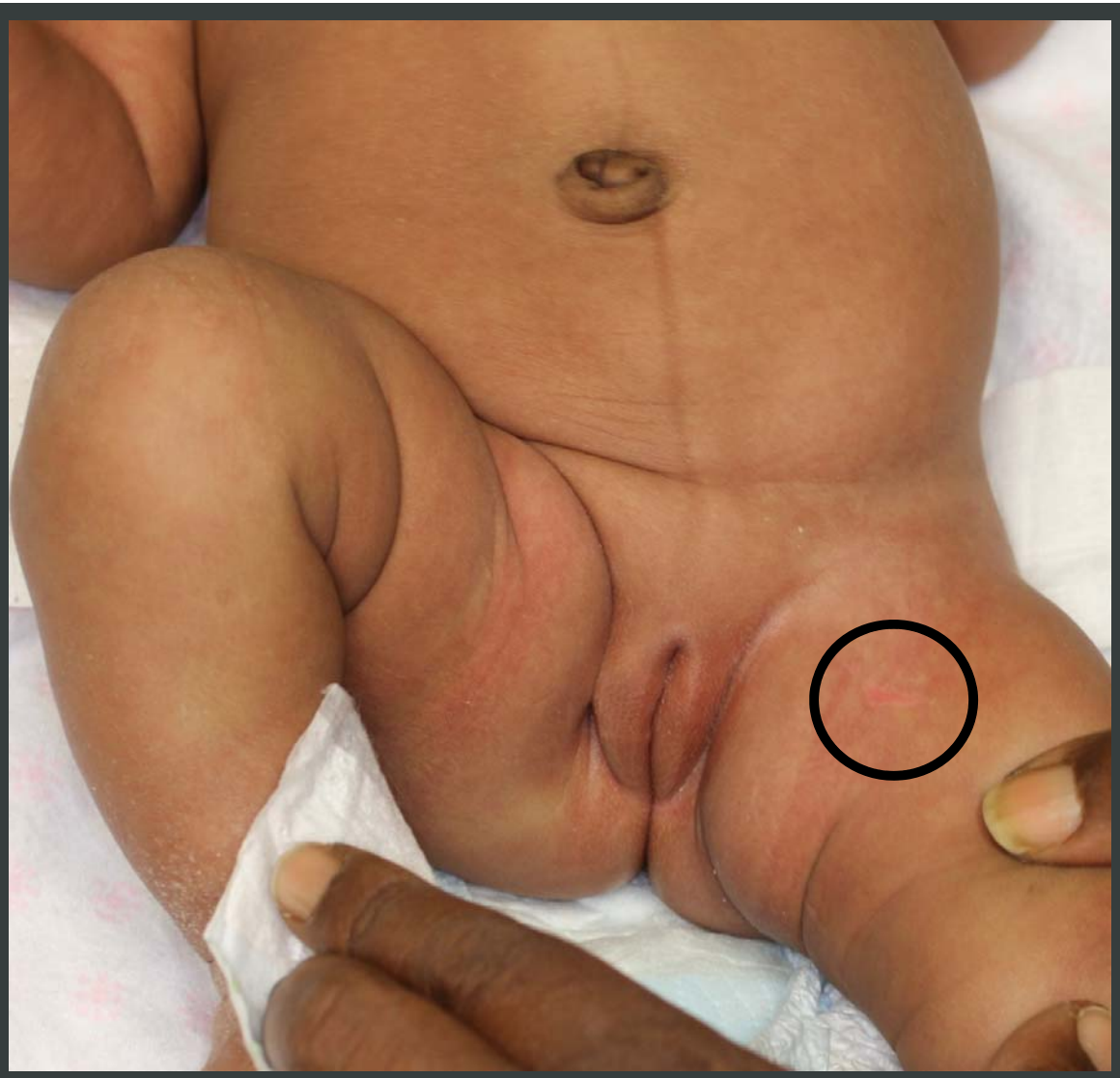
JULY 10, 2016

Clinical Case

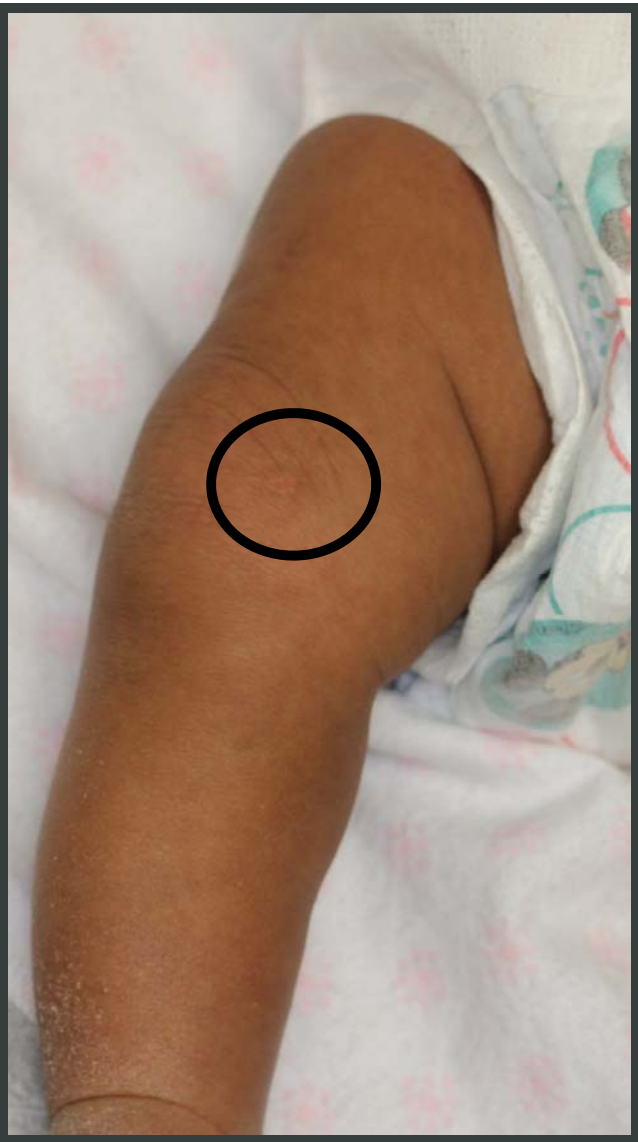
- 7 week old African American female presented with pink-hypopigmented linear macules and patches on face and neck that were noted at birth
- Prenatal workup revealed agenesis of corpus callosum, polyhydramnios, and IUGR
- Of note, patient has a half-sibling with congenital heart defect that required surgical intervention
- Mom declined further genetic testing at that time or a follow-up ultrasound
- Had many other documented congenital defects including microphthalmia, sclerocornea, and bilateral coloboma





Clinical Case

- Microarray genetics tested positive for Triple X syndrome which is felt to be an incidental finding
- Full skin exam at visit revealed a few more discrete pink, somewhat atrophic macules in groin and extremities
- Pt also noted to have large Mongolian spot on buttocks, lower back
- Differential diagnosis at time of visit included MIDAS syndrome and Hypomelanosis of Ito



MIDAS Syndrome

- Microphthalmia, Dermal Aplasia, Sclerocornea
- First described in 1988
- Also known as MLS
  Microphthalmia with Linear Skin defects
- X-linked dominant inheritance
- Male lethality in utero, though rare cases of males with 46XX, with Xp;Yp translocation have been reported
- Due to deletion or mutation of gene encoding mitochondrial holochrome C synthase (HCCS gene) located on Xp22

MIDAS Syndrome

- Clinical features include
  - Unilateral or bilateral microphthalmia
  - Linear, sometimes jagged skin defects usually on face, neck that heal with scarring and/or hyperpigmentation
  - Sclerocornea
  - Corneal opacities
  - Neurological defects
    - Agenesis of corpus callosum, hydrocephalus, mental retardation, infantile seizures
  - Congenital heart defects
  - Short stature
  - Hearing loss
  - Genitourinary defects

Contiguous Gene Syndromes

- Caused by large deletions affecting 2 or more adjacent genes
- Many genodermatoses and their syndromic associations actually represent this phenomenon
- MIDAS Syndrome often seen along with Aicardi syndrome
- Aicardi Syndrome
  - Agenesis of the corpus callosum plus chorioretinal abnormalities
- Another example is Ehlers-Danlos syndrome with congenital adrenal hyperplasia

Differential Diagnosis: Hypomelanosis of Ito

- Also know as Linear Nevoid Hypopigmentation
- A descriptive term for cutaneous findings in those with pigmentary mosaicism
- Present at birth, shortly thereafter, or during early childhood
- Hypopigmented streaks and whorls in Blaschkoid distribution often on trunk or limbs
- Approximately 30% have defects in CNS, eye, or musculoskeletal system
- Other cutaneous findings include lentigenes, hypertrichosis, or alopecia

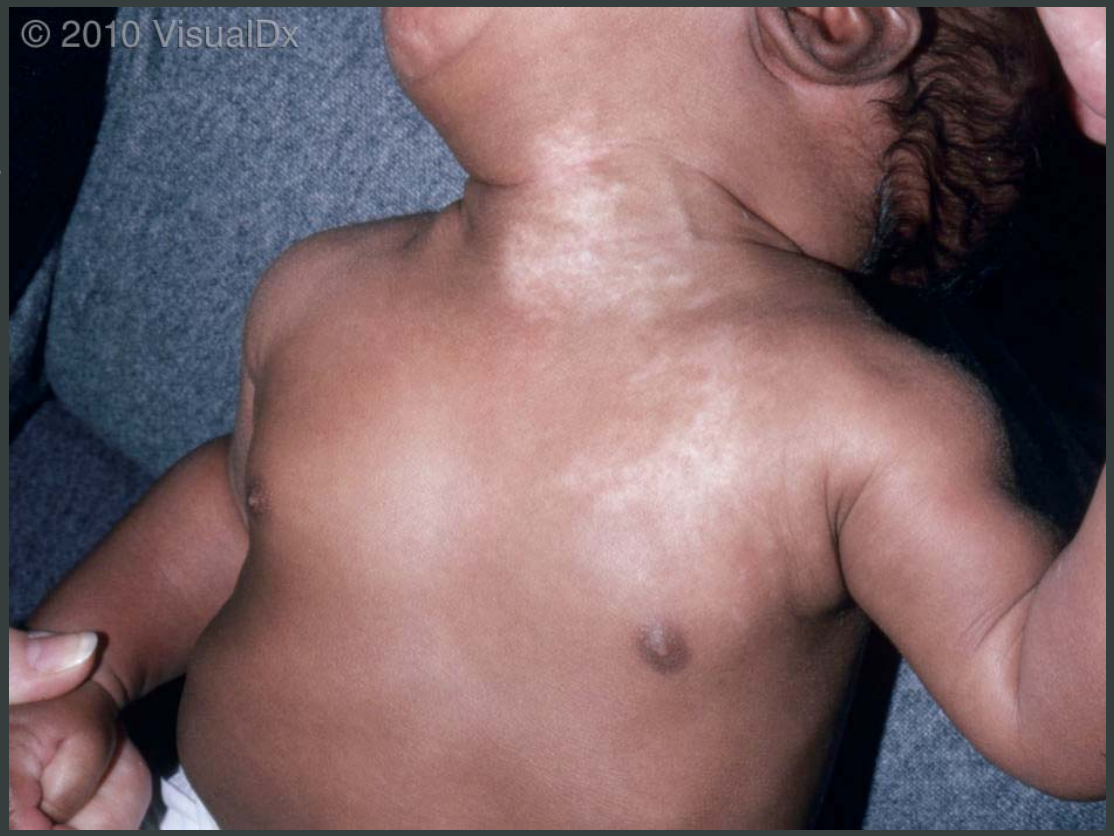


Image courtesy of Visual Dx

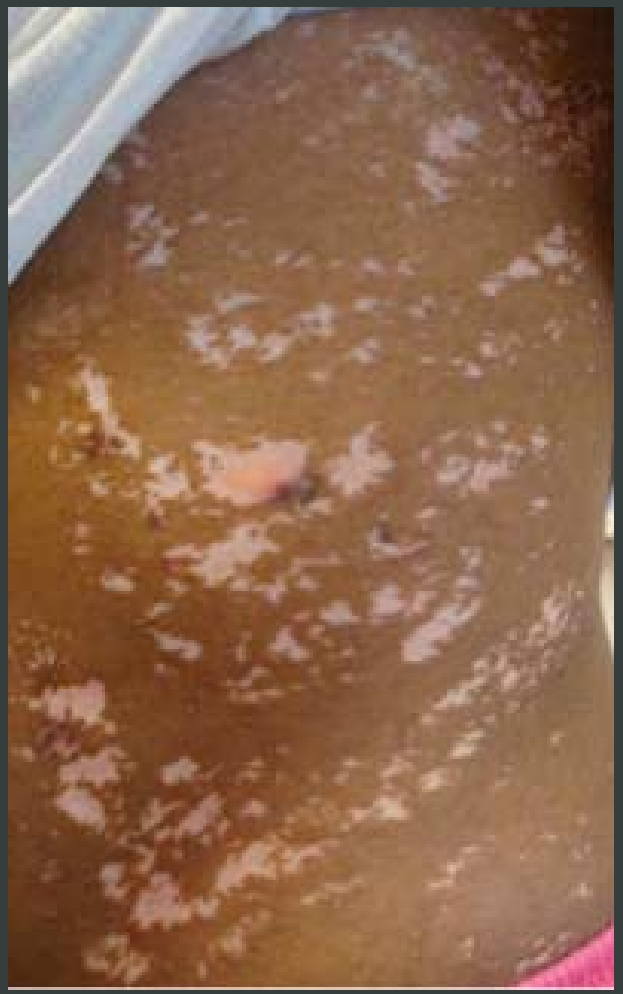


Image from American Journal of Medical Genetics

Differential Diagnosis: Focal Dermal Hypoplasia

- X-linked dominant mutation in PORCN gene
- Atrophic dermal streaks following Blaschko's lines usually present at birth
- Within affected skin can have fat herniation, telangiectasias
- Pathology shows decreased dermal collagen and decreased adnexal structures
- Perioral and/or anogenital raspberry-like papillomas
- Bony deformities including ectrodactyly and/or osteopathia striata
- Ophthalmologic abnormalities including colobomas, aniridia, or microphthalmia

Treatment and Follow-up

- We recommended symptomatic treatment and are following peripherally
- Pt now 8 months old
- Found to have sensorineural hearing loss and patent foramen ovale
- Has been seen by ophthalmology, in addition to microopthalmia, sclerocornea, and colobomas was found to have severe anterior segment dysgenesis bilaterally
- Neurology following patient and encouraged parents to continue with physical therapy
- Further genetic testing performed on sample used for microarray, looking at X chromosome in location of HCCS gene
- No deletions were noted but geneticists noted limitations of this study and recommended gene sequencing of entire HCCS gene which has not been performed as of today

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Amicrobial Pustulosis of the Folds

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Overview

- **Patient Summary**
- Diagnostic Criteria (from a 2008 Review)
- Disease Associations
- Treatment Options
- Possible Pathomechanisms

Patient Photos

Patient Summary

30-year-old pregnant female with systemic lupus erythematosus (on plaquenil) and idiopathic thrombocytopenic purpura (on eltrombopag) presents to the inpatient consult service.

- Erythematous plaques with desquamative scale, serous crust, and pustules
- In and around her ears, in the folds of the axillae, and in the folds of the groin

Patient Photos

Initial differential diagnosis:

- Broad:
  - Infectious
  - eczematous dermatitis such as atopic or contact dermatitis
  - psoriasis given the scalp/ear/intertriginous involvement
  - Other, e.g. autoimmune connective tissue disease

Initial Interventions:

- Topical steroids, topical antibiotics, and an antifungal shampoo
- ENT also recommended antibacterial/anti-inflammatory otic drops + oral antibiotics

Patient Photos

Three months later:

- Mild-moderate improvement on empiric therapy
- Due to significant persistent disease, further investigations performed
- Pustules are more prominent

Biopsy:

- Intraepidermal pustule
- PAS negative
- No bacterial colonies seen
- DIF negative (Evaluate for IgA pemphigus)

Culture:

- Sterile (undisturbed pustule near the right axilla)

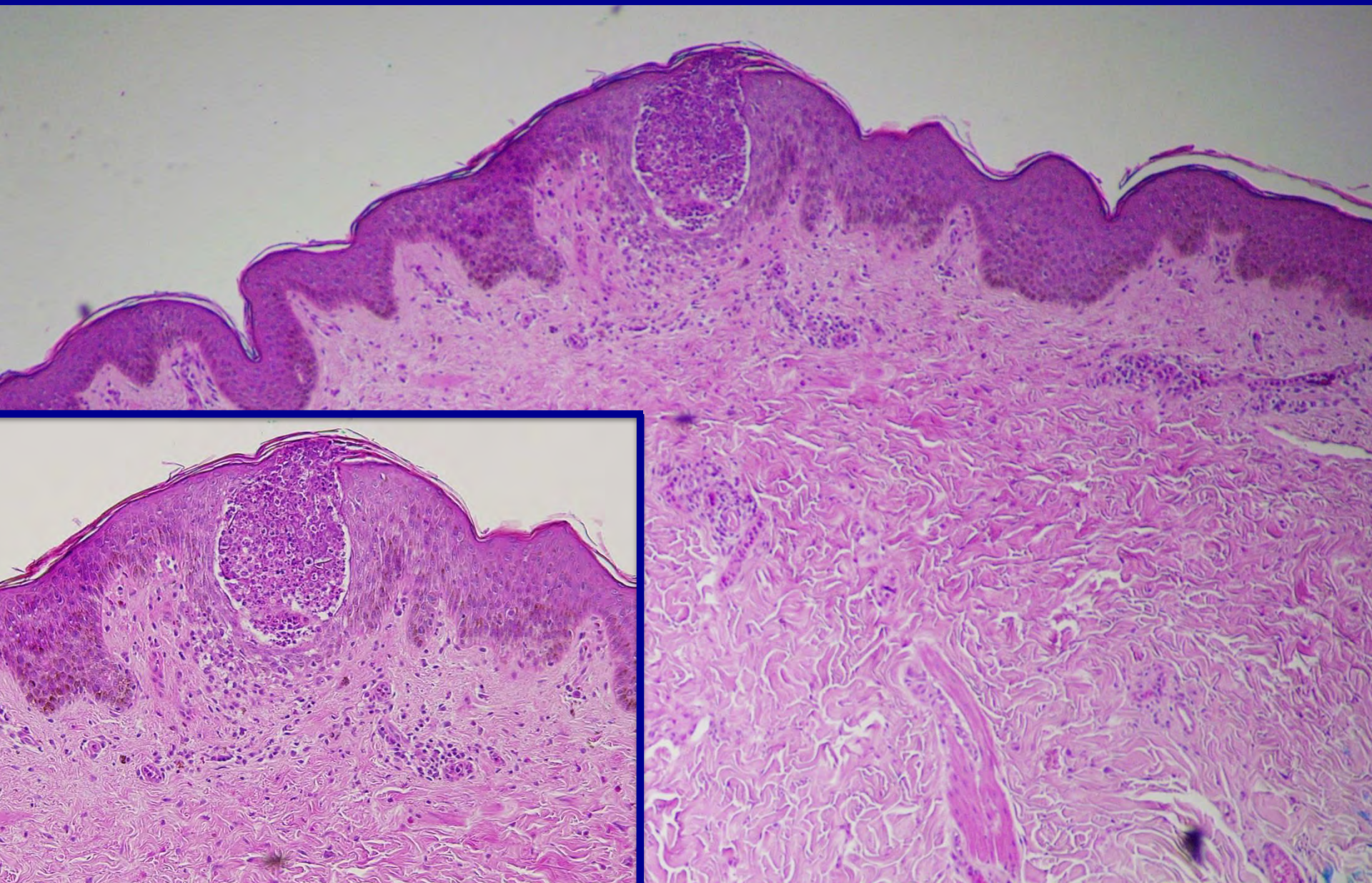
Patient Photos

Working Diagnosis:

Amicrobial Pustulosis of the Folds

Histopathology of Amicrobial Pustulosis of the Folds

- Intraepidermal pustules with focal areas of spongiosis.
- No bacterial colonies are seen.



- Patient Summary
- **Diagnostic Criteria (from a 2008 Review)**
- Disease Associations
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- Possible Pathomechanisms

Amicrobial Pustulosis of the Folds

Report of 6 Cases and a Literature Review

Angelo V. Marzano Stefano Ramoni Ruggero Caputo
Institute of Dermatological Sciences, University of Milan – Fondazione IRCCS, Ospedale Maggiore Po
Mangiagalli e Regina Elena, Milan, Italy

Table 4. Diagnostic criteria for APF

Obligate criteria	Minor criteria
Pustulosis involving 1 or more major folds, 1 or more minor folds and the anogenital area	Association with 1 or more autoimmune disorders
Histological pattern consisting of intraepidermal spongiform pustules and a mainly neutrophilic dermal infiltrate	Positive ANA at a titer of 1/160 or higher
Negative culture from unopened pustule	Presence of 1 or more serum autoantibodies (notably anti-ENA, anti-dsDNA, anti-smooth-muscle, antimitochondrial, anti-gastric-parietal-cell, antiendomysial,

The diagnosis of APF can be ascertained if obligate criteria and 1 minor criterion are present. ANA = Antinuclear antibodies; ENA = extractable nuclear antigens.

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2008 Review

- 21 cases reviewed (6 new)
- Diagnostic Criteria Proposed

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Table 1. Summary of the clinical and immunological findings of the cases of APF reported in the literature in addition to ours

F/M ratio	Mean age at diagnosis years	Involvement of patients, %			Other skin findings	Associated disorders	Autoantibodies
		major folds	minor folds	anogenital area			
21:0	33	100	100	100	Involvement of: – scalp (19) – face (13) – periungual flexures of hands with onychodystrophy (2)	SLE (5; 24%) Incomplete SLE (2; 10%) SLE-scleroderma overlap syndrome (2; 10%) SCLE (1; 5%) DLE (1; 5%)	ANA (16; 76%) Anti-dsDNA (5; 24%) Anti-SSA-Ro (4; 19%) Anti-RNP (3; 14%) Anti-smooth-muscle (2; 10%)
					Generalized eruption (5)	Myasthenia gravis (1; 5%)	Anti-Sm (1; 5%)
					Eczematous lesions over: – upper limbs (7) – trunk (4) – buttocks (3)	Idiopathic thrombocytopenic purpura (1; 5%) Palindromic rheumatism (1; 5%) Mixed connective tissue disease (1; 5%) Sjögren syndrome (1; 5%) Celiac disease (1; 5%)	Antithyroid microsomal (1; 5%) Anti-gastric-parietal-cell (1; 5%) Antimitochondrial (1; 5%) IgG antigliadin (1; 5%) IgA antiendomysial (1; 5%) LAC (1; 5%)

Figures in parentheses are numbers of cases, with percentages where appropriate. SCLE = Subacute cutaneous lupus erythematosus; DLE = discoid lupus erythematosus; ANA = antinuclear antibodies; LAC = lupus anticoagulant; RNP = ribonucleoprotein; dsDNA = double-stranded-DNA.

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ar antibodies at variable titers, were found. Interestingly, one of our above-mentioned patients developed SLE approximately 9 years after the onset of APF, thus making a strict follow-up mandatory in these patients for the possible onset of an autoimmune disease.

- Patient Summary
- Diagnostic Criteria (from a 2008 Review)
- **Disease Associations**
- Treatment Options
- Possible Pathomechanisms

Amicrobial Pustulosis of the Folds

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Associated disorders
SLE (5; 24%)
Incomplete SLE (2; 10%)
SLE-scleroderma overlap syndrome (2; 10%)
SCLE (1; 5%)
DLE (1; 5%)
Myasthenia gravis (1; 5%)
Idiopathic thrombocytopenic purpura (1; 5%)
Palindromic rheumatism (1; 5%)
Mixed connective tissue disease (1; 5%)
Sjögren syndrome (1; 5%)
Celiac disease (1; 5%)

Review of Literature on Amicrobial Pustulosis of the Folds Associated with Autoimmune Disorders

Am J Clin Dermatol 2006; 7 (6): 369-374
1175-0561/06/0006-0369/$39.95/0

Stefanie Boms[1,2] and *Thilo Gambichler*[2]

Case	Age (years)	Duration of disease (years)	Amicrobial pustulosis: folds	scalp	periorificial	Histology: SP	N-MN-I	LB	Immunologic abnormalities
1	35	5	+	+	+	−	+	−	SLE (11-year history)
2	26	8	+	+	+	+	NIA	−	SLE (8-year history)
3	31	6	+	+	+	+	NIA	+	SLE (6-year history)
4	66	1	+	−	−	+	+	+	Sharp syndrome (22-year history)
5	19	1	+	−	+	+	+	−	Chronic autoimmune erythroblastopenia, SLE-type (2-year history)
6	24	5	+	+	+	+	NIA	+	SLE (12-year history)
7	30	5	+	−	+	−	+	−	ANA 1 : 160, anti-SSA/Ro, anti-Sm
8	43	11	+	+	−	+	+	−	Subacute cutaneous lupus erythematosus (15-year history)
9	28	3	+	−	+	+	+	−	Celiac disease, specific IgA and IgG
10	28	<1	+	+	+	+	+	−	SLE (10-year history)
11	39	<1	+	+	+	−	+	+	ANA 1 : 100, anti-DNA, anti-SSA/Ro
12	16	4	+	−	+	+	+	−	Erythropenia, myasthenia gravis, ANA 1 : 320, anti-SSA/Ro
13	18	>1	+	+	+	+	+	+	Idiopathic thrombocytopenic purpura
14	50	<1	+	+	−	+	+	NIA	Sharp syndrome (10-year history)
15	54	5	+	−	+	+	+	−	Rheumatoid arthritis, ANA 1 : 80, anti-Sm
16	36	<1	+	−	+	+	+	−	Sharp syndrome, ANA 1 : 1200, anti-RNP
17	27	<1	+	+	−	+	+	(+)	ANA 1 : 640
18	63	2	+	+	+	+	+	−	Discoid lupus erythematosus (30-year history), Sjögren syndrome
19	35	<1	+	+	−	+	+	NIA	ANA 1 : 2560, elevated serum IgG
20	36	1	+	−	+	+	+	−	SLE (>10-year history)
21	14	<1	+	−	−	+	+	−	SLE (1-year history)
22	29	<1	+	+	−	+	+	+	SLE
23	21	NIA	+	+	+	+	+	+	SLE, ANA 1 : 1280
24	29	1	+	+	+	−	+	−	ANA 1 : 80, elevated rheumatoid factor
25	17	<1	+	+	+	+	+	−	ANA 1 : 1280, anti-DNA, anti-centromere protein B, anti-cardiolipin, anti-SSA/Ro, elevated serum IgG

- SLE
- MCTD
- Celiac Disease
- Idiopathic Thrombocytopenic Purpura
- Rheumatoid Arthritis
- DLE
- Sjogren's Syndrome
- **+ANA w/o overt disease**

Amicrobial pustulosis of the folds associated with Hashimoto's thyroiditis

Accepted for publication 5 December 2008

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doi:10.1111/j.1365-2230.2009.03370.x

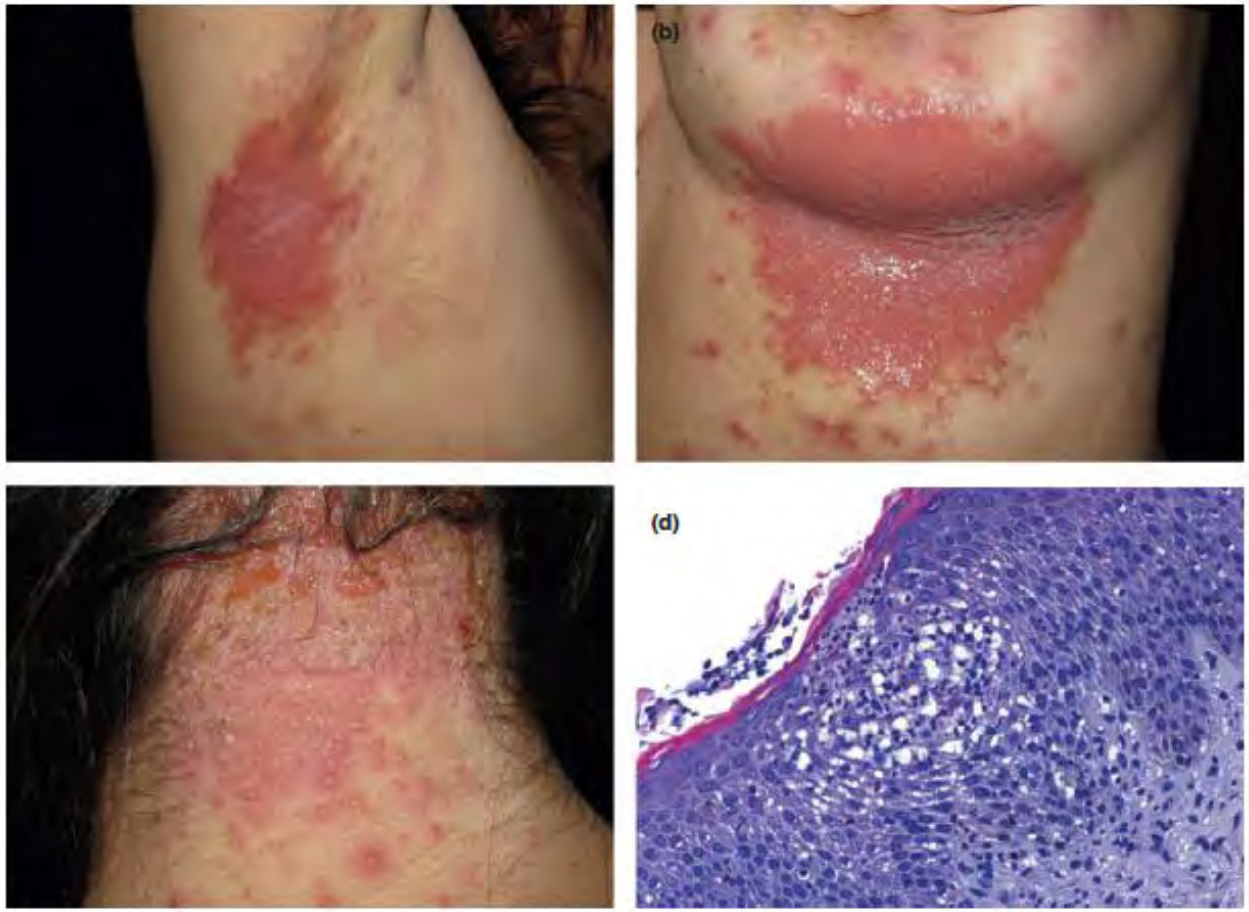

Figure 1 (a–c) Coalescing pustular lesions arising on erythematous skin and forming large crusted and eroded plaques affecting the axillae, the submammary fold and the posterior neck. (d) Skin biopsy specimen from the submammary fold showing intra-epidermal spongiform pustule (haematoxylin and eosin, original magnification × 200).

Amicrobial pustulosis associated with autoimmune disease in a patient with Sjögren syndrome and IgA nephropathy

Accepted for publication 28 August 2011

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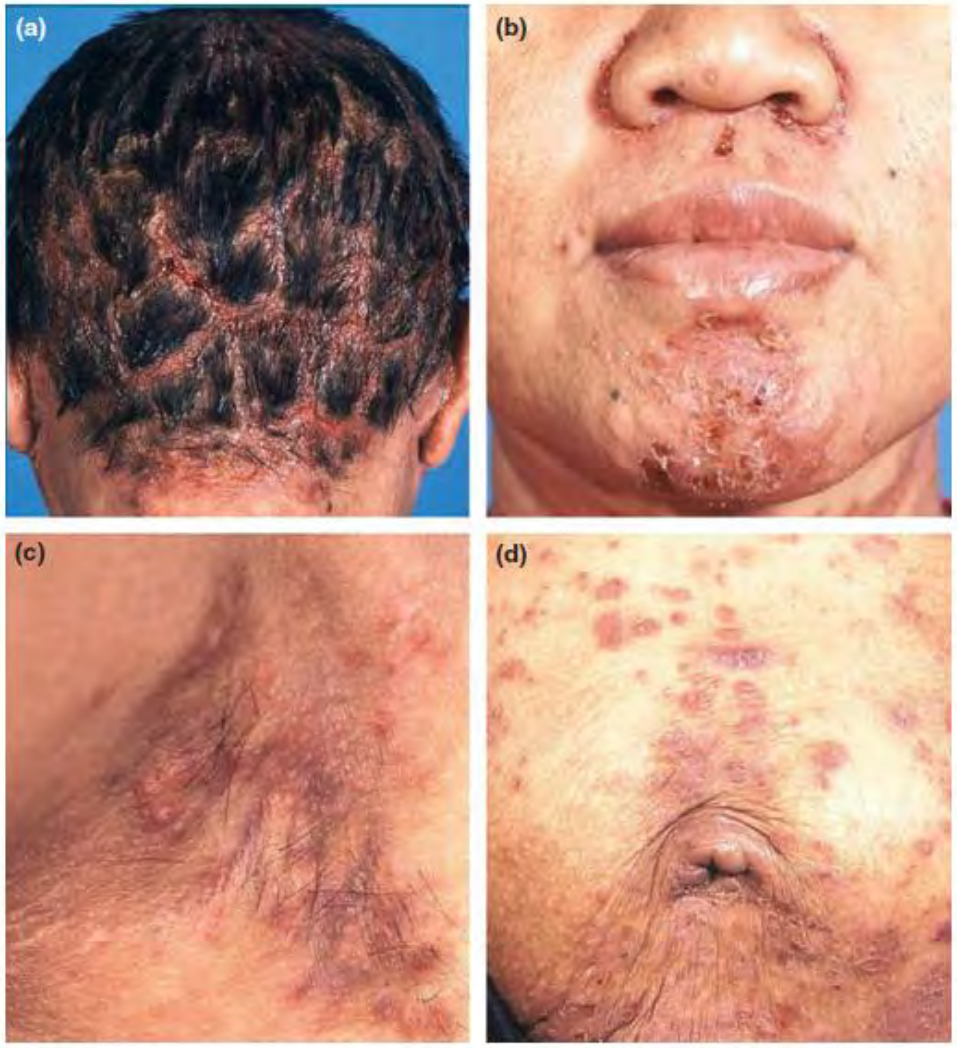

Dermatology 2013;226:1–4
DOI: 10.1159/000343595

Amicrobial Pustulosis of the Folds Associated with Autoimmune Disorders: Systemic Lupus Erythematosus Case Series and First Report on the Association with Autoimmune Hepatitis

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Mónica Fernández Sánchez[a]

Departments of [a]Dermatology and [b]Pathology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

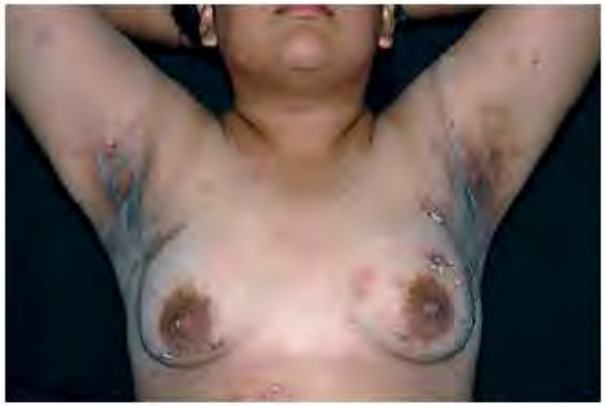


Fig. 1. Disseminated erosive and pustular dermatosis.

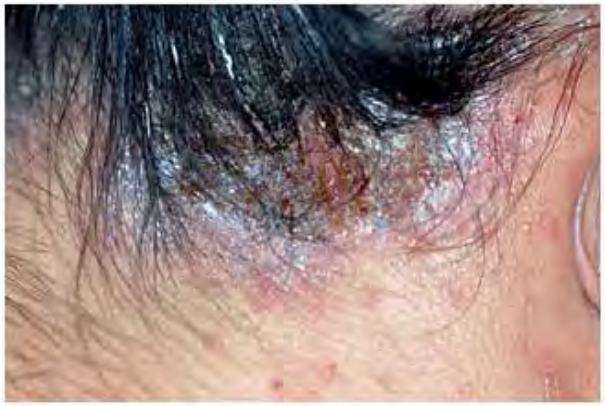


Fig. 2. Ulcerative and desquamative dermatosis over the scalp.

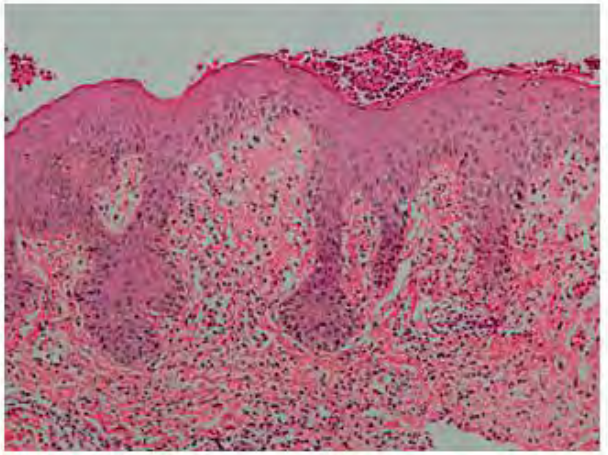


Fig. 3. Psoriasiform hyperplasia with subcorneal pustules and a perivascular and interstitial neutrophilic inflammatory infiltrate with no evidence of vasculitis or leukocytoclasis. HE. ×10.

Amicrobial Pustulosis of the Folds:

Disease Associations

- SLE
- MCTD
- SLE - Scleroderma Overlap Syndrome
- + ANA or antibodies w/o overt autoimmune disease
- Sjogren's Syndrome
- IgA Nephropathy
- Celiac Disease
- SCLE
- DLE
- Myasthenia Gravis
- Idiopathic Thrombocytopenic Purpura
- Hashimoto's Thyroiditis
- Autoimmune Hepatitis

- Patient Summary
- Diagnostic Criteria (from a 2008 Review)
- Disease Associations
- **Treatment Options**
- Possible Pathomechanisms

Review of Literature on Amicrobial Pustulosis of the Folds Associated with Autoimmune Disorders

Am J Clin Dermatol 2006; 7 (6): 369-374
1175-0561/06/0006-0369/$39.95/0

Stefanie Boms[1,2] and *Thilo Gambichler*[2]

Table II. Management of 25 women with amicrobial pustulosis of the folds associated with autoimmune disorders: review of the literature[1-17]

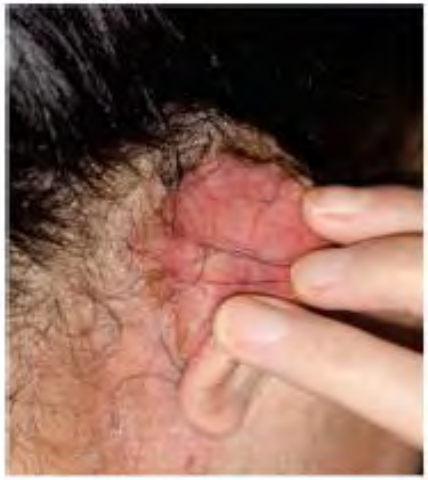
Case	Ineffective therapy	Effective therapy	Reference
1	Acitretin	Systemic corticosteroids, cyclophosphamide	1
2	Vitamin D, hydroxychloroquine	Systemic corticosteroids, acitretin	1
3	Antibacterials	Dapsone	2
4		Systemic corticosteroids	3
5		Systemic corticosteroids	4
6	Antibacterials	Systemic corticosteroids	5
7		Ceftriaxone, cimetidine, ascorbic acid (vitamin C)	6
8		Ceftriaxone, cimetidine, ascorbic acid (incomplete response)	6
9		Ceftriaxone, cimetidine, ascorbic acid (incomplete response)	6
10	Antibacterials, etretinate, dapsone	Systemic corticosteroids	7
11		Topical corticosteroids, antibacterials	7
12	Dapsone	Systemic corticosteroids	7
13	Dapsone	Topical corticosteroids, antibacterials	7
14		Systemic corticosteroids, hydroxychloroquine	8
15	Psoralen plus UVA, acitretin, antibacterials, zinc, vitamin D	Systemic corticosteroids	9
16	Dapsone	Zinc	10
17	Antibacterials, topical/systemic corticosteroids	Zinc	10
18	Topical corticosteroids	Systemic corticosteroids, cyclosporine (ciclosporin)	11
19	Antibacterials, etretinate	Dapsone, systemic corticosteroids	11
20		Colchicine	12
21		Systemic corticosteroids, dapsone	13
22	No information available		14
23	Minocycline	Levamisole (slight improvement), systemic corticosteroids	15
24	Antibacterials	Topical corticosteroids	16
25		Systemic corticosteroids, methotrexate	17

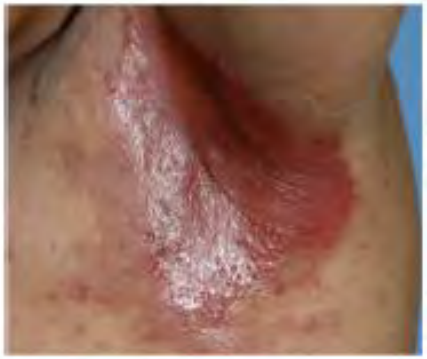
- Systemic Steroids
- Topical Steroids
- Acitretin
- Cyclophosphamide
- Ceftriazone + cimetidine + ascorbic acid (incomplete response)
- Zinc
- Colchicine
- Methotrexate

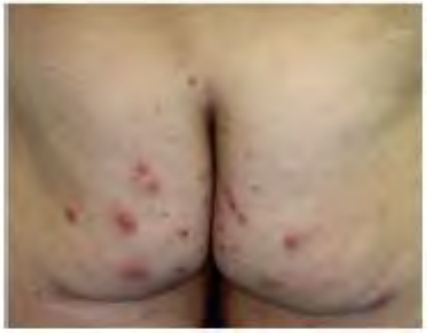
- Patient Summary
- Diagnostic Criteria (from a 2008 Review)
- Disease Associations
- Treatment Options
- **Possible Pathomechanisms**

Expression of interleukin-1 alpha in amicrobial pustulosis of the skin folds with complete response to anakinra

J Am Acad Dermatol
August 2014







Patient Summary

- 48 yo woman diagnosed with SLE in 1997
- Presented with APF in 2010
- Already on low-dose prednisone and hydroxychloroquine for SLE, started on dapsone for APF
- An inflammatory bowel disease with a neutrophilic infiltrate on biopsy developed
- Started on infliximab and high-dose steroids
- Improved, but skin disease flared when prednisone tapered to 25 mg/day
- After 15 infliximab infusions, switched to ustekinumab
- Remained resistant to therapy
- Expression level of several pro- and anti-inflammatory genes assessed

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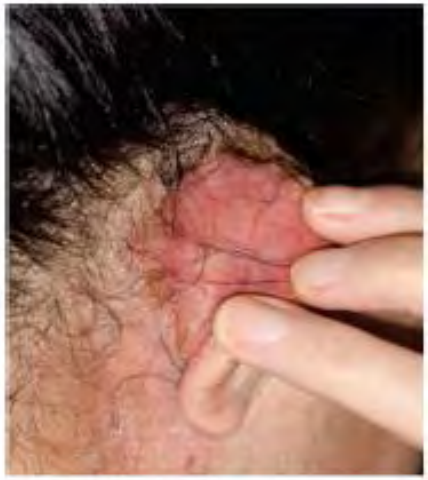

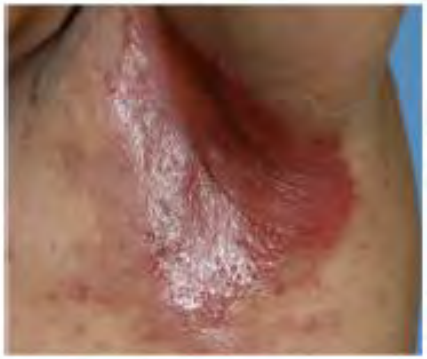

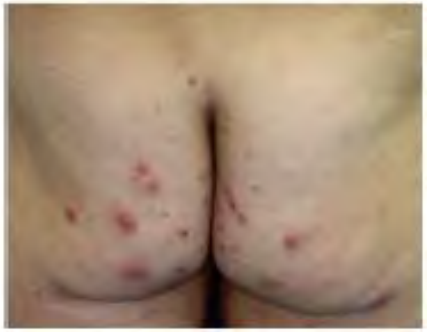

Table I. Gene expression profile obtained from lesional and nonlesional skin of patient

Gene Symbol	Description	Lesional/Nonlesional
CBLB	Cas-Br-M (murine) ecotropic retroviral transforming sequence b	D
CD40	CD40 molecule (TNF receptor superfamily member 5)	D
CDK2	Cyclin-dependent kinase 2	D
CMA1	Chymase 1, mast cell	D
CSF1	Colony stimulating factor 1 (macrophage)	D
CTLA4	Cytotoxic T-lymphocyte-associated protein 4	U
DGKA	Diacylglycerol kinase, alpha 80 kDa	D
DGKZ	Diacylglycerol kinase, zeta 104 kDa	D
EGR2	Early growth response 2	D
EGR3	Early growth response 3	D
EOMES	Eomesodermin homolog	D
FAS	Fas (TNF receptor superfamily, member 6)	U
FOXP1	Forkhead box P1	D
FOXP2	Forkhead box P2	D
GATA3	GATA binding protein 3	D
GZMB	Granzyme B	U
ICAM1	Intercellular adhesion molecule 1	U
IL10RA	Interleukin 10 receptor, alpha	U
IL1A	Interleukin 1, alpha	U
IL2RA	Interleukin 2 receptor, alpha	U
IL6	Interleukin 6	U
IL7R	Interleukin 7 receptor	U
ING4	Inhibitor of growth family, member 4	D
JAK1	Janus kinase 1	D
JAK3	Janus kinase 3	U
LEP	Leptin	D
LGALS3	Lectin, galactoside-binding, soluble, 3	D
LTA	Lymphotoxin alpha (TNF superfamily, member 1)	D
MEF2A	Myocyte enhancer factor 2A	D
NFATC1	Nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1	D
NFATC2	Nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2	D
NFATC3	Nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 3	D
NHLH2	Nescient helix loop helix 2	D
NOTCH1	Notch homolog 1, translocation-associated	D
PTGS2	Prostaglandin-endoperoxide synthase 2	U
RNF128	Ring finger protein 128	D
TNFRSF18	Tumor necrosis factor receptor superfamily, member 18	D
TNFRSF8	Tumor necrosis factor receptor superfamily, member 8	U
TNFSF8	Tumor necrosis factor (ligand) superfamily, member 8	U

Transcriptomic analysis of lesional (L) and nonlesional (NL) skin of patient was performed using Human T-cell Anergy and Immune Tolerance PCR Array (Qiagen). The modulation is expressed as the ratio of signal intensities for lesional skin over nonlesional skin. Arbitrarily, only modulation greater than 2 was considered significant.
D, Downregulation; *U*, upregulation.

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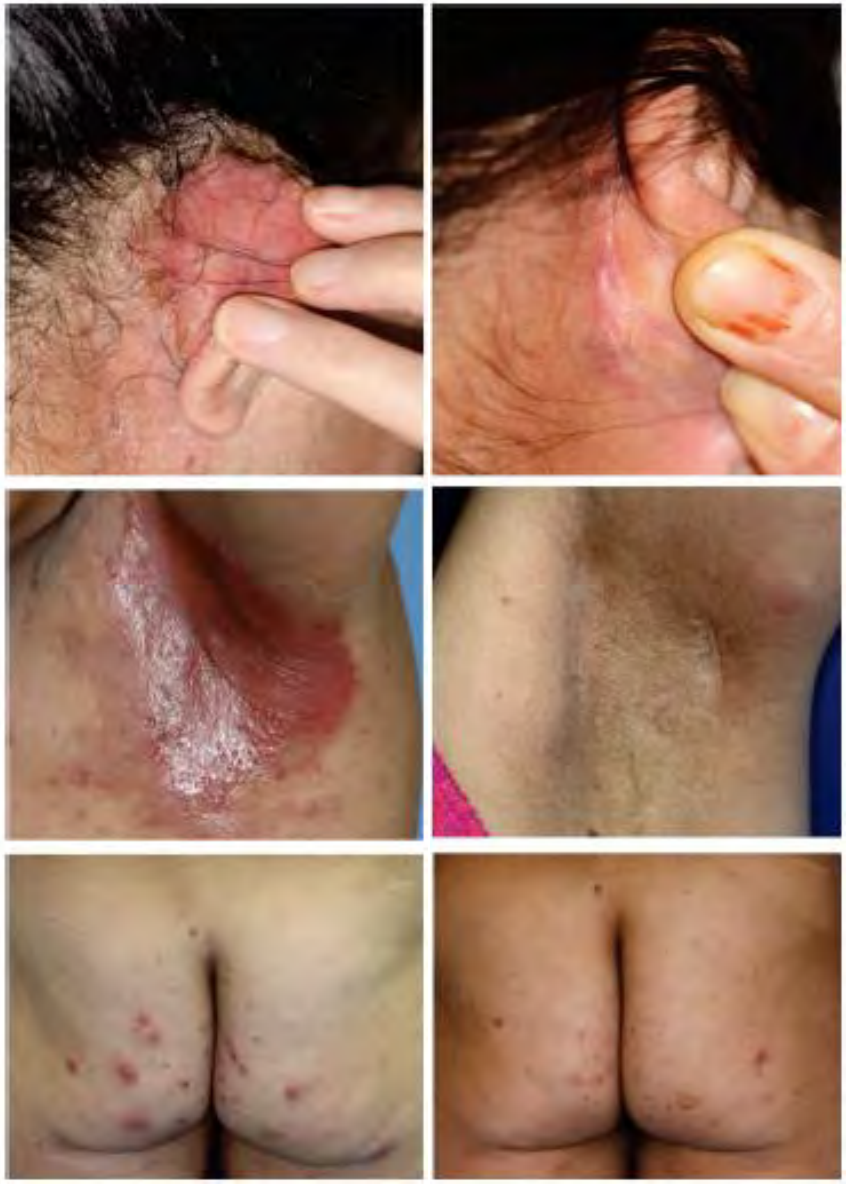

IL1A Interleukin 1, alpha
IL2RA Interleukin 2 receptor, alpha
IL6 Interleukin 6
IL7R Interleukin 7 receptor

- Anakinra (IL-1 Receptor Antagonist) was prescribed “off-label”
- One month later…
- One year later, the patient remained clear on Anakinra

Cytokine and Chemokine Profile in Amicrobial Pustulosis of the Folds

Medicine • Volume 94, Number 50, December 2015

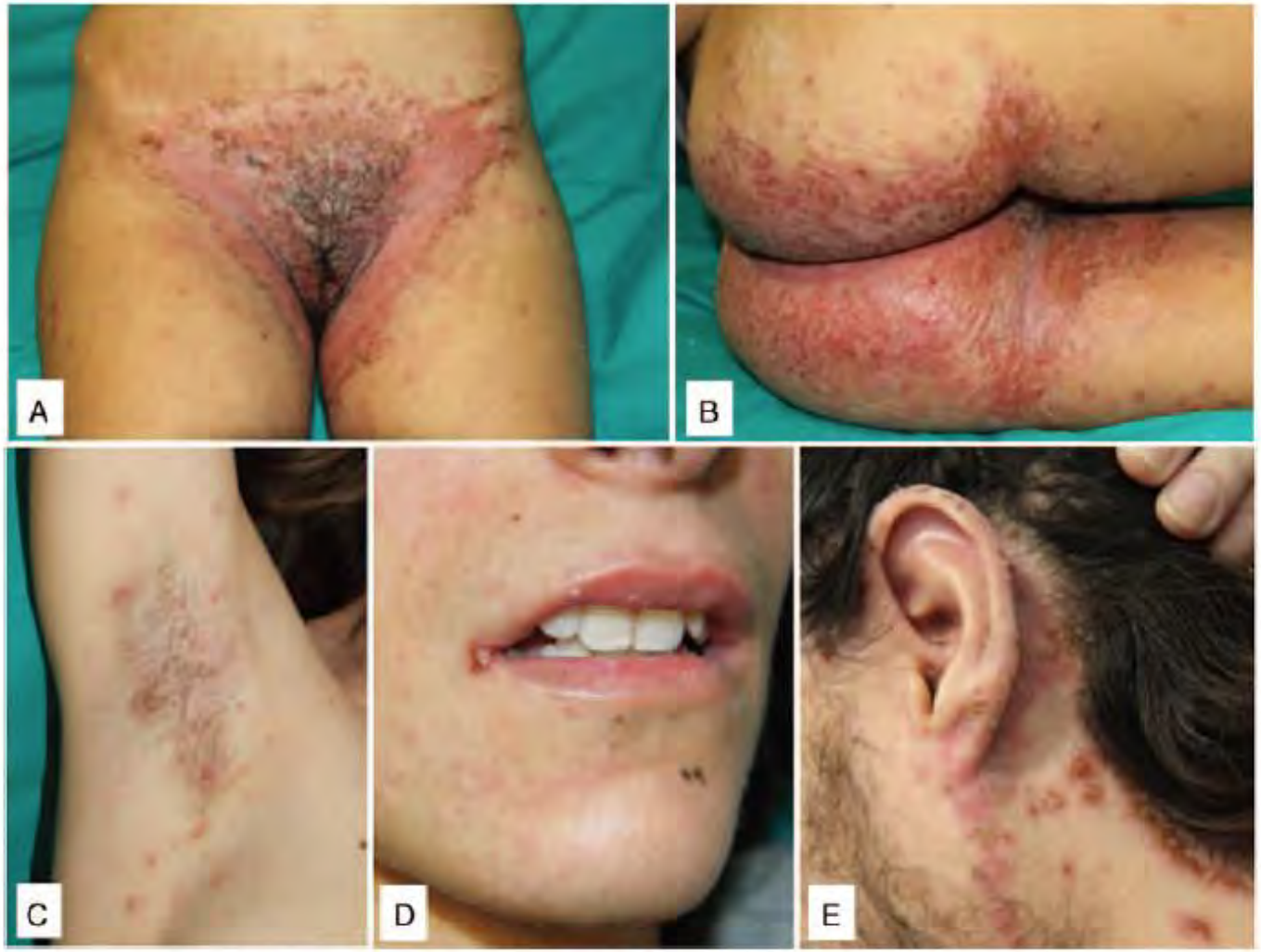

FIGURE 1. Clinical features of amicrobial pustulosis of the folds. Erythematous-erosive lesions, sometimes covered by crusts, involving the groins (A) and the anogenital region (B) in patient 11. Erythematous pustules of the axilla (C) in patient 7. Erosions with crusts involving the angle of the mouth (D) in patient 9 and the retroauricular flexures (E) in patient 8.

Cytokine and Chemokine Profile in Amicrobial Pustulosis of the Folds

Evidence for Autoinflammation

Angelo V. Marzano, MD, Simona Tavecchio, MD, Emilio Berti, MD, Carlo Gelmetti, MD, and Massimo Cugno, MD

canals.[1–4] Its histological picture is characterized by subcorneal pustules associated with a predominantly neutrophilic infiltrate in the dermis, which lead to include APF within the spectrum of neutrophilic dermatoses.[4,5] Neutrophilic dermatoses represent a clinically heterogeneous group of disorders hallmarked by an accumulation of neutrophils in the skin and rarely internal organs.[6] Recently, pyoderma gangrenosum (PG) and Sweet syndrome (SS), the 2 prototypic neutrophilic dermatoses, have been included among the autoinflammatory diseases,[7] which are characterized by recurrent episodes of sterile inflammation in the affected organs, including the skin, without circulating autoantibodies and autoreactive T cells.[8] In PG and SS, we recently demonstrated an overexpression of cytokines/chemokines and molecules amplifying the inflammatory network, supporting the view that these disorders are autoinflammatory in origin.[9] Here, we analyze the clinical picture, histopatholo-

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TABLE 1. Clinical Features, Associated Disorders, Laboratory Findings, Treatment, and Course in the 15 Patients With Amicrobial Pustulosis of the Folds (APF)

Patient	Sex/Age at Diagnosis, y	Duration of Disease, y	Associated Disorders	Autoantibodies	Treatment	Course
1	F/30	24	SLE occurred after the onset of APF	ANA 1/160 homogeneous pattern; SSA-Ro; anti-dsDNA; anti-smooth-muscle	Cimetidine 400 mg bid + ascorbic acid 3 g/d followed by corticosteroids for SLE	PR
2	F/43	30	SCLE	ANA 1/160 homogeneous pattern; SSA-Ro; anti-smooth-muscle; anti-gastric-parietal cell; antimitochondrial	Cimetidine 400 mg bid + ascorbic acid 3 g/d followed by short cycles of corticosteroids for relapses	PR
3	F/28	22	Celiac disease	IgA antitransglutaminase; IgG antigliadin; IgA antiendomysial	Cimetidine 400 mg bid + ascorbic acid 3 g/d followed by short cycles of corticosteroids for relapses	PR
4	F/28	19	None	ANA 1/320 fine speckled pattern	Cimetidine 400 mg bid + ascorbic acid 3 g/d followed by short cycles of corticosteroids for relapses	PR
5	F/27	9	None	ANA 1/320 fine speckled pattern	Cimetidine 400 mg bid + ascorbic acid 3 g/d followed by short cycles of corticosteroids for relapses	PR
6	F/41	9				PR
7*	F/35	1				CR
8†	M/38	9 mo				CR
9†	F/26	9 mo				CR
10	F/13	13			methylprednisolone 1 mg/kg per d; dapsone 1.5 mg/kg per d; cyclosporine 3.5 mg/kg per d; infliximab 5 mg/kg: 1 infusion at time 0 and after 2 and 6 wk followed by 1 infusion every 2 mo	PR
11‡	F/29	3	None	ANA 1/640 fine speckled pattern; SSA-Ro; SSB-La; anticardiolipin	Clobetasole dipropionate and intravenous methylprednisolone 1 mg/kg per d; dapsone 1.5 mg/kg per d	PR
12	M/43	5	APS	Anticardiolipin; anti-β2-glycoprotein I; LAC	Clobetasole dipropionate and intravenous methylprednisolone 0.5 mg/kg per d	PR
13	F/12	5	None	ANA 1/640 fine speckled pattern	Clobetasole dipropionate and intravenous methylprednisolone 0.5 mg/kg per d	PR
14	F/26	3	None	ANA 1/320 fine speckled pattern	Clobetasole dipropionate and intravenous methylprednisolone 0.5 mg/kg per d	PR
15	F/11	4	None	ANA 1/160 fine speckled pattern	Clobetasole dipropionate and intravenous methylprednisolone 0.5 mg/kg per d	PR

- Studied 15 patients clinicopathologically and immunologically
- Performed cytokine arrays on 9 patient samples (vs normal skin from normal controls)

Cytokine and Chemokine Profile in Amicrobial Pustulosis of the Folds

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IL-1 beta and soluble receptors I and II

TNF-alpha and soluble receptors I and II

IL-17, sIL-17R, and L-selectin

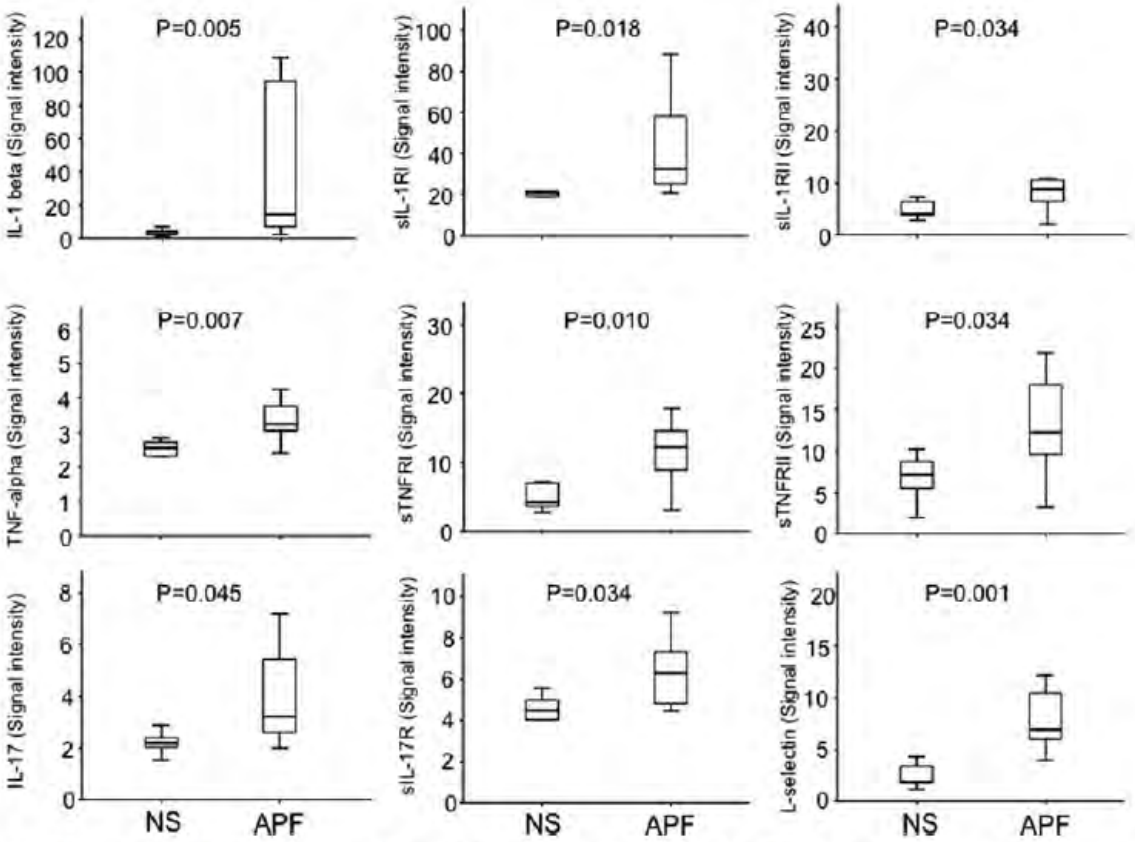

FIGURE 2. Expression of interleukin-1 (IL-1) beta and its soluble receptors I and II (sIL-1RI and sIL-1RII), tumor necrosis factor (TNF)-alpha and its soluble receptors I and II (sTNFRI and sTNFRII), interleukin-17 (IL-17) and its soluble receptor (sIL17R), and leukocyte selectin (L-selectin) in omogenate samples of lesional skin from 9 patients with amicrobial pustulosis of the folds (APF). Six normal subjects (NS) served as controls. Numerical values represent signal intensity in a cytokine array assay. Median values, interquartile ranges (boxes), and 5th and 95th percentiles (whiskers).

Cytokine and Chemokine Profile in Amicrobial Pustulosis of the Folds

Evidence for Autoinflammation

Angelo V. Marzano, MD, Simona Tavecchio, MD, Emilio Berti, MD, Carlo Gelmetti, MD, and Massimo Cugno, MD

IL-8 and RANTES

CXCL 1, 2, 3 and CXCL 16

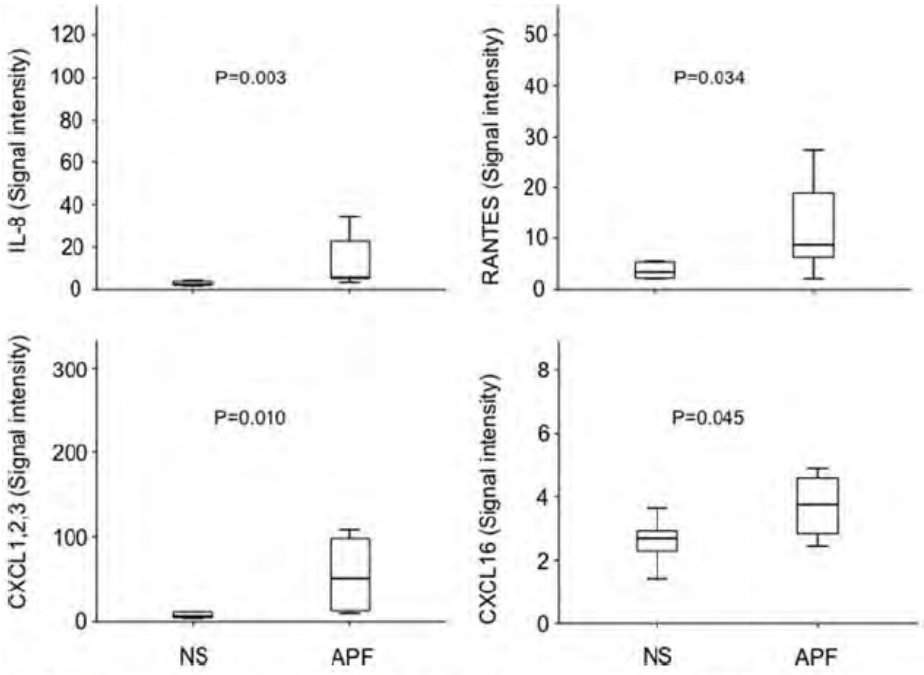

FIGURE 3. Expression of IL-8 (interleukin 8), RANTES (regulated on activation, normal T cell expressed and secreted), CXCL 1,2,3 (Chemokine [C-X-C motif] ligand 1,2,3; [C = cysteine, X = any amino acid]) and CXCL 16 (Chemokine [C-X-C motif] ligand 16) in omogenate samples of lesional skin from 9 patients with amicrobial pustulosis of the folds (APF). Six normal subjects (NS) served as controls. Numerical values represent signal intensity in a cytokine array assay. Median values, interquartile ranges (boxes), and 5th and 95th percentiles (whiskers).

Cytokine and Chemokine Profile in Amicrobial Pustulosis of the Folds

Evidence for Autoinflammation

Angelo V. Marzano, MD, Simona Tavecchio, MD, Emilio Berti, MD, Carlo Gelmetti, MD, and Massimo Cugno, MD

without a clear autoimmunity. The overexpression of cytokines/chemokines and molecules amplifying the inflammatory network supports the view that APF has an important autoinflammatory component.

- Patient Summary
- Diagnostic Criteria (from a 2008 Review)
- Disease Associations
- Treatment Options
- Possible Pathomechanisms

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Metastases to skin- what happens next?

Mike Hitchcock MBChB, MBA

Conflicts of interest

- nil

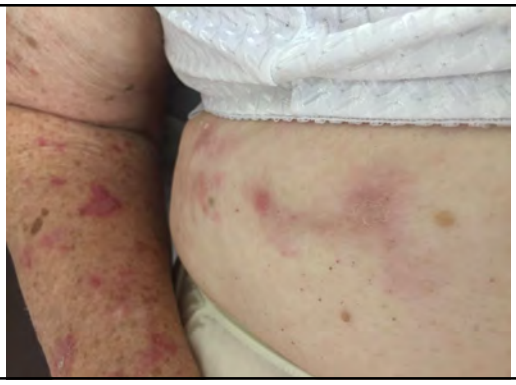
Rare but devastating

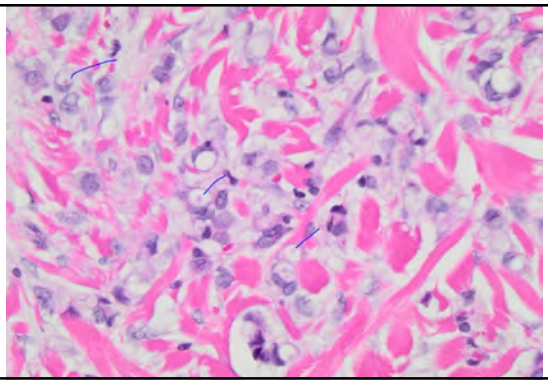
Only 1% of patients with internal malignancy have skin metastases

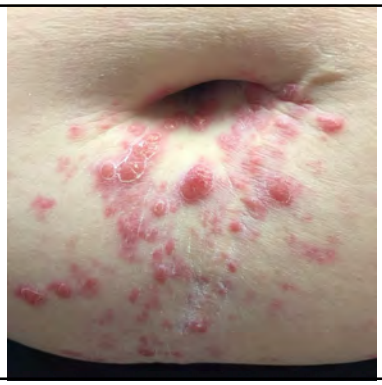
- Breast
- Lung*
- Colorectal
- Melanoma
- Esophagus
- Kidney*
- Ovary*

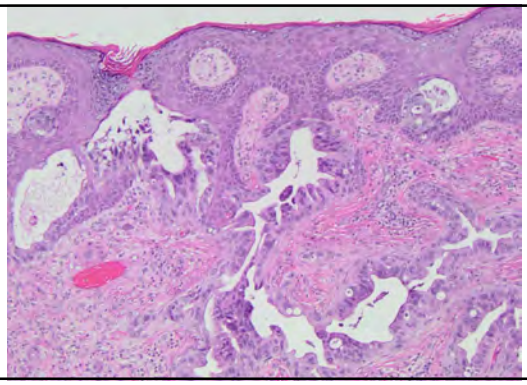
Presenting as first sign-

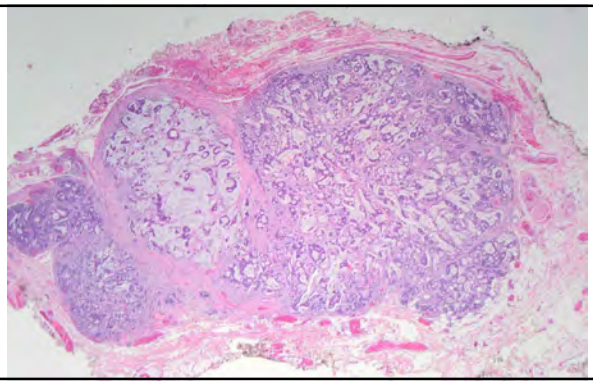
- Men- metastasis is first sign in ~ 40%
  - (lung & kidney)
- Women- metastasis is first sign in ~ 6%
  - (breast)

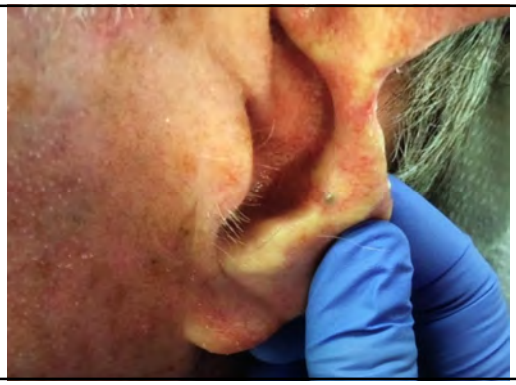


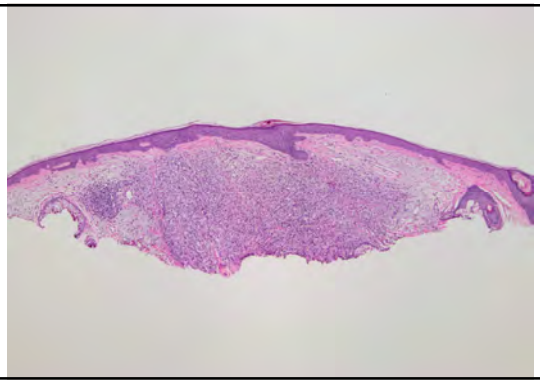


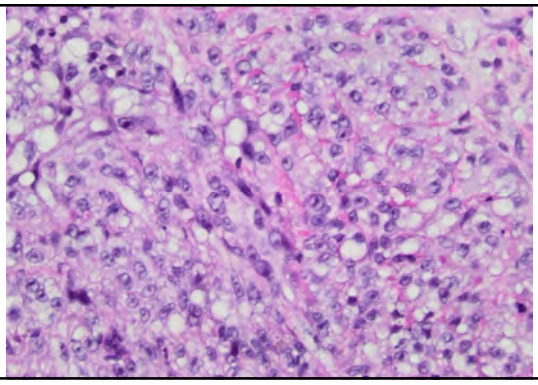


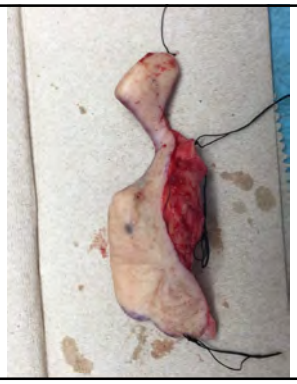


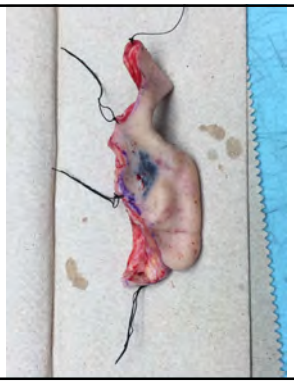


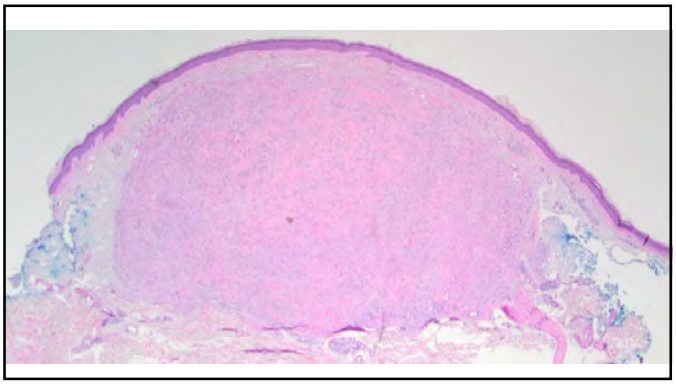


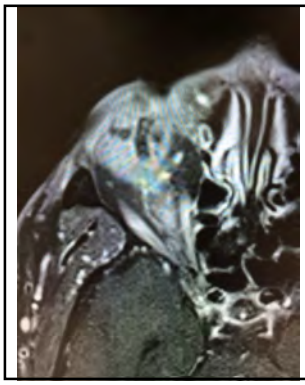


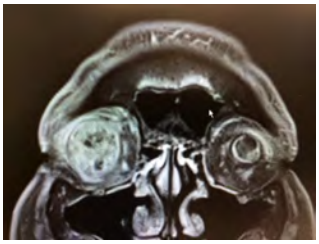


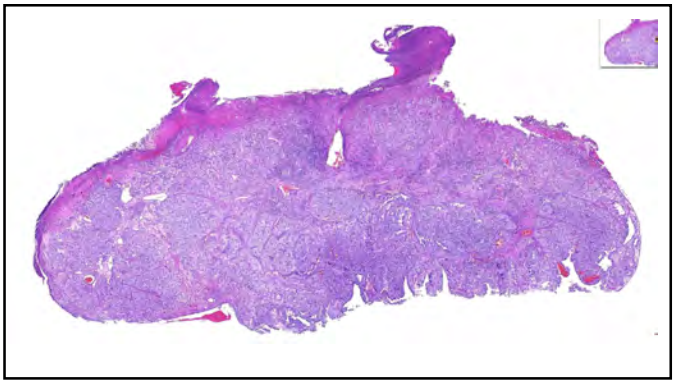


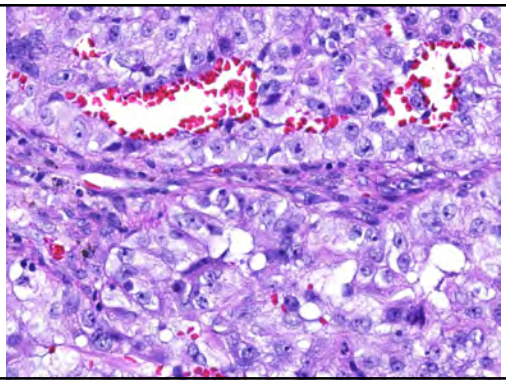




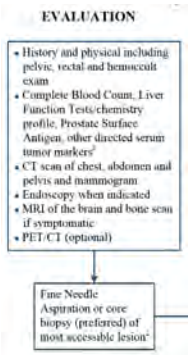








Clinical first

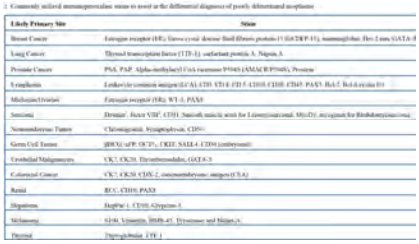


Diagnostic pathology sequence

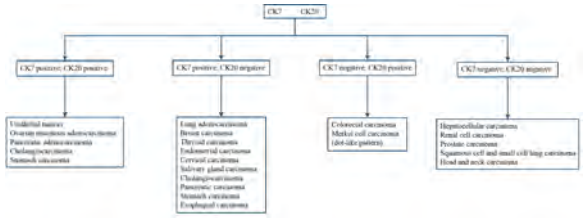
- H&E → adenocarcinoma, squamous carcinoma, other
- Immunostains →

(OK for pathologists to do diagnostic studies without further request)

Can't (shouldn't) do all stains at once



Commonly used algorithm- e.g. MD Anderson



Molecular markers

APPENDIX A: Unknown Primary Molecular Markers – MD ANDERSON APPROVED[3]

		BIOMARKER		
DISEASE SITE	CELL TYPE	FISH	IMMUNOHISTOCHEMISTRY	MOLECULAR
Unknown Primary	Breast Gastric Profile	HER2/neu	HER2/neu	
	Lung Profile	ALK rearrangement		EGFR mutation
	Small Bowel, Colon Profile			KRAS mutation

Prognostic markers- require additional clinician approval*

If known primary, e.g.
Breast- Her2neu, ER, PR, Ki67

If unknown primary… it depends what is responsive to therapy
adenocarcinoma- only a few treatable- breast, prostate

Lung- ALK positive vs negative

* Standing orders frowned upon by CMS

Meanwhile, the patient Googles - "I have metastatic cancer"

1. Paid ad- Cancer Treatment Centers of America- for profit company
2. NCI Fact sheet
3. ..
4. American Cancer Society

More likely, you'll refer to local cancer center

- NCI Comprehensive Cancer centers-

40 nationwide, three in NC

  - Duke
  - UNC
  - Wake

- American College of Surgeons accredited programs

54 in NC

Oncologist evaluates stage, tumor type, therapy

- One disease → best therapy, or options to discuss with patient

- New challenges- treat the disease or the gene?

The White House
Office of the Press Secretary

For Immediate Release January 30, 2015

FACT SHEET: President Obama's Precision Medicine Initiative

- More and better treatments for cancer: NCI will accelerate the design and testing of effective, tailored treatments for cancer by expanding genetically based clinical cancer trials, exploring fundamental aspects of cancer biology, and establishing a national "cancer knowledge network" that will generate and share new knowledge to fuel scientific discovery and guide treatment decisions.

Foundation Medicine: Personalizing Cancer Drugs

Foundation Medicine is offering a test that helps oncologists choose drugs targeted to the genetic profile of a patient's tumor cells. Has personalized cancer treatment finally arrived?

Multigene panels

Holy grail for test and drug makers in the US- FDA approval

- Labs either do a test per the label on the box, or develop their own method
- Most genetic tests are "laboratory developed tests"
  - Huge leap beyond complexity of PAS-D stain, even immunostains, proprietary techniques
- Own methods are not always valid (Theranostics)
- Challenges both for IRBs and treating clinicians

When Gene Tests for Breast Cancer Reveal Grim Data but No Guidance

By GINA KOLATA MARCH 11, 2016

But as Ms. Watts found out, "our ability to sequence genes has gotten ahead of our ability to know what it means," said Eric P. Winer, the director of the breast oncology program at Harvard's Dana-Farber Cancer Institute.

Dr. Campbell is, however, confident that someday genetic testing in breast cancer will bear fruit. For now, she says, oncologists are left in a difficult situation.

Dr. Norman Sharpless, the director of the Lineberger Comprehensive Cancer Center at North Carolina, estimates that perhaps one in 1,000 women with advanced breast cancer will benefit from using the approved and experimental drugs available today.

Multiplex gene testing- NY Times Sept 2014

Finding Risks, Not Answers, in Gene Tests

By DENISE GRADY and ANDREW POLLACK SEPT. 22, 2014

Within the next year, at least 100,000 people in the United States are expected to undergo these tests. The costs, about $1,500 to $4,000, are covered by some, but not all, insurers.

But some doctors worry that the newer tests for up to 30 genes may open a can of worms, because the ability to find mutations has outpaced the understanding of what they mean. In some cases, tests find cancer-associated mutations for which there are no preventive measures, and the patient is left with a bleak prognosis.

How to Cover Genetic Tests Confounds Health Insurers

UnitedHealthcare announced requirement for genetic test pre-authorization later this year

GENETIC TESTING IS WHERE the science of laboratory medicine is advancing rapidly and in ways that improve patient outcomes. Yet payers are overwhelmed by the flood of new molecular assays and genetic tests that lab companies have made available to clinicians. Two experts in managed care contracting and lab test pricing explain why payers cannot stay up with the requests for coverage

Testing, testing…

Health Insurers Balk at Paying for Multigene Panels While Clinical Pathology Laboratories and Physicians Pursue Evidence of Clinical Utility

September 2, 2015

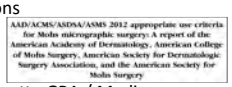
News reports state that Anthem and Cigna have denied payment for some multigene panel tests, saying that the tests are unproven. Other insurers, such as UnitedHealthcare and Priority Health, pay for such tests but only for certain patients

A conflict is building between patients and health insurers over the reluctance among health plans to pay for new, expensive molecular diagnostic assays and genetic tests that clinical laboratory companies offer.

What are dermatopathologists doing?

The American Society of Dermatopathology

- 1,300 members nationwide
- Following lead of the dermatologic surgeons
  - American College of Mohs Surgery
  - American Society for Mohs Surgery
  - American Society for Dermatologic Surgery Association


AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: A report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery

- In collaboration with Elaine Jeter MD, Palmetto GBA / Medicare

Evidence based medicine- appropriate use

The RAND/UCLA Appropriateness Method User's Manual

by Kathryn Fitch, Steven J. Bernstein, Maria Dolores Aguilar, Bernard Burnand, Juan Ramon LaCalle, Pablo Lazaro, Mirjam van het Loo, Joseph McDonnell, Janneke Vader, James P. Kahan

Related Topics: Evidence Based Health Practice, Health Care Quality, Medical Professionals

Citation

Read Online

Health systems should function in such a way that the amount of inappropriate care is minimized, while at the same time stinting as little as possible on appropriate and necessary care. The ability to determine and identify which care is overused and which is underused is essential to this functioning. To this end, the "RAND/UCLA Appropriateness Method" was developed in the 1980s. It has been further developed and refined in North America and, increasingly, in Europe.

For select cancers, genetic testing is recommended

- 2+ Her2neu by immunoperoxidase needs FISH testing to determine if true positive
- BRAF testing of metastatic melanomas
- ALK for lung cancers
- …

Mutation doesn't equal therapeutic efficacy -still depends on the tumor

- C-kit amplified in DFSP→ sensitive to imatinib
- C-kit amplified in Langerhans cell disease NOT sensitive to imatinib

Arch Dermatol. 2009 Aug;145(8):949-50. doi: 10.1001/archdermatol.2009.164.

Langerhans cell histiocytosis: treatment failure with imatinib.

Wagner C, Mohme H, Krömer-Olbrisch T, Stadler R, Goerdt S, Kurzen H.

Treatments approvals make news

F.D.A. Approves Combining 2 Cancer-Fighting Drugs

FDA Approves Costly Ipilimumab-Nivolumab Combination For Melanoma Treatment.

The Wall Street Journal (10/2, Loftus, Winslow, Subscription Publication) reports that the FDA approved a combination of Yervoy (ipilimumab) and Opdivo (nivolumab) to be taken together for advanced melanoma treatment, drugs expected to cost each patient $250,000 in their first year. The article highlights the high price of drug treatment cocktails, citing the annual cost by Novartis as $226,428 per patient.

If FDA approved, insurers tend to pay

- But then what protocol
  - Ipilimumab anti-CTLA4 moAb $39K per dose, 4 doses, finite or indefinite
  - Pembrolizumab programmed death receptor-1, 2 mg/kg administered as an intravenous infusion over 30 minutes every three weeks for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor- no set end points

Foreign experience- New Zealand

Melanoma drug Opdivo to be Pharmac funded

Pharmac said the clinical data for Opdivo, or nivolumab, is stronger than that for Merck Sharp & Dohme's pembrolizumab, an almost identical immunotherapy drug, sold as Keytruda.

Pharmac chief executive Steffan Crausaz said funding went for Opdivo rather than Keytruda because of clinical data.

Foreign experience- Canada

References

- Schwartz RA, Cutaneous metastatic disease JAAD 1995:33: 161-182
- Miller DM et al. Commentary: Molecular testing in melanoma JAAD 2014:70; 863-870
- http://www.radionz.co.nz/news/national/303027/melanoma-drug-opdivo-to-be-pharmac-funded
- MD Anderson Hospital Cancer of unknown primary algorithm, 2014

To Bleed or Not to Bleed?

North Carolina Dermatology Association
2016 Summer meeting

Abel Torres, MD, JD
Professor and Chairman
Director of Mohs Surgery
Department of Dermatology
Loma Linda, CA/Cleveland, OH

Sailesh Konda, MD/ Andrea Smith,MD Tanya Nino,MD
Procedural Dermatology Fellows
Department of Dermatology

LOMA LINDA UNIVERSITY
HEALTH

MetroHealth

DISCLOSURES IN PAST

- None at Present and None Relevant To This Talk

Mr. Jones

- Mr. Jones is a 72 year old male who presents to your clinic for excision of his scalp BCC.
- On review of his medical history he has history of coronary artery disease s/p 2 stents within the last year
- He states that he has stopped taking all his medications 2 weeks prior to surgery

Mr. Jone's Medication List

- Clopidogrel 75 mg PO Qday
- Simvastatin 40 mg PO Qday
- Metoprolol 25 mg PO BID

Was Mr. Jones Right? What is the Risk of Continuing vs. Stopping Anticoagulants and Antiplatelet Therapy during Dermatologic Surgery?

Why Hemostasis is Important?

- Inadequate hemostasis can directly or indirectly lead to:
  - Post-operative hemorrhage
  - Hematoma formation
  - Flap or graft necrosis
  - Wound dehiscence
  - Infection
  - Suboptimal Scar Formation
  - Stress and Anxiety for Patient (and Surgeon)

- Many studies have shown that clopidogrel, warfarin, and multiple anticoagulants increase bleeding risk
- Only one group published data suggesting significantly increased severe bleeding complications while on warfarin
  - 21 patients on warfarin, 5 (24%) experienced a major bleeding complication

Bordeaux et al. Prospective evaluation of dermatological surgery complications including patients on multiple antiplatelet and anticoagulant medications. J Am Acad Dermatol 2011;65:3

Bunick et al. Hemorrhagic complications in dermatologic surgery. Dermatologic Therapy; 2011;24.

Cook-Norris et al. Complications of cutaneous surgery in patients taking clopidogrel-containing anticoagulation. J Am Acad Dermatol 2011; 65:3.

Table 2 Summary of Studies Examining the Incidence of Dermatologic Surgical Complications in Patients on Blood Thinners

Drug and Study	No. of Patients	Controlled Study	Increased Severe Complications*
Aspirin and NSAIDs			
Otley et al[10]	286	Yes, retrospective	No
Billingsley & Maloney[11]	97	Yes, prospective	No
Lawrence et al[20]	61	Yes, prospective	No
Bartlett[17]	52	Yes, prospective	No
Shalom and Wong[16]	41	Yes, prospective	No
Kargi et al[18]	37	Yes, prospective	No
Warfarin			
Otley et al[10]	26	Yes, retrospective	No
Billingsley & Maloney[11]	12	Yes, prospective	No
Lam et al[14]	13	Yes	No
Alcalay[12,13]	16	Yes, prospective	No
Kargi et al[18]	21	Yes, prospective	Yes
Syed et al[15]	47	Yes, prospective	No

*Excessive bleeding (>1 hr despite pressure), hematoma, flap/graft necrosis, wound dehiscence, or infection.

Hurst EA, Yu SS, Grekin RC, Neuhaus IM. Bleeding complications in dermatologic surgery. Semin Cutan Med Surg. 2007;26:189-95.

- However, no reports exist regarding life-threatening hemorrhage from continued antithrombotic therapy in dermatologic surgery
- 63% percent of dermatologic surgeons never discontinue medically necessary aspirin and 56% never discontinue warfarin

Kirkorian AY, Moore BL, Siskind J, Marmur ES. Perioperative management of anticoagulant therapy during cutaneous surgery: 2005 survey of Mohs surgeons. Dermatol Surg. 2007;33:1189-1197.

DERMATOLOGIC SURGERY

Thrombotic complications related to discontinuation of warfarin and aspirin therapy perioperatively for cutaneous operation

Olympia Kovich, MD, and Clark C. Otley, MD *Rochester, Minnesota*

- Survey of ACMS surgeons :
  - 168 responded
  - **46 reports of patients with thrombotic events when warfarin or aspirin were held perioperatively**

Table I. Types of thrombotic complications

Thrombotic outcome	Patients experiencing complications, % (No.)
Stroke	49 (24)
Transient ischemic attack	17 (8)
Myocardial infarction	10 (5)
Cerebral embolism	6 (3)
Death	6 (3)
Deep venous thrombosis	6 (3)
Pulmonary embolus	4 (2)
Blindness	2 (1)

Table II. Thrombotic complications associated with warfarin versus aspirin

Thrombotic outcome	Warfarin, % (No.)	Aspirin, % (No.)
Stroke	63 (15)	29 (7)
Transient ischemic attack	38 (3)	62 (5)
Myocardial infarction	0 (0)	100 (5)
Cerebral embolism	67 (2)	33 (1)
Death	33 (1)	67 (2)
Deep venous thrombosis	67 (2)	0 (0)
Pulmonary embolus	100 (2)	0 (0)
Blindness	100 (1)	0 (0)

Serious Adverse Vascular Events Associated With Perioperative Interruption of Antiplatelet and Anticoagulant Therapy

MURAD ALAM, MD* AND LEONARD H. GOLDBERG, MD, FRCP†‡

*Division of Cutaneous and Aesthetic Surgery, Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, and †Department of Medicine (Dermatology), University of Texa M. D. Anderson Cancer Center, and ‡DermSurgery Associates, Houston, Texas

- Two high-risk patients with cardiovascular disease, antithrombotic meds stopped prior to Mohs surgery:
  - **Pulmonary embolism**
  - **Clotted prosthetic aortic valve**

BRIEF COMMUNICATIONS / CASE REPORT

Postoperative Stroke After Stopping Warfarin for Cutaneous Surgery

CARL F. SCHANBACHER, MD* AND RICHARD G. BENNETT, MD*†

*University of California at Los Angeles School of Medicine and †University of Southern California School of Medicine, Los Angeles, California

BACKGROUND. Two patients undergoing cutaneous surgery had thromboembolic strokes within 1 week after surgery. Both pa-

started soon after surgery, the patient is at increased risk for thromboembolism. Although it is commonly believed that con-

- 2 patients having Mohs for small BCCs
- Warfarin discontinued prior to surgery
- **Both had post-operative strokes**

ORIGINAL ARTICLE

Controversies in Perioperative Management of Blood Thinners in Dermatologic Surgery: Continue or Discontinue?

JOSEPH ALCALAY, MD,* AND RONEN ALKALAY, MD†

Mohs Surgery Unit, Assuta Medical Center, Tel Aviv, Israel; and †Department of Dermatology, Hadassah University Hospital, Faculty of Medicine, Hebrew University, Jerusalem, Israel

- Review of literature and authors' data from 2790 Mohs patients
- Conclusion: cutaneous surgery with anticoagulants and antiplatelet drugs is extremely safe
- Discontinuation of anticoagulants may increase the risk of cerebral and cardiovascular complications

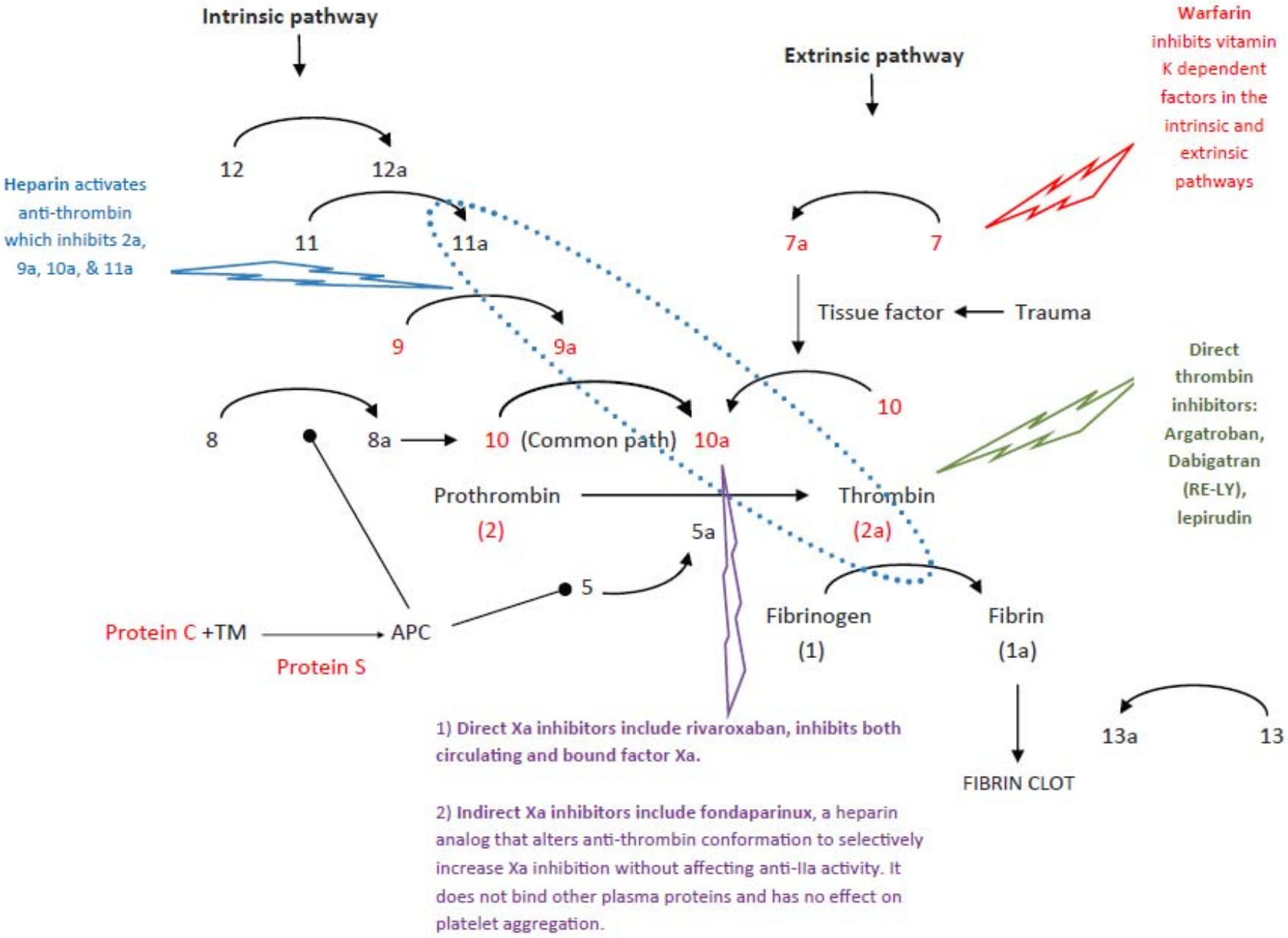
Dermatol Surg 2004;30:1091–1094.

PRE-OPERATIVE CONSIDERATIONS

- Anticoagulation
- Hypertension
- Medical comorbidities
- Anatomy

Bunick CG, Aasi SZ. Hemorrhagic complications in dermatologic surgery. Dermatologic Therapy, Vol. 24, 2011, 537–550.

ANTICOAGULANTS



Callahan S, Goldsberry A, Kim G, Yoo S. The Management of Antithrombotic Medication in Skin Surgery. Dermatol Surg 2012;38:1417–1426

Heparin Induced Skin Necrosis

- Heparin Induced Trombocytopenia (HIT) with decr plts and paradoxical clotting
- Locally or Systemic / F>M / Subcut
- 1-17 (Avg = 7) days s/p Injections
- Heparin Ab complex with PF4, Plts, heparin
- In abscence of this, Protein S and C nl
- 4T's = Thrombocytopenia >50%, Timing 5-10 d sp/Rx, Thrombosis skin or new, No AlTernative Cause
- Rx: D/C heparin and Local Rx
- If no HIT then can try different Heparin

http://www.dermnetnz.org/reactions/heparin-necrosis.htmlAuthor:
Dr Delwyn Dyall-Smith FACD, Dermatologist

VITAMIN K ANTAGONISTS (VKAS)

3 dominant clinical indications

- Mechanical heart valves
- Chronic atrial fibrillation
- Venous thromboembolism

Vitamin K Antagonists (VKAs)

Warfarin

- Inhibits synthesis of vitamin-K dependent clotting factors II (thrombin), VII, IX, X
- Monitoring effects via PT and INR
- If necessary, effects can be reversed with oral Vitamin K, fresh frozen plasma, or recombinant factor VIIa

VITAMIN K ANTAGONISTS (VKAS)

Warfarin

- Warfarin does not affect platelets, so it actually does not have as much of an effect on intra- or immediate postoperative bleeding.
- Instead, warfarin interferes with the formation of a fibrin plug, which in turns affects the clotting cascade and often impairs hemostasis 72 to 96 hours post surgery.

CISN

- Obese Middle Aged Female (F:M = 3:1)
- Pain , purpura, bulla, eschar
- 3-5 days s/p Rx usually with high loading
- Hereditary or induced Protein C Deficiency
- Post Partum Prot S/ Purple Toe Syndrome 3-8wk
- D/c Coumadin/ IV Heparin/FFP
- O2, Steroids, Vasodilators = No effect
- Progressive, skin subcut fat, rarely fascia and muscle
- Surgical treatment in >50% of cases

http://en.wikipedia.org/wiki/Warfarin_necrosis

Antiplatelet Drugs

- **Irreversible platelet inhibitors**
  - **Aspirin:** irreversibly inhibits cyclooxygenase
  - **Thienopyridines:** potent irreversible inhibitors of the adenosine diphosphate receptor on platelets
    - **Clopidogrel**
    - **Ticlopidine**
    - **Prasugrel**
- 7-10 days required for an entire platelet pool to be replenished

Reversible Platelet Inhibitor	Half Life
Dipyridamole	10 hours
Cilostazol	10 hours
Ibuprofen	2-6 hours
Ketoprofen	2-6 hours
Indomethacin	2-6 hours
Celecoxib	7-15 hours
Naproxen	7-15 hours
Diflunisal	7-15 hours
Meloxicam	> 20 hours
Nabumetone	> 20 hours
Piroxicam	> 20 hours

Assessing Risk for Perioperative Bleeding

What Procedures are "High Risk?"

PERIOPERATIVE ANTITHROMBOTIC THERAPY MANAGEMENT:

- **Assess risk for perioperative bleeding**
  - ACCP has also identified a group of surgeries associated with a high risk for bleeding in the context of perioperative anticoagulant/antiplatelet drug use
  - Dermatologic procedures are NOT in this high risk category

Douketis JD et al. Perioperative management of antithrombotic therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP guidelines. CHEST 2012; 141(2)(Suppl):e326S–e350S.

Dermatologic Procedures

- Wide local excisions
- Mohs surgeries without major reconstructive plastic surgery repair
- Biopsies
- **Incidence of major bleeding with continuation of anticoagulant therapy appears to be LOW in above procedures**

Douketis JD et al. Perioperative management of antithrombotic therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP guidelines. CHEST 2012; 141(2)(Suppl):e326S–e350S.

Risk for bleeding: High risk surgeries

- Urologic surgery and procedures consisting of transurethral prostate resection, bladder resection, or tumor ablation; nephrectomy; or kidney biopsy in part due to untreated tissue damage (after prostatectomy) and endogenous urokinase release[32-34]
- Pacemaker or implantable cardioverter-defibrillator device implantation in which separation of infraclavicular fascial layers and lack of suturing of unopposed tissues within the device pocket may predispose to hematoma development[35-38]
- Colonic polyp resection, typically of large (ie, > 1-2 cm long) sessile polyps, in which bleeding may occur at the transected stalk following hemostatic plug release[39]
- Surgery and procedures in highly vascular organs, such as the kidney, liver, and spleen
- Bowel resection in which bleeding may occur at the bowel anastomosis site

- Major surgery with extensive tissue injury (eg, cancer surgery, joint arthroplasty, reconstructive plastic surgery)[40,41]

WHAT TO DO ABOUT ANTICOAGULANTS?

LET'S START WITH VKA THERAPY

WHAT TO DO ABOUT ANTICOAGULANTS?
LET'S START WITH VKA THERAPY

- For Wide local excisions, Mohs without major plastic surgical reconstructions, and biopsies: **Continue VKA therapy around time of surgery**

- For Mohs with *major plastic surgical reconstructions* – can ***consider*** holding VKA and using bridging anticoagulation **based on risk for thromboembolism**

PERIOPERATIVE ANTITHROMBOTIC THERAPY MANAGEMENT:

- **Assess risk for thromboembolism**
  - Risk stratification by the American College of Chest Physicians (ACCP)

RISK STRATIFICATION FOR THROMBOEMBOLISM

Patients at HIGH risk

Mechanical heart valve:
- Any mitral valve prosthesis
- Any caged-ball or tilting disc aortic valve prosthesis
- Stroke or TIA within 6 months

Atrial Fibrillation:
- $CHADS_2$ score of 5 or 6
- Stroke or TIA within 6 months
- Rheumatic valvular heart disease

Venous Thromboembolism :
- VTE within 3 months
- Severe thrombophilia (e.g. Deficiency of protein C, protein S, or antithrombin 3; antiphopholipid antibodies, other abnormalities)

→ **Bridging anticoagulation not indicated** if interrupting VKA therapy

Douketis JD et al. Perioperative management of antithrombotic therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP guidelines. CHEST 2012; 141(2)(Suppl):e326S–e350S.

RISK STRATIFICATION FOR THROMBOEMBOLISM

Patients at MODERATE risk

Mechanical heart valve:
- Bileaflet aortic valve prosthesis and: atrial fibrillation, prior stroke or TIA, HTN, DM, CHF, Age > 75 y

Atrial Fibrillation:
- $CHADS_2$ score of 3 or 4
- Chf,Hbp,Age 75,Dm,Stroke or TIA-2,V= Vascular Dz,Age = 65-75, Sex = female-1Criteria

Venous Thromboembolism :
- VTE within 3-12 months
- Nonsevere thrombophilia (heterozygous factor V Leiden or prothrombin gene mutation)
- Active cancer treated within 6 months or palliative

No-bridging approach **based on individual patient and surgery risk factors**

Douketis JD et al. Perioperative management of antithrombotic therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP guidelines. CHEST 2012; 141(2)(Suppl):e326S–e350S.

RISK STRATIFICATION FOR THROMBOEMBOLISM

Patients at LOW risk

Mechanical heart valve:
- Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke

Atrial Fibrillation:
- $CHADS_2$ score of 0-2 (assuming no prior stroke or TIA)

Venous Thromboembolism :
- VTE > 12 months previous and no other risk factors

NO Bridging during interruption of VKA therapy

Douketis JD et al. Perioperative management of antithrombotic therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP guidelines. CHEST 2012; 141(2)(Suppl):e326S–e350S.

WHAT WAS BRIDGING ANTICOAGULATION? BRIDGING TRIAL = NOT EFFECTIVE

- Administration of a short-acting anticoagulant, either:
  - Subcutaneous (SC) low-molecular-weight heparin (LMWH) ***or***
  - IV unfractionated heparin (UFH)
- 10- to 12-day period during interruption of VKA therapy
- UFH can be stopped 4-6 hours prior to surgery
- LMWH can be stopped 24 hours prior to surgery

Douketis JD et al. Perioperative management of antithrombotic therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP guidelines. CHEST 2012; 141(2)(Suppl):e326S–e350S.

What to do about Aspirin?

CONTINUE ASPIRIN…

- In patients taking ASA for **secondary prevention** of CV disease and are having minor dermatologic procedures
  - Established coronary artery disease
  - Peripheral arterial disease
  - Atherosclerotic aortic disease
  - Carotid artery disease

- Patients at **moderate to high risk for perioperative adverse CV events** having minor dermatologic procedures:
  - Ischemic heart disease
  - Compensated or prior CHF
  - Diabetes mellitus
  - Renal insufficiency
  - Cerebrovascular disease

Douketis JD et al. Perioperative management of antithrombotic therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP guidelines. CHEST 2012; 141(2)(Suppl):e326S–e350S.

Discontinue Aspirin

- In patients at low risk for cardiovascular events, taking aspirin for **primary prevention**
- Discontinue 7-10 days before surgery

Douketis JD et al. Perioperative management of antithrombotic therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP guidelines. CHEST 2012; 141(2)(Suppl):e326S–e350S.

What to do about Clopidogrel?

CLOPIDOGREL

- No current evidence suggests that continuation of clopidogrel during dermatologic surgery is associated with life-threatening or major adverse events
- **Therefore, benefit of intra- and postoperative hemostasis does not outweigh the potentially lethal risks associated with discontinuation of clopidogrel**

Callahan S, Goldsberry A, Kim G, Yoo S. The Management of Antithrombotic Medication in Skin Surgery. Dermatol Surg 2012;38:1417–1426

However, Clopidogrel does increase bleeding risk

- Long duration of action, peak after 3 to 5 days, with slow platelet recovery
- No antidote to reverse effects:
  - Even platelet transfusion will not help, because circulating drug metabolite inactivates the acquired platelets,
- What do you do if you anticipate a surgery with potential for extensive tissue injury/major plastic surgical reconstruction?
  - Defer elective dermatologic surgery if possible

CLOPIDOGREL – STENT DILEMMA

- In patients with a coronary stent who are receiving dual antiplatelet therapy and require surgery:
  - **Defer surgery** for at least 6 weeks after placement of a bare-metal stent and for at least 6 months after placement of a drug-eluting stent instead of undertaking surgery within these time periods
- In patients who *require* surgery within 6 weeks of placement of a bare-metal stent or within 6 months of placement of a drug-eluting stent:
  - **Continue** dual antiplatelet therapy around the time of surgery instead of stopping dual antiplatelet therapy 7 to 10 days before surgery

Douketis JD et al. Perioperative management of antithrombotic therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP guidelines. CHEST 2012; 141(2)(Suppl):e326S–e350S.

What's New on the Scene?

NOACs (New Oral Anticoagulants)

- Direct Thrombin Inhibitors
  - eg. Dabigatran (Pradaxa)

- Factor Xa-Inhibitors
  - eg. Rivaroxaban (Xarelto), Apixaban (Eliquis)

* NOACs are now prescribed to more than 60% of patients with newly diagnosed atrial fibrillation.

Desai NR, Krumme AA, Schneeweiss S, Shrank WH. Patterns of Initiation of Oral Anticoagulants in Patients with Atrial Fibrillation - Quality and Cost Implications. Am J Med. 2014 May 20. [Epub ahead of print]

NOACs: Mechanism of Action

Fenger-Eriksen C1, Münster AM, Grove EL. New oral anticoagulants: clinical indications, monitoring and treatment of acute bleeding complications. Acta Anaesthesiol Scand. 2014 Jul;58:651-9.

NOACs: Current Indications for Therapy

Table 2. Summary of current TGA approved indications for warfarin and individual NOACs				
Clinical indication	**Warfarin**	**Apixaban**	**Dabigatran**	**Rivaroxaban**
VTE prophylaxis following elective hip or knee surgery	Yes	Yes	Yes	Yes
VTE prophylaxis in acutely ill medical at-risk inpatients	No	No	No	No
VTE prophylaxis for surgery following hip fracture, minor orthopaedic or non-orthopaedic procedures	No	No	No	No
VTE treatment	Yes	YES	YES	Yes**
Thromboprophylaxis for non-valvular atrial fibrillation	Yes	Yes	Yes	Yes
Thromboprophylaxis for patients with significant valve disease* and atrial fibrillation	Yes	No	No	No
Thromboprophylaxis for patients with mechanical prosthetic cardiac valve replacement	Yes	No	No	No
VTE, venous thromboembolism * Mitral stenosis, bioprosthetic heart valve or mitral valve repair[24] ** Excluding patients with active cancer or antiphospholipid syndrome				

Brieger D. Anticoagulation: a GP primer on the new oral anticoagulants. Aust Fam Physician. 2014 May;43(5):254-9.

Acta Anaesthesiol Scand 2014; ••: ••–••
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/aas.12319

Review Article

New oral anticoagulants: clinical indications, monitoring and treatment of acute bleeding complications

C. Fenger-Eriksen[1], A.-M. Münster[2] and E. L. Grove[3]
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New oral anticoagulants like the direct thrombin inhibitor, dabigatran (Pradaxa®), and factor Xa-inhibitors, rivaroxaban (Xarelto®) and apixaban (Eliquis®) are available for prophylaxis and treatment of thromboembolic disease. They are emerging alternatives to warfarin and provide equal or better clinical outcome together with reduced need for routine monitoring. Methods for measuring drug concentrations are available, although a correlation between plasma drug concentrations and the risk of bleeding has not been firmly established. Standard laboratory measures like prothrombin time and activated partial thromboplastin time are not sensitive enough to detect thrombin or factor Xa inhibition provided by new oral anticoagulants. Thus, these standard tests may only be used as a crude estimation of the actual anticoagulation status. Further challenges regarding patients receiving new oral anticoagulants who presents with major bleeding or need for emergency surgery pose a unique problem. No established agents are clinically available to reverse the anticoagulant effect, although preclinical data report prothrombin complex concentrate as more efficient than fresh frozen plasma or other prohaemostatic agents.

This review summaries current knowledge on approved new oral anticoagulants and discusses clinical aspects of monitoring, with particular focus on the management of the bleeding patient.

Accepted for publication 10 March 2014

NOACs: Advantages

- More predictable effects
- Do not require routine monitoring
- Fewer major bleeding events (? Pradaxa)
- More effective prophylaxis against VTE
- Even with major bleeding events, "trended" towards lower mortality
- Less Intracranial Events
- Diet not a significant factor
- Apixaban = decreased cardiac events

Fenger-Eriksen C1, Münster AM, Grove EL. New oral anticoagulants: clinical indications, monitoring and treatment of acute bleeding complications. Acta Anaesthesiol Scand. 2014 Jul;58:651-9.

NOACs: Disadvantages

- Reduced renal clearance can lead to supratherapeutic levels
- No specific reversal agent available
  - Variable success with using PCC, rFVIIa, aPCC, fibrinogen, and FFP in animal/human studies
  - Dialysis can remove dabigatran
    - Rivaroxaban/apixaban are highly protein-bound
- Monitoring Difficult at Best
- Bleeding Events high in Frail Renal Impaired

Fenger-Eriksen C1, Münster AM, Grove EL. New oral anticoagulants: clinical indications, monitoring and treatment of acute bleeding complications. Acta Anaesthesiol Scand. 2014 Jul;58:651-9.

NOACs: Specific Antidotes

- r-Antidote (PRT064445)
  - Recombinant protein binds Xa inhibitor site
  - Reverses rivaroxaban (Soon)
- aDabi-Fab
  - Monoclonal antibody against dabigatran (now)
- PER977
  - Small synthetic molecule directly binds Xa and IIa
  - Reverses dabigatran, rivaroxaban, apixaban

* Tested in animal models; none are FDA approved

Lu G, DeGuzman FR, Hollenbach SJ, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med. 2013 Apr;19:446-51.

NOACs: When is Monitoring Indicated?

- Patients needing acute surgery
- Patients with suspected Supratherapeutic Levels
- Patients with reduced Hepatic and/or Renal Function

- ***"Patients undergoing elective surgery or invasive procedures do not require routine laboratory screening…patients may safely undergo these procedures 24-72 hours after the last dose administration"***

Fenger-Eriksen C1, Münster AM, Grove EL. New oral anticoagulants: clinical indications, monitoring and treatment of acute bleeding complications. Acta Anaesthesiol Scand. 2014 Jul;58:651-9.

MONITORING OF THE NOACS

Table 6. Effect of the NOACs on routinely performed coagulation assays			
	Dabigatran	**Rivaroxaban**	**Apixaban**
Significant anticoagulant effect unlikely	APTT and TT normal	PT normal	Normal PT **DOES NOT** exclude presence of therapeutic apixaban
Anticoagulant effect present	TT prolongedAPTT prolonged	PT prolonged	PT prolonged or normal
Specific assays to quantify drug presence	Dilute thrombin clotting time (Hemoclot assay)	Modified Anti Xa assay specific for rivaroxaban	Modified Anti Xa assay Specific for apixaban
APTT, activated partial thromboplastin time; TT, thrombin time			

Brieger D. Anticoagulation: a GP primer on the new oral anticoagulants. Aust Fam Physician. 2014 May;43(5):254-9.

NOACs and bleeding complications

Table 2

Preoperative withdrawal of new oral anticoagulants treatment prior to elective surgery/invasive procedures.

Drug	Creatinine clearance (ml/min)	Risk of bleeding	
		Low (h)	High (h)
Dabigatran	> 50	36	72
Pradaxa®	30–50*	48	72–96
Rivaroxaban	> 50	24	48
Xarelto®	30–50	36	72
Apixaban	> 50	24	48
Eliquis®	30–50	36	72

*This recommendation applies to all patients more than 75 years old despite normal renal function.

Fenger-Eriksen C1, Münster AM, Grove EL. New oral anticoagulants: clinical indications, monitoring and treatment of acute bleeding complications. Acta Anaesthesiol Scand. 2014 Jul;58:651-9.

10. Dr Bercovitch ultimately feels that accepting the guide is not ethically wrong. What should the resident do if his hospital bans all such gifts? Accept it as an act of civil disobedience? Every resident signs a contract with their hospital that includes language that essentially says that any violation of the rules is a terminable offense. Obviously this would not happen, but how can we let residents put themselves in this position?

11. We agree that if a resident can consider all of this and reach an ethical resolution in his mind, the risk of influence may be minimal. But the problem is that few question it, and those who do may face peer pressure (eg, "How can I not use what everyone else is using?").

In conclusion, we agree that this is not a flagrant or egregious violation by any single person. Despite the excellent discussion by Dr Bercovitch, after analyzing the situation, it does

REFERENCES

1. Coyle SL. Physician-Industry Relations. Part 1: Individual Physicians. Ann Intern Med 2002;136:396-402.
2. PhRMA's code on interactions with healthcare professionals. Available at: http://www.phrma.org/sites/default/files/108/phrma_marketing_code_2008.pdf. Accessed Aug 22, 2012.

http://dx.doi.org/10.1016/j.jaad.2012.10.035

A new oral anticoagulant in the setting of dermatologic surgery

To the Editor: Dabigatran is an oral direct thrombin inhibitor recently approved for use in the United States. Direct thrombin inhibitors act by binding competitively and reversibly to factor IIa (thrombin), thereby interrupting the coagulation cascade (Fig 1).[1] Vitamin K antagonists, such as warfarin, act by inhibiting the activity of vitamin K–dependent carboxylase, which is needed for the activation of coagulation factors II, VII, IX, and X.[2] Heparins indirectly inhibit thrombin by catalyzing the function of antithrombin.[1]

Schmitt AR, Zender CA, Bordeaux JS. A new oral anticoagulant in the setting of dermatologic surgery. J Am Acad Dermatol. 2013;68:869-70.

Hemorrhagic Complications of Direct Thrombin Inhibitors—Subarachnoid Hemorrhage During Dermabrasion for Scar Revision

Dabigatran etexilate is an oral anticoagulant that functions by direct thrombin inhibition. Dabigatran is indicated for atrial fibrillation and stroke prophylaxis, but in the event of hemorrhage, no proven reversal agent exists. As many as 25–38% of patients who present for cutaneous surgery are taking an antithrombotic agent.[1] Current recommendations are to continue medically necessary aspirin, warfarin, and clopidogrel, but the direct thrombin inhibitors have yet to be studied.[2] Familiarity with the new oral anticoagulants is critical so that optimal outcomes can be ensured and complications avoided. The authors report a case of an elderly patient being treated with dabigatran for atrial fibrillation who developed a subarachnoid hemorrhage (SAH) during dermabrasion for scar revision.

A 69-year-old woman presented for dermabrasion for a scar secondary to Mohs micrographic surgery and flap repair on the nose. She was taking dabigatran 150 mg twice daily for atrial fibrillation. She presented a few minutes late to her appointment because of gastrointestinal discomfort. During infiltration of 10 mL of anesthetic (bicarbonate buffered 1% Xylocaine with 1:100,000 epinephrine) she began to exhibit symptoms of anxiety. These were attributed to the effect of the epinephrine, and the procedure was allowed to continue. After the procedure, she complained of an uneasy feeling and chest and shoulder discomfort. Within minutes, she became diaphoretic and exhibited pallor.

Emergency medical services were notified, and she was placed on 2 L of oxygen by nasal cannula. She was also offered an aspirin tablet because her signs and symptoms were consistent with a cardiac event. The patient declined the aspirin stating that she was told it could interfere with her Pradaxa.

Fakhouri TM, Harmon CB. Hemorrhagic complications of direct thrombin inhibitors-subarachnoid hemorrhage during dermabrasion for scar revision. Dermatol Surg. 2013;39:1410-2

Other Causes of Bleeding to Consider

- ETOH
  - Inhibits Platelets
  - Decreased Coagulation
  - Increased Fibrinolysis
  - Potent Vasodilator

Recommend avoiding ETOH Consumption 48 hours before and after surgery

Other factors to consider: Hypertension

- There may be an unmeasurable increased risk of hematoma and post-operative bleeding when BP is elevated.
- Recent studies show BP comes down after starting surgical procedure.
- If BP $\leq$ 180 /110, and no other medical contraindications, cutaneous surgery may proceed. (Caveat=>100 d = Demand Ischemia with Diastolic CHF
- If BP 181-200/101-110, small risk of cardiovascular lability → surgeon preference determines whether or not to proceed.
- If BP >200/110, recommend defer procedure + consult with PMD.

Alcalay J, Alkalay R, Grossman E. Blood pressure levels decrease during Mohs micrographic surgery. J Drugs Dermatol 2005: 4 (4): 469–470.
Bunick CG, Aasi SZ. Hemorrhagic complications in dermatologic surgery. Dermatologic Therapy, Vol. 24, 2011, 537–550.

Other factors to consider: Medical comorbidities

- Do you have any known bleeding problems?
- Do you have any known diseases that cause you to bleed easily?
- Have you ever experienced uncontrollable bleeding during or after a medical procedure?
- Does anyone in your family have problems with excessive bleeding? Do you have any liver disease or history of liver transplantation?
- Have you ever been diagnosed with a low platelet count (or thrombocytopenia)?
- How much alcohol do you drink?
- Physical signs of easy bruising during the preoperative evaluation?
- If answers/signs suggest an abnormality:
  - CBC
  - PT
  - PTT
  - Bleeding time

Bunick CG, Aasi SZ. Hemorrhagic complications in dermatologic surgery. Dermatologic Therapy, Vol. 24, 2011, 537–550.

Other factors to consider: OTC

- OTC linked to increased bleeding: Pepto-Bismol® (Bismuth subsalicylate), Alka-Seltzer® (Contains ASA)

Other factors to consider: Supplements

- Supplements linked to increased bleeding: bilberry, bromelain, fish oil, flaxseed oil, garlic, methylsulfonylmethane, selenium, and vitamin E
- Supplements with potential adverse effects: echinacea, ephedra (ma huang), ginkgo, ginseng, kava, St. John's wort, valerian, feverfew, and ginger
- Retrospective study: 49/200 (24.5%) of cosmetic patients were taking supplements

Zwiebel SJ, Lee M, Alleyne B, Guyuron B. The incidence of vitamin, mineral, herbal, and other supplement use in facial cosmetic patients. Plast Reconstr Surg. 2013 Jul;132:78-82

Other factors to consider: Anatomy

- Majority of Mohs surgeries on head and neck
- Danger zones:
  - Frontal branch of the temporal artery located at the temple
  - Facial artery at its crossing over the mandibular rim
  - Angular artery adjacent to the nose

Robinson JK. Anatomy for procedural dermatology. In: Robinson JK, Hanke CW, Siegel DM, Fratila A, eds. Surgery of the skin. New York, NY: Moby Elsevier, 2010:3–27

HEMATOMA

- Four stages: early formation, gelatinous, organized, and liquefaction
- Risk greatest first 48 hours post-op
- Emergency: periorbital/cervical locations
  - Mass effect on underlying vital structures
- Medium for bacterial infection

Bunick CG, Aasi SZ. Hemorrhagic complications in dermatologic surgery. Dermatologic Therapy, Vol. 24, 2011, 537–550.

Hematoma Management

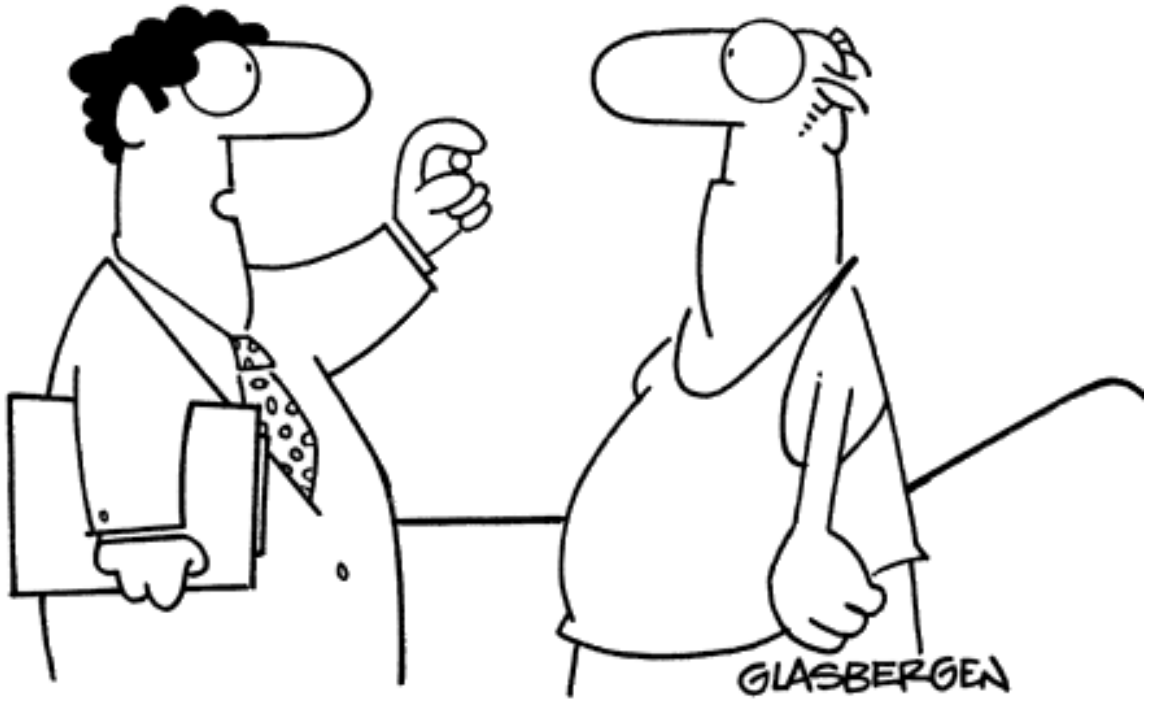
- +/- Needle aspiration
  - Early formation/liquefaction stages
- Partial or complete opening of surgical wound
- Suture ligation/electrosurgery of culprit vessels
  - Debate: +/- epinephrine?
- Reclosure vs. healing by secondary intention
- Antibiotics

Bunick CG, Aasi SZ. Hemorrhagic complications in dermatologic surgery. Dermatologic Therapy, Vol. 24, 2011, 537–550.

Clinical Pearls

Quick Clot = Combat Gauze

- Kaolin + Rayon + Polyester Gause
- Aluminum Silicate
- FDA Medcial Device Approval as adjuvant for superficial wounds with new version for patients on anticoagulant therapy
- Gauze = no significant contraindication v Powder = ? Chemical burn reaction.
- Temporary measure with RC studies in animals and no RC studies in humans



**"To prevent a heart attack, take one aspirin every day.
Take it out for a jog, then take it to the gym,
then take it for a bike ride..."**

The End

No longer just the skin: the association of the metabolic syndrome with cutaneous diseases

Abby S. Van Voorhees, MD
Eastern Virginia School of Medicine
July 10, 2016

Conflict of Interest Statement

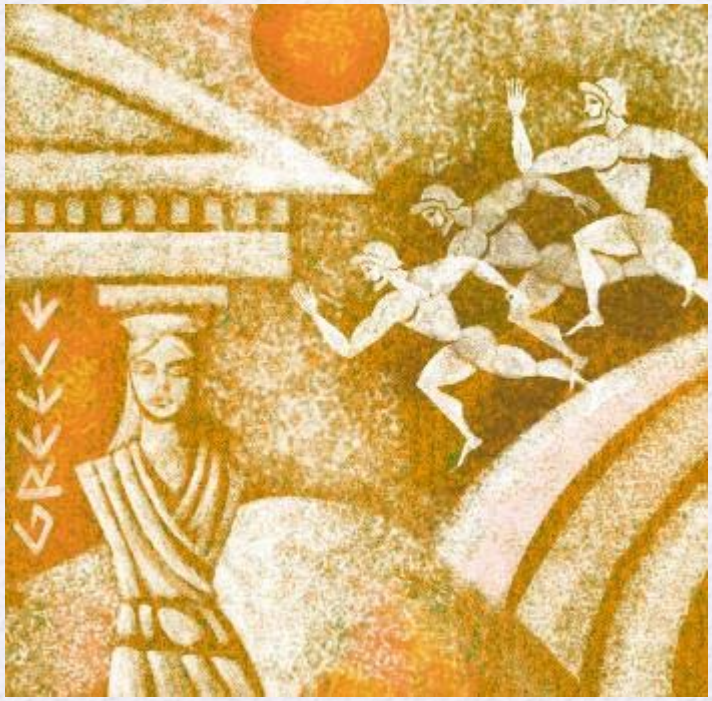
- I have participated in clinical trials as an investigator for the following companies: Abbott
- I have served as an advisor/consultant to the following companies: Dermira, Astra Zeneca, Novartis, Pfizer, Celgene, AbbVie, Merck
- I am a scientific advisor for Corrona Psoriasis Registry
- I receive a portion of ex-spouse pension from Merck

Cutaneous diseases

- Psoriasis
- Hidradenitis supprativa
- Atopic dermatitis
- Vitiligo
- Lichen planus
- PCOS/Acne

Historical Perspective

- Oldest recorded skin disease
- Regarded as a variant of leprosy
- First described 460 BC



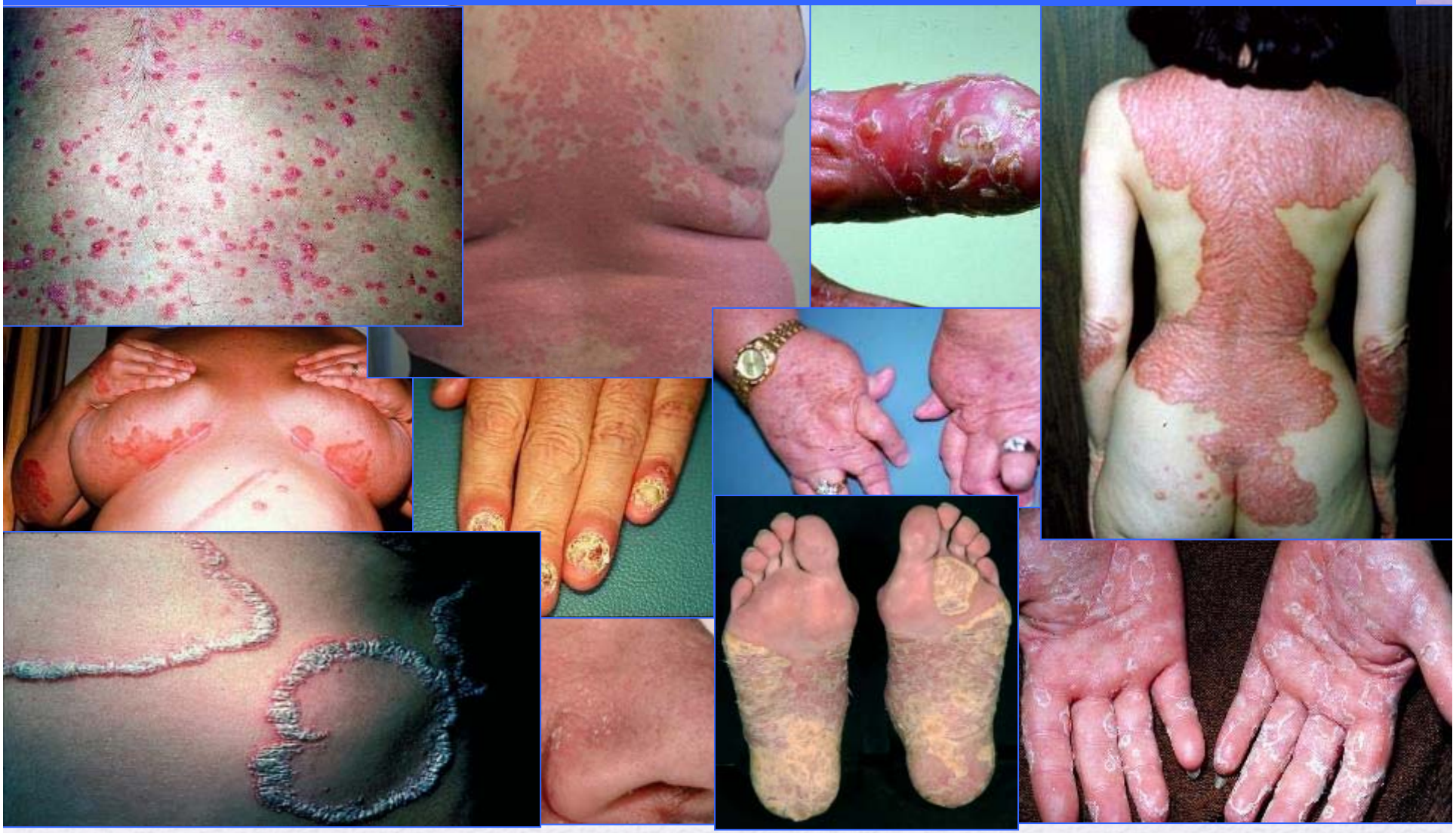
Epidemiology of Psoriasis

- Incidence
  - 2-3% of US population
  - 5% of Scandinavian population
  - Decreased incidence in Native Americans, Japanese and African Americans
  - Worldwide incidence: 0.9%-2.9%

Age of Onset of Psoriasis

- Most common: 20’s
- Second peak: 50-60’s
- Childhood: mean 8.1 years

Psoriatic disease



Courtesy of the National Psoriasis Foundation

Griffiths CE et al, Br J Dermatol 2007

What are symptoms of psoriasis?

- Psoriasis can make the skin itch, burn, sting and/or bleed
- Flaking and scaling are most common symptoms
- Constant itching is often described as the most frustrating symptom

Comorbid diseases

no longer
“just a skin disease”

Comorbidities in Psoriasis

- Psoriatic arthritis
- Inflammatory bowel disease
- Uveitis
- Renal disease
- Hepatosteatosis
- COPD
- Sleep apnea
- Depression & anxiety
- Peripheral vascular disease
- Malignancy
- Diabetes
- Dyslipidemia
- Obesity
- Hypertension
- Myocardial infarction
- Stroke
- Aortic valve stenosis
- Aortic aneurysm
- Migraine
- Alcoholism
- Smoking

Jamnitski A, et al. Ann Rheum Dis 2013, Yeung H, et al. JAMA Dermatol. 2013

Shared pathways?

- Chronic type 1 helper (Th1) T cell and Th 17-mediated inflammation
- Monocyte and neutrophil modulation
- Increased oxidative stress
- Endothelial cell dysfunction
- Increased uric acid
- Angiogenesis
- Increased circulating microparticles

Genome Wide Association Studies (GWAS) data Common immune process

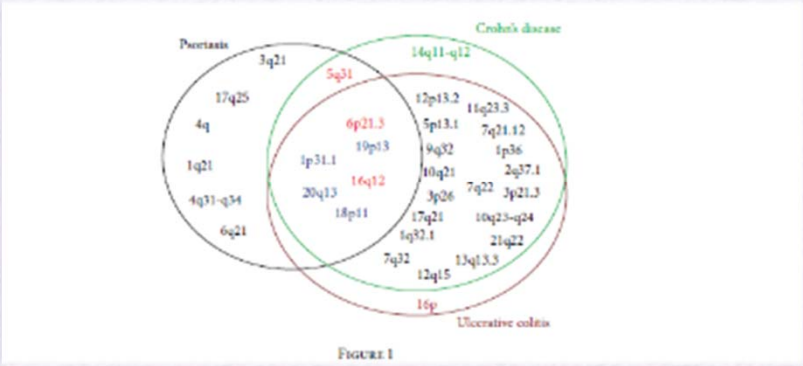


FIGURE 1

Skroza N, BioMed Research International 2013

Genome-wide Association Analysis of Psoriatic Arthritis and Cutaneous Psoriasis Reveals Differences in Their Genetic Architecture

Philip E. Stuart,[1,34] Rajan P. Nair,[1,34] Lam C. Tsoi,[1,2,3,34] Trilokraj Tejasvi,[1,4] Sayantan Das,[2] Hyun Min Kang,[2] Eva Ellinghaus,[5] Vinod Chandran,[6,7] Kristina Callis-Duffin,[8] Robert Ike,[9] Yanming Li,[2] Xiaoquan Wen,[2] Charlotta Enerbäck,[10] Johann E. Gudjonsson,[1] Sulev Kõks,[11,12] Külli Kingo,[13] Tõnu Esko,[14] Ulrich Mrowietz,[15] Andre Reis,[16] H. Erich Wichmann,[17,18,19] Christian Gieger,[20,21] Per Hoffmann,[22,23] Markus M. Nöthen,[22,23] Juliane Winkelmann,[24,25] Manfred Kunz,[26] Elvia G. Moreta,[27] Philip J. Mease,[28] Christopher T. Ritchlin,[29] Anne M. Bowcock,[30] Gerald G. Krueger,[8] Henry W. Lim,[31] Stephan Weidinger,[15] Michael Weichenthal,[15] John J. Voorhees,[1] Proton Rahman,[32] Peter K. Gregersen,[33] Andre Franke,[5] Dafna D. Gladman,[6,7] Gonçalo R. Abecasis,[2] and James T. Elder[1,4,*]

Metabolic syndrome

- **Obesity: waist circumference**
  - **>102 cm men, > 88 cm women**
- **Dyslipidemia**
  - **Elevated triglycerides**
  - **Reduced HDL cholesterol**
- **Hypertension**
- **Impaired glucose tolerance**

The heavy psoriasis patient

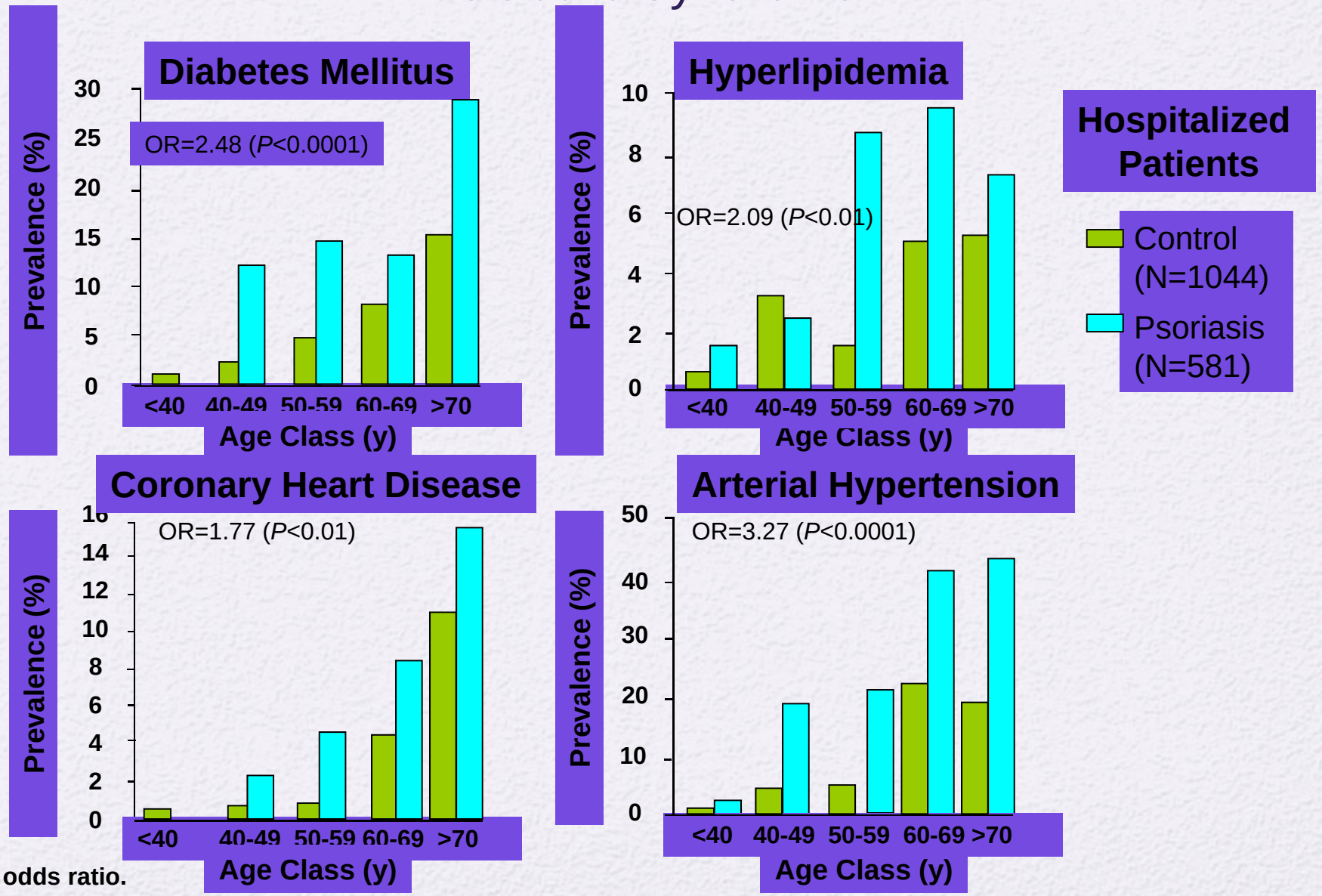
Table II. Skin disorders and most common noncutaneous disorders concurrently diagnosed in patients with psoriasis

Disease	Total No. of patients	No. of patients with concurrent psoriasis	O/E	*p*
Cutaneous				
Erythroderma	207	57	4.31	<0.0001
Candida infections	1906	161	1.26	<0.05
Dermatophyte infections	2683	142	0.75	<0.01
Acne	1575	104	0.74	<0.01
Condylomata acuminata	743	33	0.53	<0.001
Erysipelas	629	17	0.41	<0.001
Zoster	940	20	0.36	<0.0001
Allergic contact dermatitis	3569	86	0.33	<0.0001
Impetigo contagiosa	731	12	0.30	<0.0001
Urticaria	2010	27	0.17	<0.0001
Eczema herpeticatum	133	1	0.10	<0.01
Atopic dermatitis	1701	5	0.04	<0.0001
Noncutaneous				
Chronic tonsillitis	119	40	3.62	<0.0001
Obesity	113	25	2.05	<0.05
Hypertension	337	58	1.90	<0.01
Heart failure	782	103	1.83	<0.001
Diabetes mellitus	471	61	1.47	<0.05

- **Association of psoriasis with obesity, diabetes and cardiac disease**
- **Genetics versus diet, nutrition, and exercise**

Henseler T, Christophers E, J Amer Acad Dermatol 1995

Psoriasis and the Metabolic Syndrome



OR = odds ratio.
Control = patients hospitalized for reasons other than psoriasis.
Sommer et al. *Arch Dermatol Res.* 2006;298:321-328.

Obesity and weight gain as risk factors for psoriasis

- 78,626 women followed for 14 yrs. in nursing health study
- Relative risk 1.4 (BMI 25-30) vs. 2.69(BMI>35)
- Increase risk of psoriasis in those with
  - Weight gain from age 18
  - Increase in waist circumference
  - Increase in hip circumference
  - Increase in hip-waist ratio
- Adiposity and weight gain are strong risk factors for psoriasis in women

Setty AR, Curhan G, Choi HK, Arch Intern Med, 2007

Risk of metabolic syndrome related to disease severity-2012

Table 3. Association between psoriasis severity and components of the metabolic syndrome independent of other components

Psoriasis extent	High blood pressure, OR (95% CI)	Raised triglyceride levels, OR (95% CI)	Low HDL, OR (95% CI)	Hyperglycemia, OR (95% CI)	Obesity (BMI $>30\ kg\ m^{-2}$), OR (95% CI)
No psoriasis, *n*=40,650	1.0	1.0	1.0	1.0	1.0
Psoriasis overall, *n*=4,065	1.07 (0.96–1.19)	1.20 (1.10–1.31)	0.98 (0.89–1.08)	1.16 (1.06–1.27)	1.25 (1.16–1.34)
By extent					
Mild psoriasis (⩽2%), *n*=2,044	1.03 (0.89–1.20)	1.10 (0.98–1.25)	0.99 (0.87–1.13)	1.11 (0.97–1.26)	1.14 (1.03–1.27)
Moderate psoriasis (3–10%), *n*=1,377	1.02 (0.85–1.24)	1.31 (1.13–1.51)	0.94 (0.80–1.11)	1.16 (0.99–1.35)	1.34 (1.18–1.53)
Severe psoriasis (>10%), *n*=475	1.32 (0.91–1.92)	1.46 (1.13–1.88)	1.05 (0.80–1.39)	1.31 (1.00–1.71)	1.66 (1.33–2.07)

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio.

Langan S, et al, J Invest Dermatol 2012

Lipid abnormalities

- OR: 1.10 to 3.38 for mild psoriasis
- OR: 1.36-5.55 for severe psoriasis
- more atherogenic lipid profile
  - decreased high density lipoprotein (HDL) cholesterol efflux capacity (CEC)

Psoriasis and the independent risk of diabetes

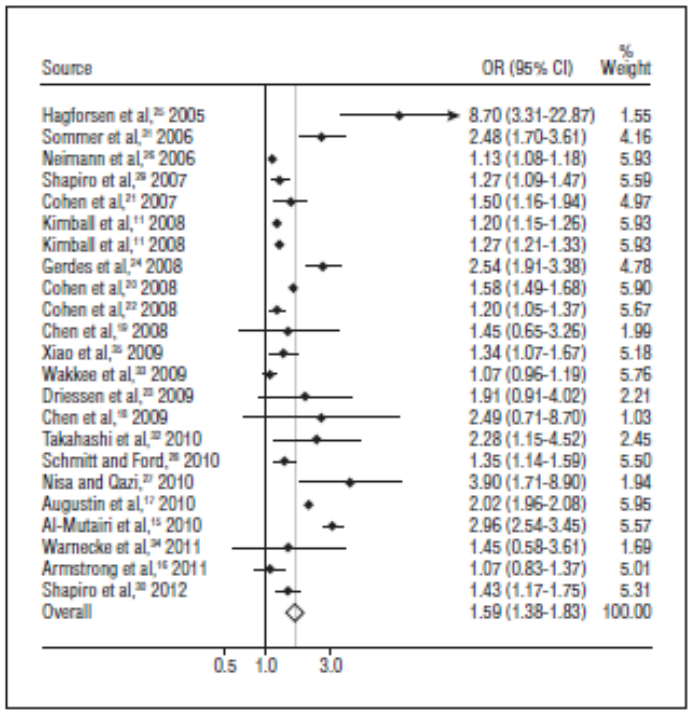


Figure 2. Random-effects meta-analysis of the prevalence of diabetes in patients with psoriasis compared with controls. OR indicates odds ratio; dashed vertical line, estimated pooled effect size estimate; lines with solid diamonds, odds ratios (ORs) and 95% CIs; and open diamond, a visual summary of the overall 95% CI of the effect estimate of psoriasis on the prevalence of diabetes (1.38-1.83).

Armstrong A, et al, JAMA Dermatol 2013

Psoriasis and diabetes
Risk parallels severity of disease

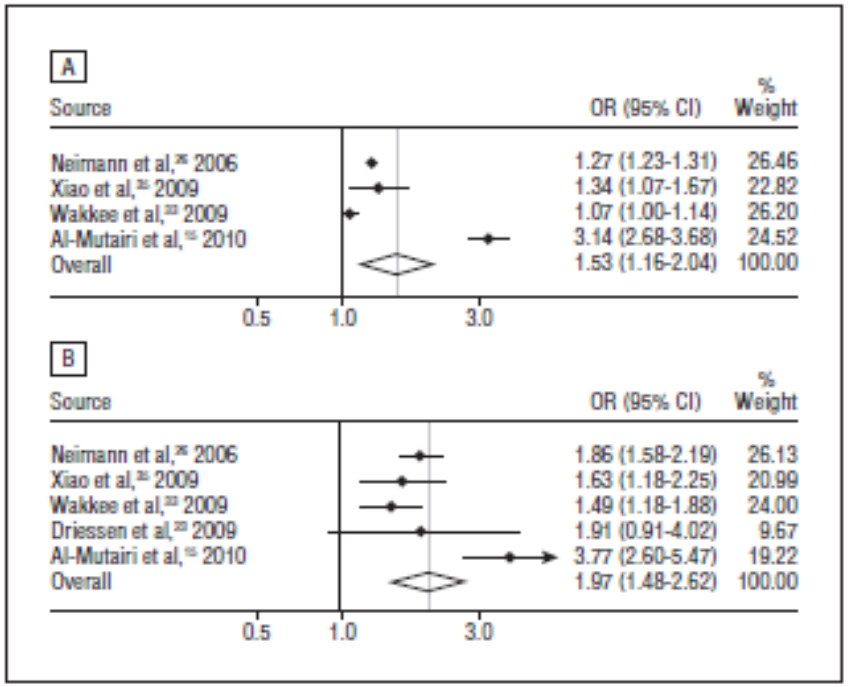


Figure 3. Random-effects meta-analysis of the prevalence of diabetes. A, Patients with mild psoriasis compared with controls. B, Patients with moderate to severe psoriasis compared with controls. OR indicates odds ratio; dashed vertical line, pooled effect size estimate; lines with solid diamonds, ORs and 95% CIs; and open diamond, a visual summary of the overall 95% CI of the effect estimate of psoriasis on the prevalence of diabetes.

Armstrong A. et al. JAMA Dermatol 2013

Increased risk of diabetes severity

- Increased risk of diabetic complications and insulin resistance correlate with disease severity
  - Diabetes with systemic complications 1.34
- Independent of traditional risk factors including BMI

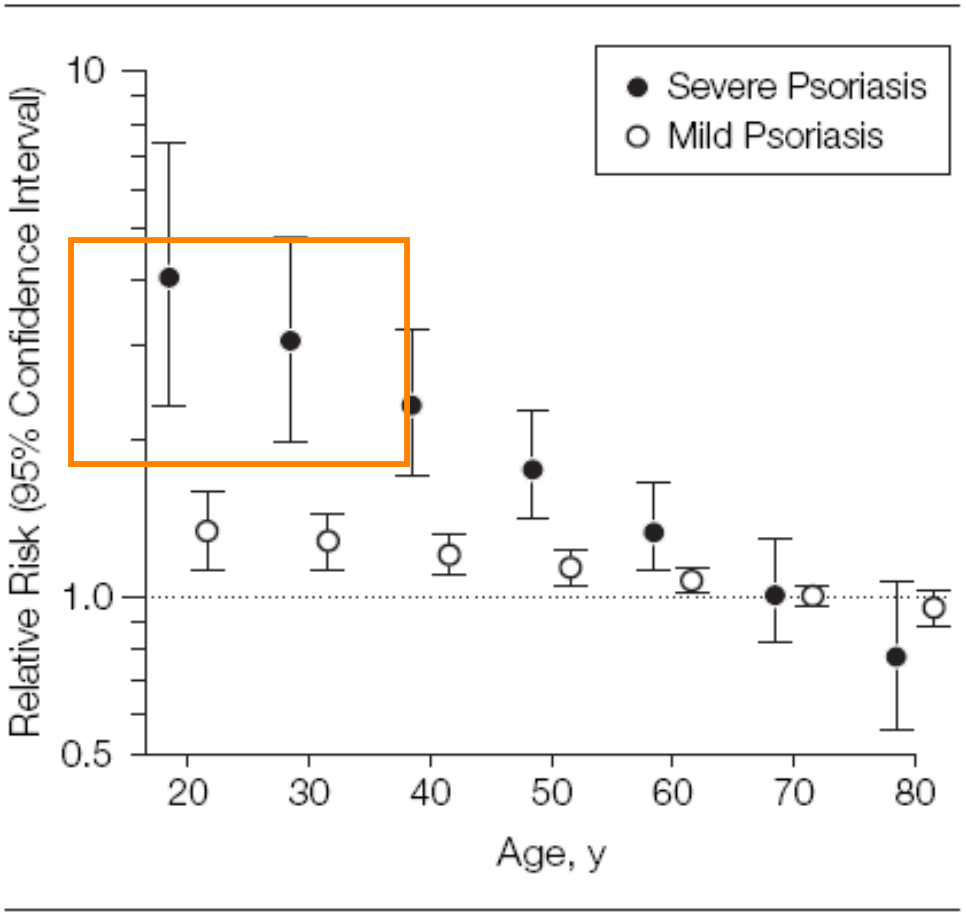
Armstrong A, et al, J Amer Acad Dermatol 2015;
Yeung H, et al, JAMA Dermatol 2013

Adjusted Relative Risk of MI in psoriasis patients based on age

- **556995 controls; 127139 mild psoriasis; 3,837 severe psoriasis**
- **5.4 yr mean follow-up**

- **Incidence of MI/1000PYs*:**
  Healthy controls: 3.58
  Mild psoriasis: 4.04
  Severe psoriasis: 5.13

- **RR greatest in young patients with severe psoriasis 3.1 for severe disease at 30**



Adjusted relative risk is shown on a log scale.

*adjusted for age, diabetes, MI, dyslipidemia, hypertension, sex and smoking status

Gelfand et al. JAMA 2006

Psoriasis and the independent risk of myocardial infarction-2013

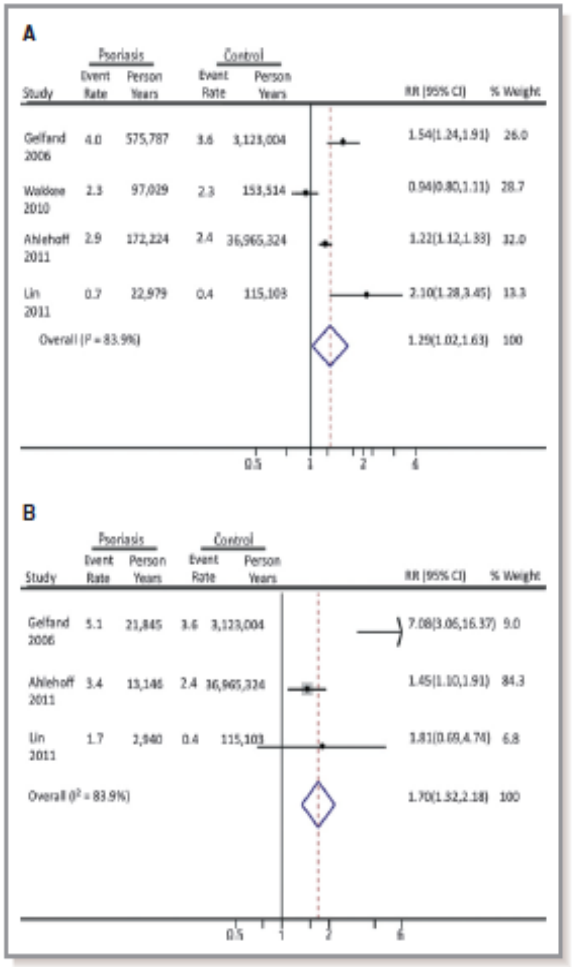


Figure 3. Myocardial infarction among patients with psoriasis. A, Risk of myocardial infarction among patients with mild psoriasis. B, Risk of myocardial infarction among patients with severe psoriasis. Rates are reported as events/1000 person-years.

Armstrong E, et al, J Amer Heart Ass 2013

Psoriasis and the risk of cardiovascular death

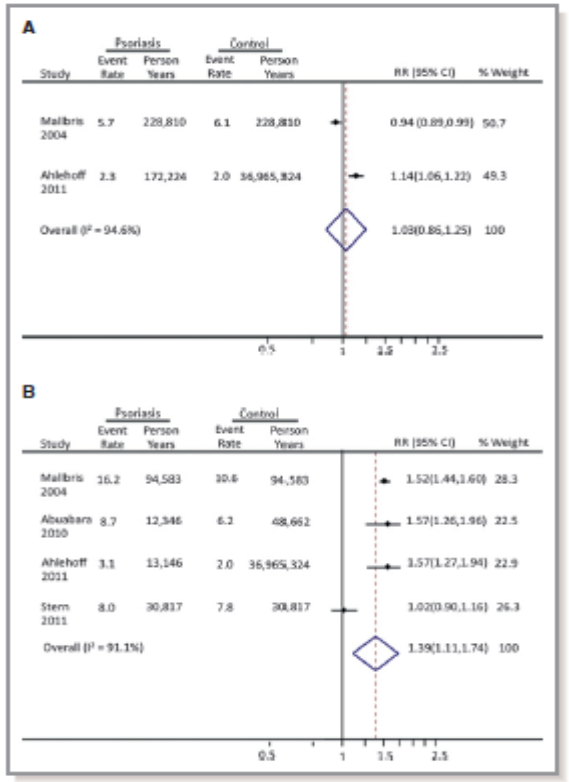


Figure 2. Cardiovascular death among patients with psoriasis. A, Risk of cardiovascular death among patients with mild psoriasis. B, Risk of cardiovascular death among patients with severe psoriasis. Rates are reported as events/1000 person-years.

Armstrong E, et al, J Amer Heart Ass 2013

Psoriasis and the independent risk of cerebrovascular accident

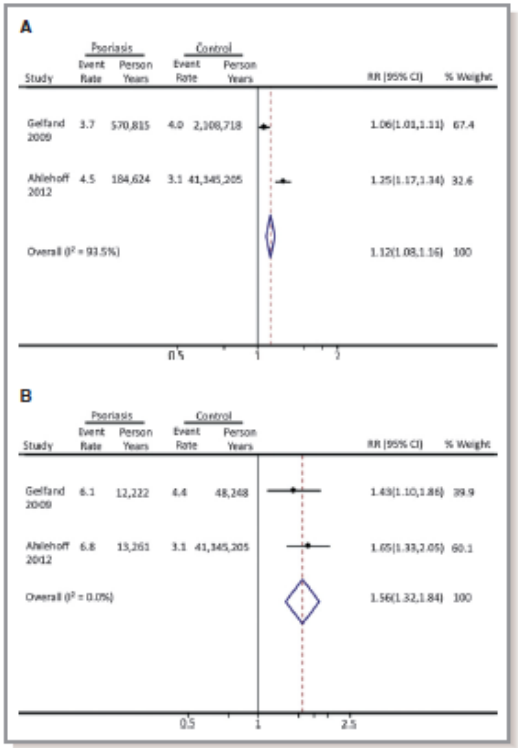


Figure 4. Stroke among patients with psoriasis. A, Risk of stroke among patients with mild psoriasis. B, Risk of stroke among patients with severe psoriasis. Rates are reported as events/1000 person-years.

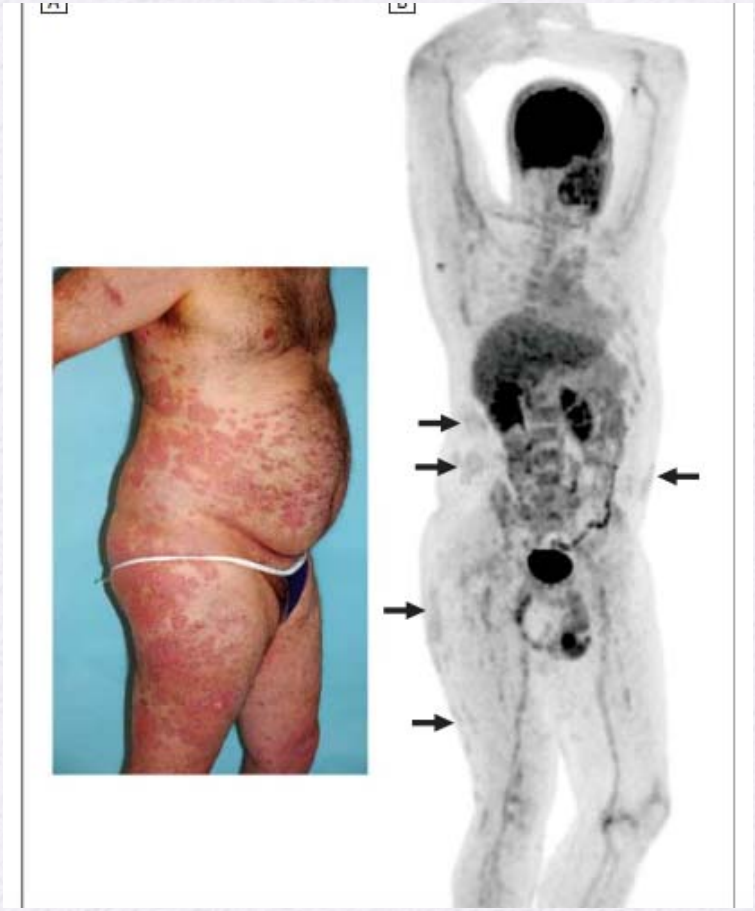
Armstrong E, et al, J Amer Heart Ass 2013

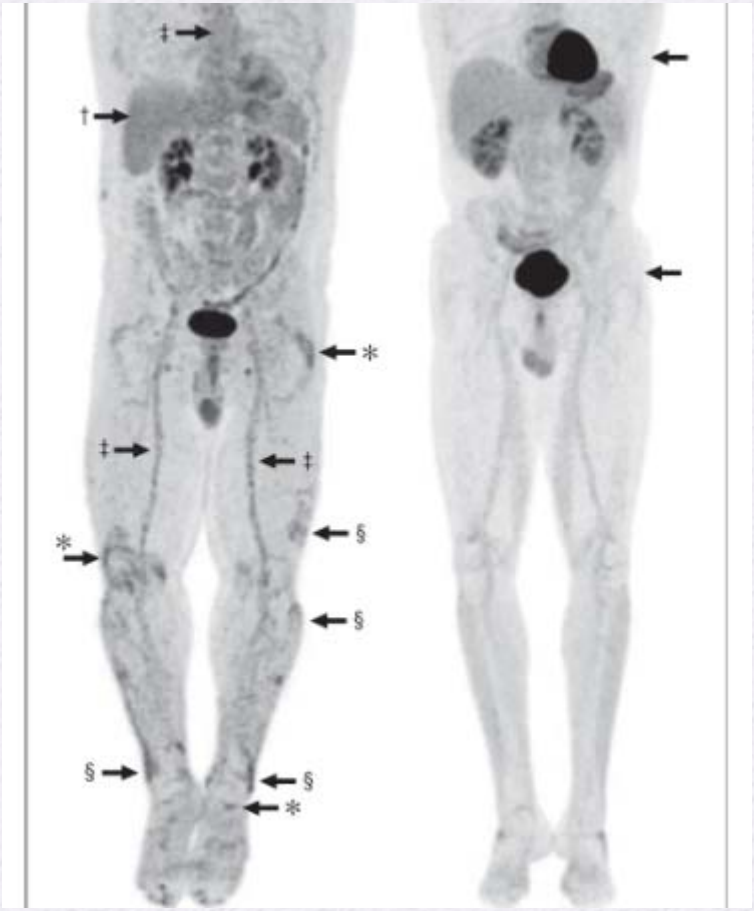
Psoriasis and the risk of MACE

- Cohort study, attributable risk of severe psoriasis on MACE: 6.2% over 10 year period*
- Addition of Psoriasis to Framingham Risk score results in reclassification of risk level to a higher risk category**
- Risk of MACE for those with severe psoriasis = that for diabetes***

***Mehta N, et al, Am J Med, 2011;Ogdie A, et al, Ann Rheum Dis 2015;**

Demonstration of inflammation





Mehta N, et al, JAMA Dermatol 2011

Smoking

- Increase risk of smoking in both males and females with severe psoriasis*
  - 46.6% males vs. 39.2% females
- Smoking is an independent risk factor of psoriasis*
  - Past smokers 1.39
  - Current smokers 1.94
    - 1-14 cigarettes 1.81
    - 15-24 cigarettes 2.04
    - > 25 cigarettes 2.29

Gerdes S, et al, Dermatology, 2010, *Li W et al, Am J Epidemiol 2012
Armstrong A, et al, Br J Dermatol 2011

Alcohol

- 22-32% of patients with psoriasis reported difficulty with alcohol*
  - 7% heavy alcohol intake
- Non-light beer associated with increased risk of psoriasis**
  - 1.72 psoriasis and alcohol
    - -2.3 drinks/wk

*Mc Aleer MA, et al, Br J Dermatol 2011
**Qureshi AA, et al, Arch Dermatol 2010

When a patient comes to clinic it is appropriate to:

- A. Counsel the patient about weight reduction
- B. Inquire about smoking history
- C. Evaluate baseline lipids
- D. Educate them about the potential risk of cardiac disease
- E. All of the above

When a patient comes to clinic it is appropriate to:

- A. Counsel the patient about weight reduction
- B. Inquire about smoking history
- C. Evaluate baseline lipids
- D. Educate them about the potential risk of cardiac disease
- E. All of the above

Psoriasis: gateway to health care

- Undiagnosed comorbidities
  - 2.3% diabetes
  - 9.1% hypertension
  - 4.9% hyperlipidemia
- Untreated comorbidities
  - 19.1% diabetes
  - 21.8% hypertension
  - 38.6% hyperlipidemia

Kimball AB, et al, J Amer Acad Dermatol 2011

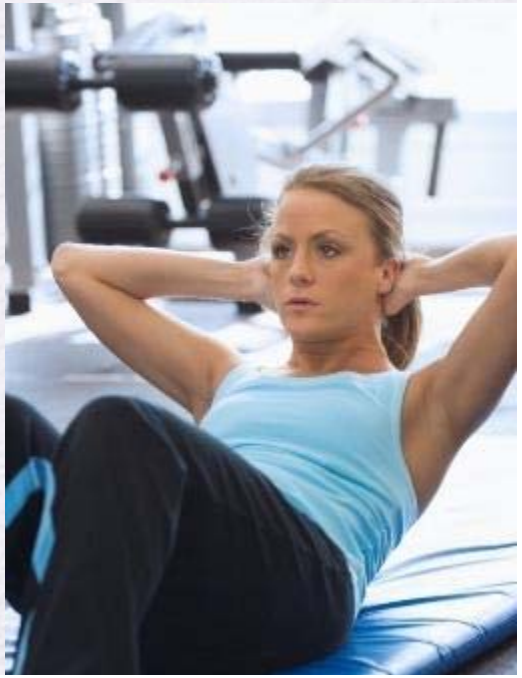
Need for improvement

- Among dermatologists, screening for CV risk factors was infrequent
  - blood pressure 2.6%
  - glucose 1.2%
  - cholesterol 4.3%
  - BMI 9.7%
- Survey of 127 United States (U.S.) dermatologists in 2015 revealed that less than 50% screened for hypertension, dyslipidemia, or diabetes in patients with psoriasis

- Alamdari, H.S., et al., *Psoriasis and cardiovascular screening rates in the united states.* Journal of Drugs in Dermatology, 2013. **12**(1): p. e14-e19.
- Manalo, I.F., K.E. Gilbert, and J.J. Wu, *Survey of trends and gaps in dermatologists' cardiovascular screening practices in psoriasis patients: Areas still in need of improvement.* J Am Acad Dermatol, 2015. **73**(5): p. 872-4 e4.

Exercise

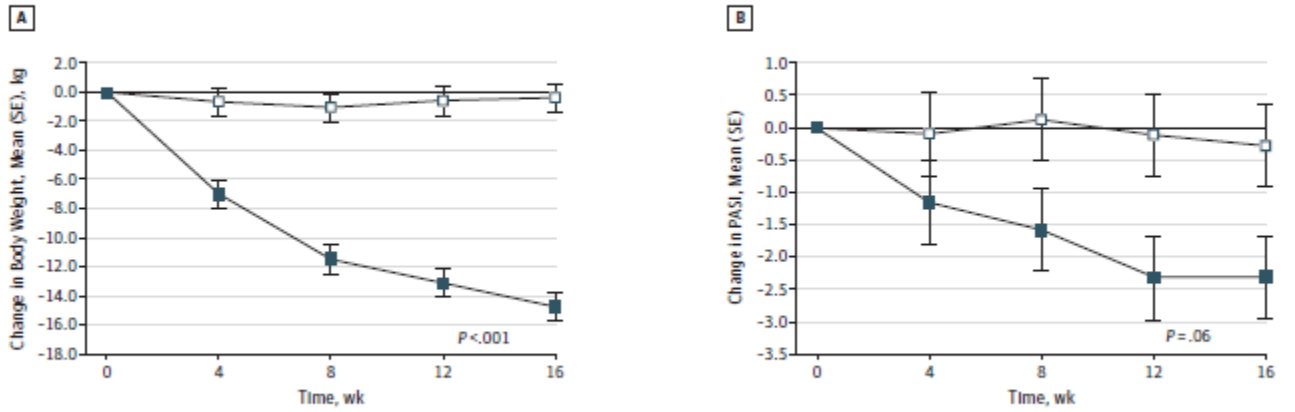
- Nursing health study of 116,430 women ages 27-44
- Age, alcohol and smoking adjusted
- Increased physical activity was inversely proportional to the risk of psoriasis
  - Vigorous exercise- 0.66
  - Not related to BMI



Frankel HC, et al, Arch Dermatol 2012

Effect of Weight loss on Psoriasis

Figure 2. Mean Changes Over Time From Baseline Body Weight (A) and Psoriasis Area and Severity Index (PASI) (B)

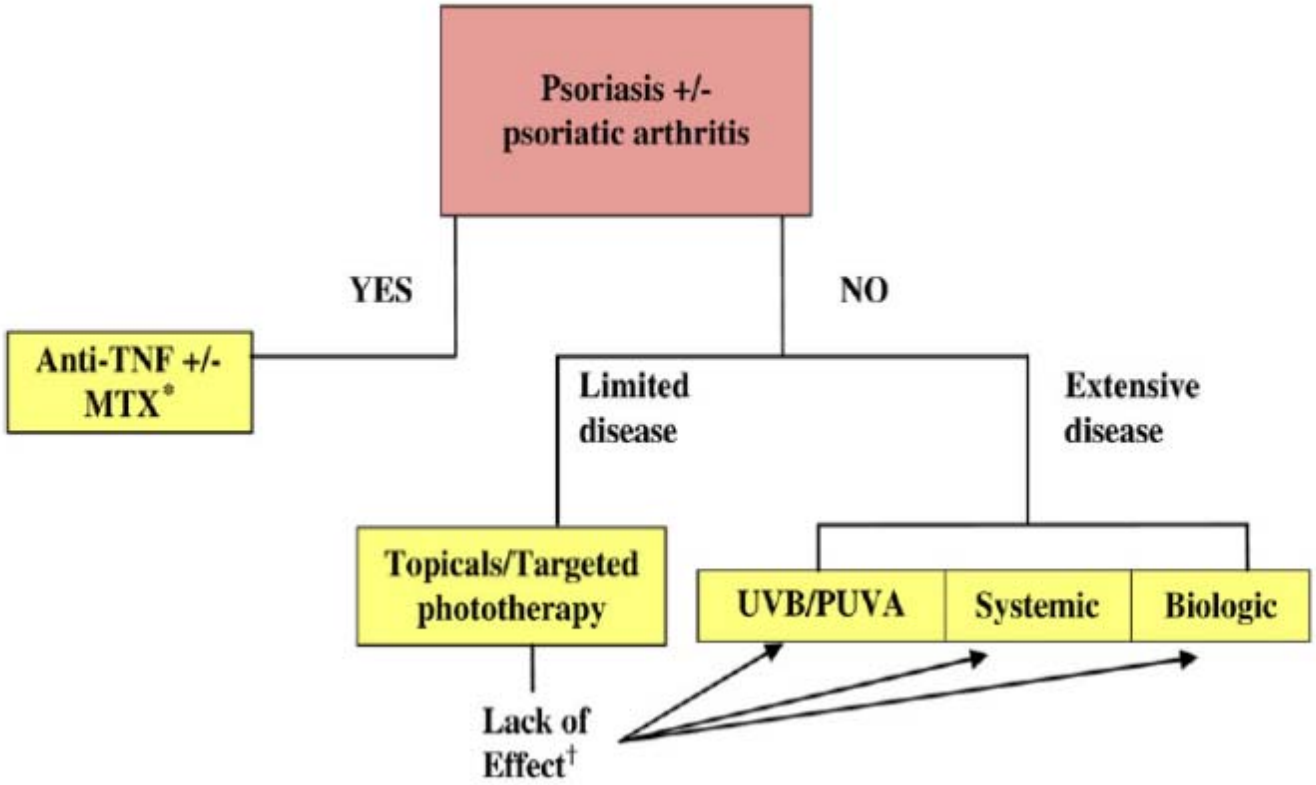


Filled symbols represent low-energy diet group; open symbols, control group.

Jensen P, et al, JAMA Dermatol 2013

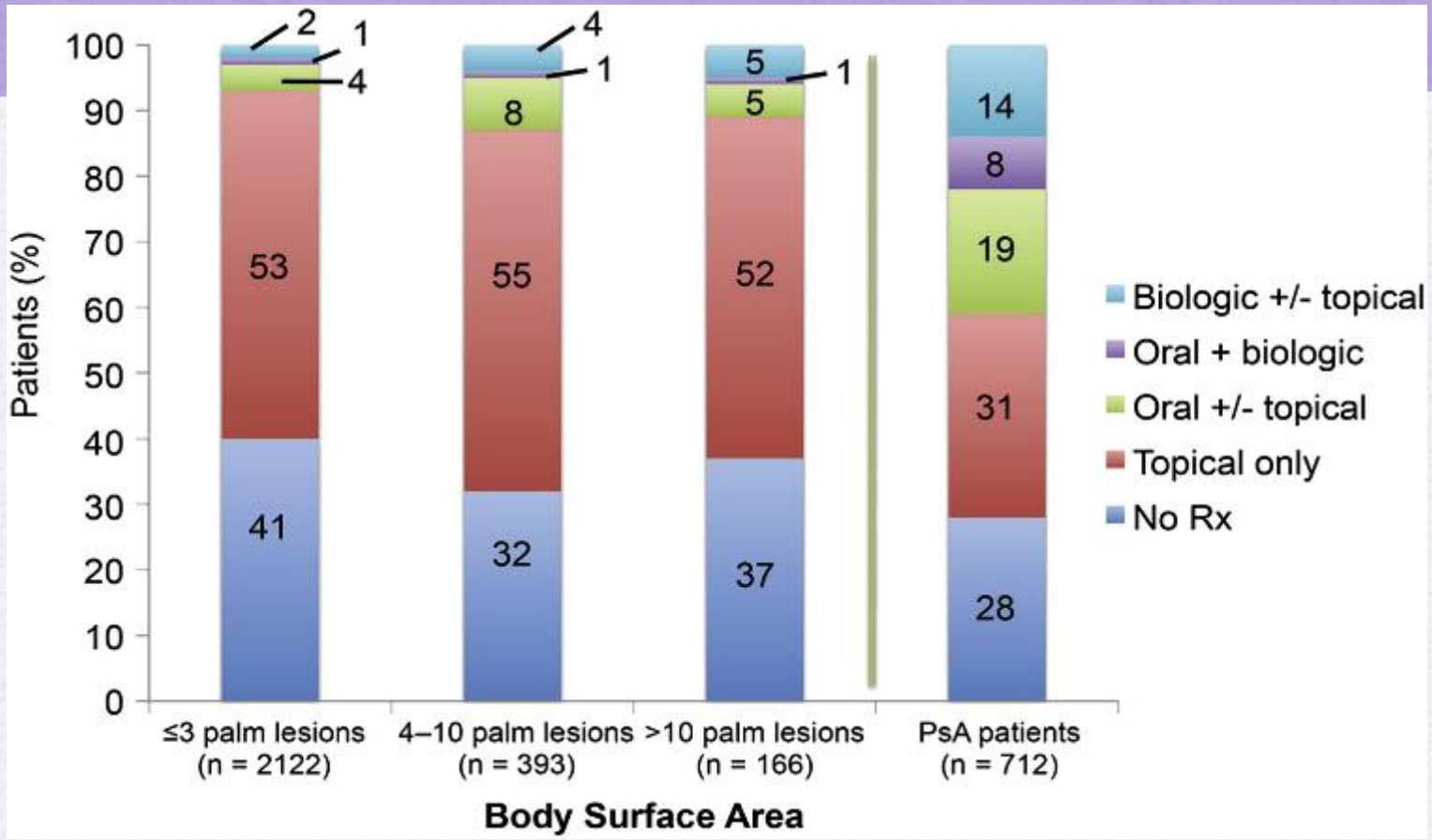
New meaning to the age-old adage about the heartbreak of psoriasis

AAD Treatment Guidelines for Moderate to Severe Psoriasis



Menter A, et al. *J Am Acad Dermatol.* 2008

Current Treatment Patterns in Psoriasis



Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey: a large, multinational, population-based survey of over 3426 psoriasis patients in North America and Europe

Lebwohl MG, et al. *J Am Acad Dermatol.* 2014

Does treatment lower the risk?

what we can learn from RA

Table 2 Incidence rates of cardiovascular events by medication exposure

	MI			TIA/stroke			Cardiovascular-related death			Composite cardiovascular events*		
	Event	Person years of exposure	Incidence rate (95% CI)	Event	Person years of exposure	Incidence rate (95% CI)	Event	Person years of exposure	Incidence rate (95% CI)	Event	Person years of exposure	Incidence rate (95% CI)
Non-biological DMARDs	5	2.272	2.20 (0.27 to 4.13)	8	2.287	3.53 (1.09 to 5.97)	4	2.264	1.77 (0.04 to 3.50)	17	2.264	7.51 (3.95 to 11.07)
Methotrexate	17	7.153	2.38 (1.26 to 3.51)	23	7.143	3.22 (1.91 to 4.53)	8	7.132	1.12 (0.35 to 1.90)	48	7.132	6.73 (4.83 to 8.63)
TNF antagonist	4	7.853	0.51 (0.01 to 1.01)	14	7.841	1.79 (0.85, 2.72)	5	7.837	1.02 (0.31 to 1.73)	23	7.837	2.93 (1.74 to 4.13)

Incidence rates expressed per 1000 patient years of exposure.
*Composite includes myocardial infarction (MI), transient ischaemic attack (TIA)/stroke and cardiovascular-related deaths.
DMARDs, disease-modifying antirheumatic drugs; TNF, tumour necrosis factor.

Greenberg JD, et al, Ann Rheum Dis 2011

How about in psoriasis?

Table 2. Incidence Rates of MI by Treatment Received

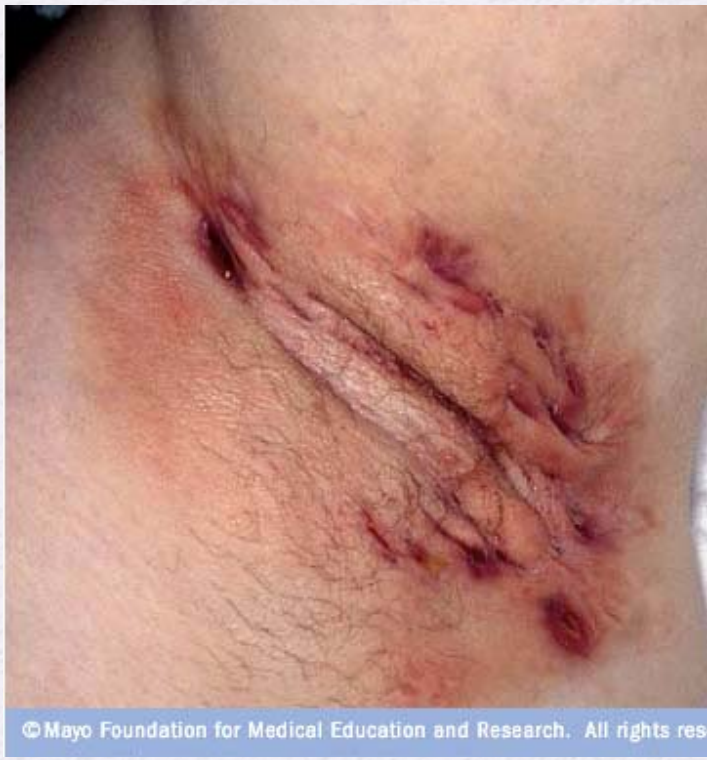
Characteristic	Treatment Cohort[a]			*P* Value
	Topical	Oral/Phototherapy	TNF Inhibitor	
MI events, No.	152	41	28	
Patient follow-up, y	22 592	10 650	9182	
Incidence rate, per 1000 patient-years	6.73	3.85	3.05	<.001

Abbreviation: MI, myocardial infarction.
[a] See the "Setting and Participants" subsection of the "Methods" section for a description of the cohorts.

Wu JJ, et al, Arch Dermatol 2012

Hidradenitits supprativa (HS)

- Chronic, destructive, scarring inflammatory skin disease
- Prevalence 1-4%
- More common in women
- Interesting stats
  - 18-44, most common age
  - Strongly ass with obesity
  - Strongly ass with smoking



Clinical presentation

- Areas of involvement: axillary, inguinal, and perianal areas
  - Less common: submammary, periumbilical, retroauricular,nuchal areas
- Fistulating sinuses
- Malordorous purulence
- Scarring

Pathogenesis

- Occlusion of hair follicular infundibulum
- Dilation of hair follicle with subsequent rupture of follicle & discharge of contents
- Inflammatory response
  - Involvement of proinflammatory cytokines: IL- 1 beta,IL-10, IL-12, IL-23, TNF
- Increase in susceptibility to secondary infections

Lim Z and Oon H. Ann Dermatol 2016

HS & other inflammatory disorders

- Inflammatory bowel disease
  - 9x more likely to develop HS than general pop
- Arthritis and spondyloarthropathy
  - Peripheral
  - African American men> others
  - HS precedes arthritis x several years, then chronic

Kohorst JJ, et al, J Amer Acad Dermatol, 2015

Metabolic syndrome and HS

Increased incidence
Prevalence 50.6% versus 30.2% controls

Extent of comorbidities is larger than just metabolic parameters

Table III. Components of metabolic syndrome in hidradenitis suppurativa and control groups

Variable	Response	N	Patients with HS	Control subjects	OR (95% CI)	*P* value
Obesity	No	103	29 (12.5%)	74 (33.6%)	3.6 (2.2-5.6)	<.001
(N = 453)	Yes	350	204 (87.6%)	146 (66.4%)		
Hypertriglyceridemia	No	246	105 (51.7%)	141 (71.6%)	2.4 (1.6-3.6)	<.001
(N = 400)	Yes	154	98 (48.3%)	56 (28.4%)		
Low HDL	No	196	93 (46.3%)	103 (51.5%)	1.2 (0.8-1.8)	.295
(N = 401)	Yes	205	108 (53.7%)	97 (48.5%)		
Glucose intolerance	No	317	149 (61.3%)	168 (75.7%)	2.0 (1.3-2.9)	<.001
(N = 465)	Yes	148	94 (38.7%)	54 (24.3%)		
Hypertension	No	243	133 (54.7%)	110 (49.6%)	0.8 (0.6-1.2)	.264
(N = 465)	Yes	222	110 (45.3%)	112 (50.5%)		

CI, Confidence interval; HDL, high-density lipoprotein; HS, hidradenitis suppurativa; OR, odds ratio.

Table II. Comorbidity burden in patients with hidradenitis suppurativa versus matched control subjects

Comorbidities	Patients with HS, % (n) N = 1733	Control subjects, % (n) N = 1733	Mantel-Haenszel χ^2 (*P* value)
Current or former smoker	29.5 (511)	0.92 (16)	473 (<.0001)
Obesity	11.6 (201)	0.75 (13)	168 (<.0001)
Hypertension	34.3 (594)	3.0 (52)	489 (<.0001)
Dyslipidemia	33.8 (620)	1.6 (28)	567 (<.0001)
Diabetes mellitus	20.4 (353)	1.5 (26)	296 (<.0001)
Thyroid disorder	21.6 (373)	2.1 (37)	278 (<.0001)
Psychiatric disorder	57.8 (1000)	7.2 (124)	761 (<.0001)
Arthropathies	52.5 (908)	3.0 (52)	815 (<.0001)
Polycystic ovarian syndrome	4.0 (70)	0.17 (3)	61.4 (<.0001)
Alcohol dependence	4.2 (73)	0.52 (9)	49.9 (<.0001)
Lymphoma	1.8 (32)	0.52 (9)	12.9 (<.0004)
Drug dependence	6.5 (113)	0.40 (7)	93.6 (<.0001)
Squamous cell carcinoma	0.52 (9)	0 (0)	—

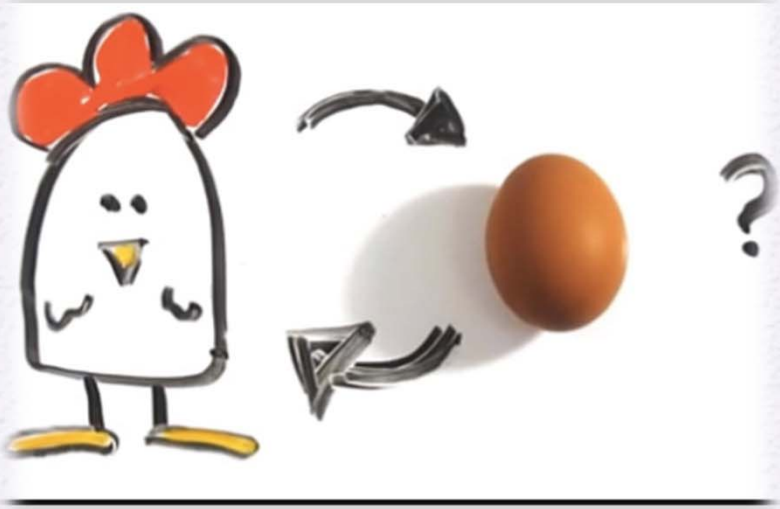
HS, Hidradenitis suppurativa.

Sabat R, et al, PLOS 2012, Gold DA, et al, J Amer Acad Dermatol 2014, Shlyankevich J,
et al, J Amer Acad Dermatol 2014; Gold DA, et al, J Amer Acad Dermatol 2014

Chicken and egg

Metabolic syndrome increases risk of HS

Smoking rates in HS 40-92%



Sabat R, et al, PLOS 2012

HS & CRP

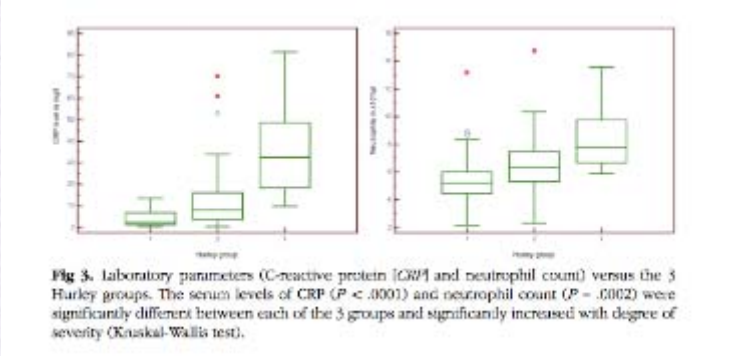


Fig 3. Laboratory parameters (C-reactive protein [CRP] and neutrophil count) versus the 3 Hurley groups. The serum levels of CRP ($P < .0001$) and neutrophil count ($P = .0002$) were significantly different between each of the 3 groups and significantly increased with degree of severity (Kruskal-Wallis test).

- Evidence of increase of inflammatory load
- CRP and obesity were independent predictors for severe disease
- CRP is effective for assessing the extent of disease severity and grade of inflammation

Schapoor Hessan, et al, J Amer Acad Dermatol 2015

Risk of adverse cardiac events

Table 3. Unadjusted and Adjusted IRRs in Patients With HS Compared With Matched Controls

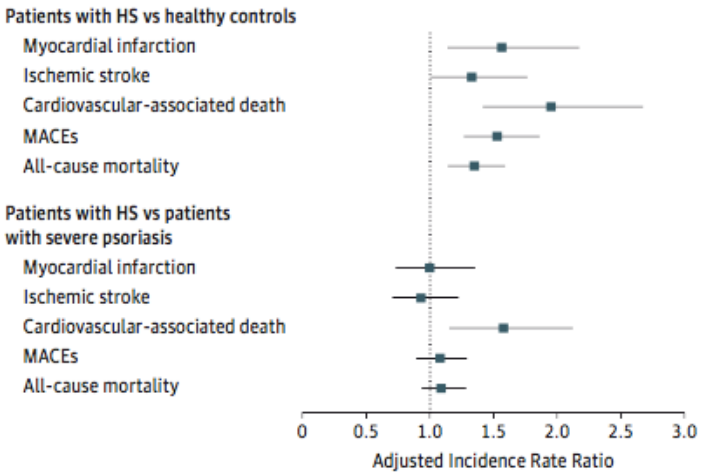
Characteristic	Unadjusted IRR (95% CI)	P Value	Fully Adjusted[a] IRR (95% CI)	P Value
Myocardial infarction	2.16 (1.61-2.84)	<.001	1.52 (1.14-2.17)	.005
Ischemic stroke	1.73 (1.32-2.25)	<.001	1.38 (1.01-1.76)	.04
CV-associated death	2.54 (1.87-3.44)	<.001	1.95 (1.42-2.67)	<.001
MACEs	2.07 (1.73-2.48)	<.001	1.53 (1.27-1.86)	.001
All-cause mortality	1.96 (1.68-2.29)	<.001	1.35 (1.15-1.59)	.005

Abbreviations: CV, cardiovascular; HS, hidradenitis suppurativa; IRRs, incidence rate ratios; MACEs, major adverse CV events.

[a] Adjusted for age, sex, smoking, comorbidities, medication, and socioeconomic status.

Egeberg A, et al, JAMA Dermatol 2016

Figure. Risk of Adverse Cardiovascular Outcomes



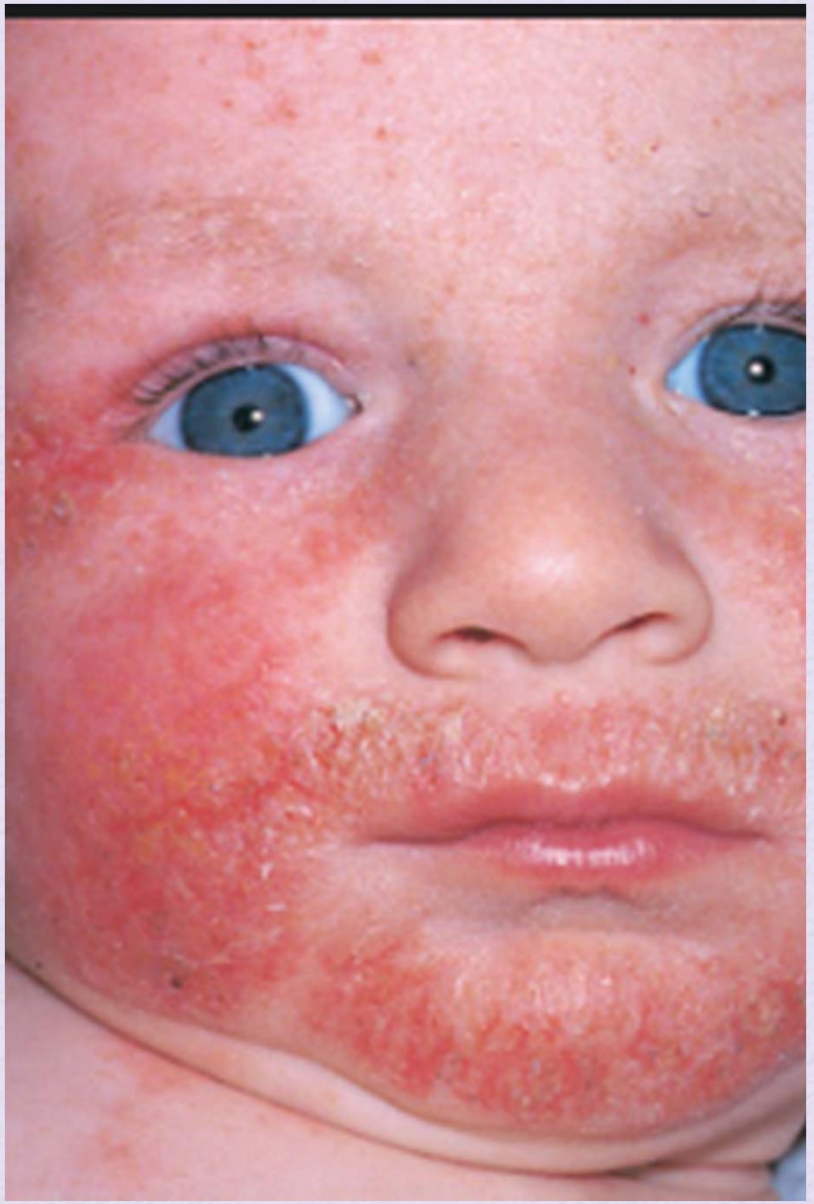
Adjusted incidence rate ratios (data markers) with 95% CIs in patients with hidradenitis suppurativa (HS) compared with healthy controls and patients with severe psoriasis. MACEs indicates major adverse cardiovascular events.

Atopic disease

Atopic dermatitis

Asthma

Hay fever (allergic rhinitis)



Atopic dermatitis

- Chronic, recurrent inflammatory disease
- Multifactorial etiology:
  - Genetic predisposition
  - Immune dysfunction
  - External environmental factors
- Increased incidence
  - 20% children
  - 10% adults

Pathogenesis of AD

- Defective skin barrier
- Dysregulated T-cell responses
- Th2 inflammation

Atopic dermatitis & the metabolic syndrome

- Long-standing association of asthma with obesity
- Now clear association of atopic dermatitis with obesity*.
  - Overweight: OR 1.24 children, OR 1.15 adults
  - Obesity: OR 1.44 children, OR 1.56 adults
- Korean women: OR 2.92 metabolic syndrome**
  - OR 1.73 increased waist circumference
  - OR 2.20 increased triglycerides

***Zhang A, Silverberg JI, J Amer Acad Dermatol 2015;**
**** Lee JH, et al, Acta Derm Venereal 2016**

Atopic dermatitis & HTN in children

- Central obesity unrelated to severity of AD
- Elevation of BP
  - Systolic BP OR 2.94
  - Diastolic BP OR 3.68
  - Systolic BP 90th percentile or higher OR 2.06

Silverberg JI, et al, JAMA Dermatol, 2015

Atopic dermatitis & heart disease in adults

- Flexural eczema ass with increased risks:
  - CAD (p<0.04)
  - Heart attach (p<0.01)
  - Heart failure (p<0.02)

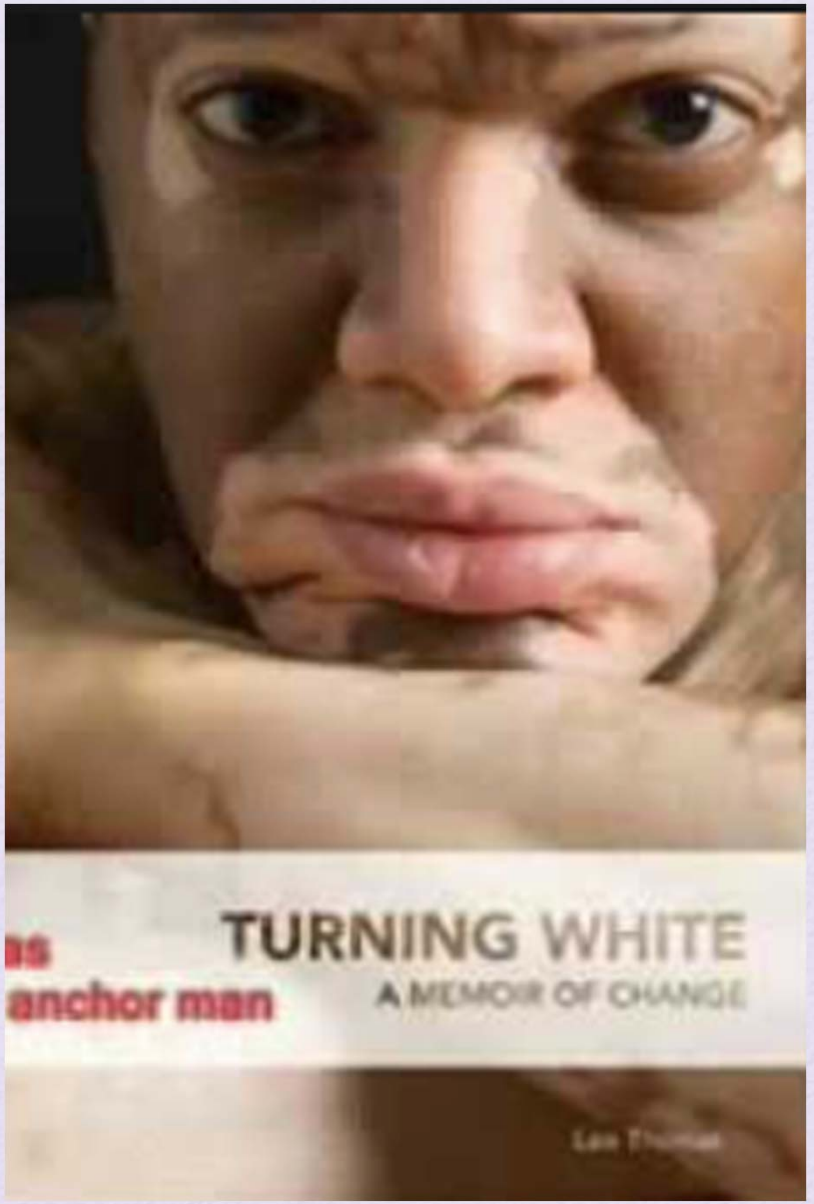
Silverberg, JI. Allergy 2015

Vitiligo

- Acquired, autoimmune, depigmenting disease affecting 1% of world's population
- Associated with other autoimmune disorders including: alopecia areata, autoimmune thyroid disease, Addison's disease, pernicious anemia, type 1 diabetes mellitus, myasthenia gravis
- Believed to be mediated by interleukin 1 and 6

Michael Jackson

The name to the disease



Vitiligo and concurrent diseases

Table 2. Prevalence of comorbidities

Comorbidity	Prevalence (n = 2,441)
Thyroid disease	287 (11.8%)
Hypothyroidism	187 (7.6%)
Thyroiditis	47 (2.0%)
Hyperthyroidism	29 (1.2%)
Graves' disease	24 (1.0%)
Psoriasis	186 (7.6%)
Rheumatoid arthritis	72 (2.9%)
Alopecia areata	59 (2.4%)
Inflammatory bowel disease	55 (2.3%)
Ulcerative colitis	33 (1.4%)
Crohn's disease	14 (0.6%)
Unspecified	8 (0.3%)
Systemic lupus erythematosus	53 (2.2%)
Diabetes mellitus type I	20 (0.8%)

Table 4. Incidence of laboratory abnormalities

Laboratory value	Incidence
ANA ≥1:160	181 (41.0%)
ANA <1:160 or –	257 (59.0%)
Rheumatoid factor +	16 (66.7%)
Rheumatoid factor –	8 (33.3%)
Thyroid-stimulating hormone	
Low	34 (5.4%)
Normal	571 (91.0%)
High	22 (3.5%)
Free T4	
Low	27 (9.2%)
Normal	238 (80.7%)
High	30 (10.2%)
Thyroglobulin Ab +	0
Thyroglobulin Ab –	5 (100%)
Thyroid peroxidase Ab +	40 (44.9%)
Thyroid peroxidase Ab –	49 (55.1%)
25-OH vitamin D	
Low	159 (24.0%)
Insufficient	215 (33.0%)
Normal	286 (43.0%)

Ab = Antibodies; ANA = anti-nuclear antibodies.

Sheth VM, Guo Y, Qureshi AA, Dermatol, 2013

Vitiligo - Comorbid autoimmune diseases

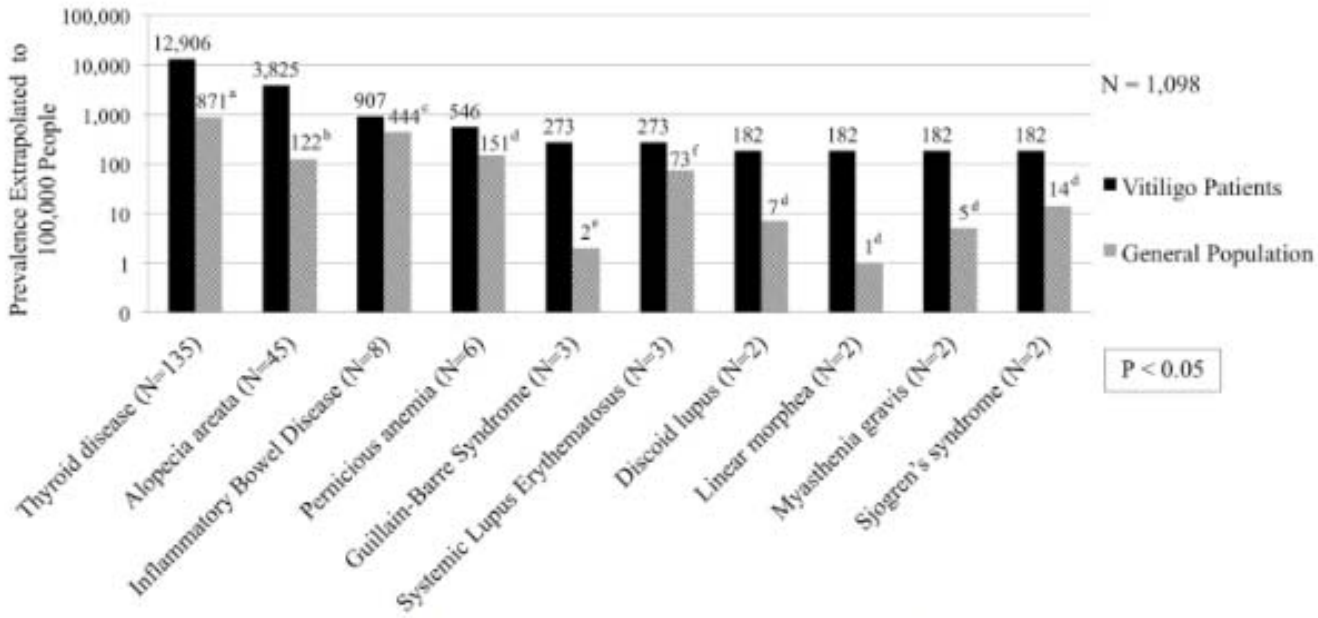
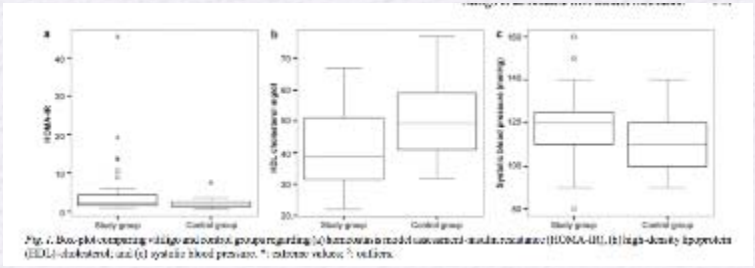


Fig 1. Prevalence of comorbid autoimmune disease extrapolated to 100,000 patients with vitiligo. Autoimmune diseases with a statistically significant higher prevalence in patients with vitiligo compared with the general population are shown. The Y-axis is in logarithmic scale. *P* values were less than .05 for each disease shown. [a]Data derived from Hollowell et al[30]; [b]data derived from Safavi[25]; [c]data derived from Kappelman et al[28]; [d]data derived from Hayter and Cook[19]; [e]data derived from Alshekhlee et al[27]; [f]data derived from Somers et al.[29]

Gill L, et al, J Amer Acad Dermatol 2016

Vitiligo & the metabolic syndrome



- Increased levels of:
  - Insulin resistance
  - Total cholesterol
  - Triglycerides
  - LDL/HDL
  - C-peptide levels
  - Blood pressure
- Lower levels of:
  - HDL-C levels

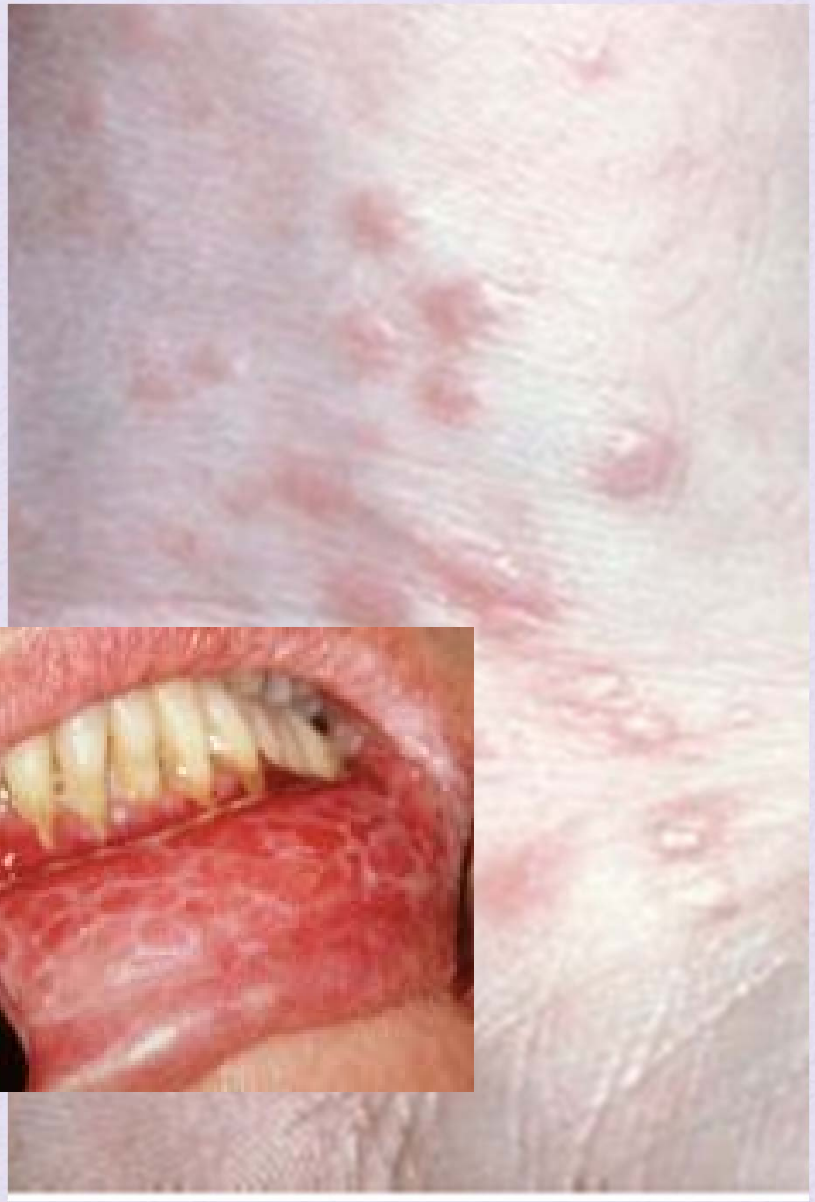
Karadag AS, et al, Acta Derm Venereol 2011

Lichen planus

Idiopathic inflammatory disease

Affects skin and mucosal surfaces

T cell mediated disease



Lichen planus & comorbid disease

- Elevation of lipids
- Other parameters of metabolic syndrome not found

Table 4 Mean (SD) LDL-C (mg/dL), Total Cholesterol (mg/dL), Total Cholesterol/HDL and LDL-C/HDL-C in Patients with Lichen Planus and their Respective Controls

	Patients (n = 200)		*P*	Men (n = 100)		*P*	Women (n = 100)		*P*
	LP	No LP	Value	LP	No LP	Value	LP	No LP	Value
LDL-C (mg/dL)	120.1 (30.0)	103.9 (28.9)	.0001	124.2 (29.2)	107.6 (33.5)	.01	115.7 (30.5)	100 (22.7)	.006
Total cholesterol (mg/dL)	200.1 (35.6)	183.4 (35.8)	.001	201.3 (32.1)	185.1 (37.8)	.023	198.8 (39.4)	181.7 (33.8)	.026
Total cholesterol/HDL-C	3.7 (1.2)	2.9 (1.1)	.0001	4.0 (1.2)	3.2 (1.2)	.0012	3.4 (1.4)	2.6 (0.7)	.0006
LDL-C/HDL-C	2.2 (1.0)	1.6 (0.8)	.0001	2.4 (0.9)	1.8 (0.9)	.0012	1.9 (1.1)	1.4 (0.7)	.081

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; LP = lichen planus.

LP and CRP

Table 5 Mean (SD) CRP, Fibrinogen, ESR in Men and Women with Lichen Planus and their Respective Controls

	Patients (n = 200)		*P*	Men (n = 100)		*P*	Women (n = 100)		*P*
	LP	No LP	Value	LP	No LP	Value	LP	No LP	Value
CRP (mg/dL)	0.53 (0.56)	0.31 (0.45)	.004	0.59 (0.72)	0.32 (0.57)	.03	0.46 (0.32)	0.31 (0.28)	.018
Fibrinogen (mg/dL)	357.9 (77.9)	305.1 (89.3)	.001	336.6 (72.2)	292.9 (99)	.013	380.5 (78.1)	318.1 (76.7)	.0001
ESR (mm/h)	14.2 (12.5)	9.9 (7.5)	.004	12.7 (11.6)	7.7 (4.1)	.005	15.8 (13.3)	12.3 (9.4)	.13

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LP = lichen planus.

Polycystic ovarian syndrome (PCOS)

- 2-7% of population
- 2003 Rotterdam consensus criteria-
  - Oligoanovulation
  - Polycyctic ovaries (transvaginal U/S)
  - Clinical signs of hyperandrogenism (HA)
- Cutaneous signs of HA
  - Acne, hirsuitism, androgenic alopecia, acanthosis nigricans, seborrheic dermatitits

Risks associated with PCOS

- Obesity
- Infertility
- Malignancy
- Insulin resistance
- Sleep apnea
- Nonalcoholic steatohepatitis
- Depression & anxiety

PCOS features and risk levels

Table 5. Summary of Key Cutaneous Findings of PCOS Among a High-Risk Population

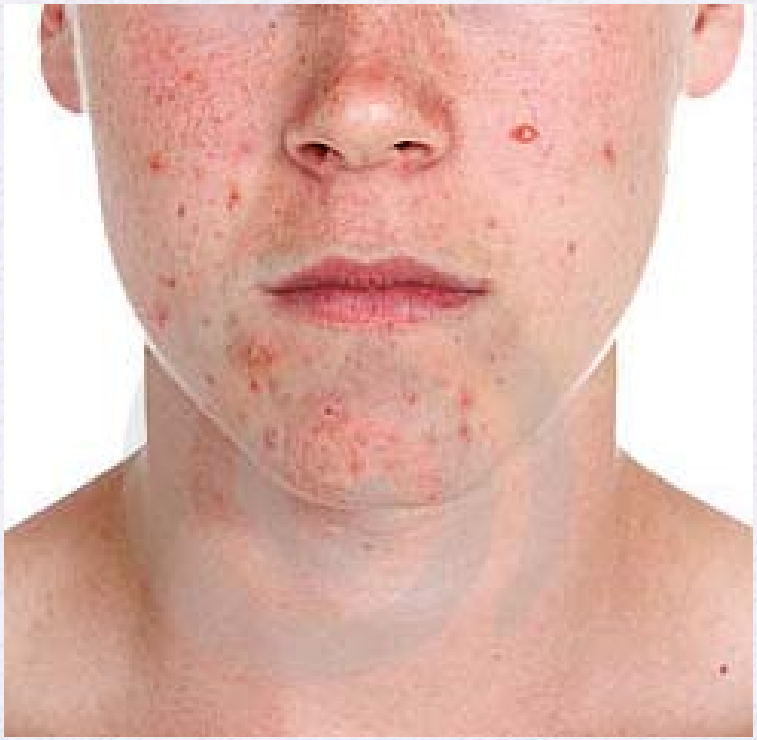
Cutaneous Finding	Key Distribution	Systemic Association	Comment
Acne	Face (forehead)	None	Increased prevalence among patients who meet PCOS diagnosis but no significant difference in distribution or lesional counts, not associated with biochemical hyperandrogenism, not a reliable marker of hyperandrogenism in PCOS
Hirsutism	Truncal is most specific (chest, abdomen, or back), less specific are chin and thigh, nonspecific are upper lip and upper arm	Elevated free testosterone level, increased insulin resistance, increased BMI, dyslipidemia (HDL-C, triglycerides)	Excellent marker for PCOS and warrants selective endocrine and metabolic diagnostic evaluation, requires a comprehensive skin examination
Acanthosis nigricans	Axillae	Elevated free testosterone level, increased insulin resistance, increased glucose intolerance, increased BMI, dyslipidemia (total cholesterol, LDL-C, HDL-C, or triglycerides)	Excellent marker for PCOS and warrants selective endocrine and metabolic diagnostic evaluation, requires a comprehensive skin examination
Androgenic alopecia	Scalp	Lower prevalence of polycystic ovaries, associated with clinical but not biochemical hyperandrogenism	Not a reliable marker for PCOS

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCOS, polycystic ovary syndrome.

Schmidt TH, et al, JAMA Dermatol 2016

Acne

Teen age male



Adult male

Acne

- Long known to be associated with an increase in androgens
- Teen age acne: Physiologic insulin resistance in adolescents leads to hyperinsulinemia which leads to acne
- Post-adolescent male acne: Increase prevalence of insulin resistance (22%) compared with controls (11%)

Gaps

- Lack of appreciation of concurrent illnesses & comorbid diseases both in dermatology and internal medicine
- Lack of monitoring of at risk individuals
- Lack of information about potential of treatment to impact both primary disease and comorbid conditions

Nothing short of revolutionary

The future of dermatology